Durable complete response to immunotherapy with anti-PD-1 antibody nivolumab in a patient with oral squamous cell carcinoma presenting with lung metastasis: A case report

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Abstract
Although the optimal treatment method for metastatic oral cancer remains largely unknown, the present case suggests that immunotherapy is a potentially promising alternative for metastatic oral cancer in which other therapies are no longer effective.

Keywords
anti-PD-1, complete remission, immune checkpoint inhibitor, lung metastasis, nivolumab, oral squamous cell carcinoma

1 | INTRODUCTION

The optimal treatment method for metastatic oral cancer remains largely unknown. We present a case of complete remission of lung metastases in a Japanese patient with oral squamous cell carcinoma via immunotherapy with nivolumab. The present case further supports the efficacy of immunotherapy for treating metastatic oral cancer.

Oral cancer is the most frequent type of head and neck cancer,1 and squamous cell carcinoma accounts for approximately 90% of all oral cancers.2 More than 50% of oral cancers are diagnosed at an advanced stage with lymph node metastasis.3 Although recent advancements in multimodal therapies have enhanced the locoregional control of oral cancer, distant metastasis remains poorly controlled clinically and is one of the principal adverse prognostic factors.4 The incidence of distant metastasis in oral cancer is estimated to range from 15% to 20%,5,6 most commonly to the lung.7 Because of a poor prognosis of patients with a short life expectancy, therapeutic intervention is controversial and usually involves palliative care. Palliative chemotherapy and/or molecular-targeted therapy directed to epidermal growth factor receptor (EGFR)
have been commonly used for treating metastatic oral cancer, having demonstrated prolonged median survival among patients with metastatic diseases.8–10

Recently, cancer immunotherapy typically based on the blockade of negative immunomodulators such as PD-1, CTLA-4, and PD-L1 offers a novel insight into the treatment of cases of recurrent or metastatic cancers refractory to other therapies.11 Nivolumab, a human monoclonal IgG4 antibody targeting PD-1 on T cells, was approved in Japan in 2017 and has been used to treat platinum-refractory recurrent and/or metastatic head and neck cancer. Although nivolumab has been clinically successful in prolonging the overall survival of patients with recurrent and/or metastatic head and neck cancer, limited data are available regarding the long-term durable response to nivolumab in metastatic oral cancer.12

Here, we report the first case of a durable radiological complete response to nivolumab in a Japanese patient with oral squamous cell carcinoma presenting with lung metastasis.

2 CASE PRESENTATION

A 59-year-old Japanese man presented with a painful ulcerous mass on the floor of his mouth.

He had initially become aware of slight pain and ulceration on the left side of the floor of his mouth 2 months before visiting our hospital. However, the ulcer had gradually enlarged, accompanied by the simultaneous onset of severe pain. Therefore, he first consulted a general dental practitioner and was then referred to our hospital for treatment of the pain in the floor of his mouth.

His medical history revealed deep vein thrombosis, and his family history was unremarkable. He had a history of smoking for 40 years from 20 years of age, with no alcohol consumption or any other harmful habits. On initial assessment, no systemic symptoms were evident. Several enlarged lymph nodes were palpable on the left side of the neck at levels I and II. Intraoral examination revealed an indurated mass of 30 × 20 mm² on the left side of the floor of the mouth, and the mucosal surface of the mass was partially ulcerated (Figure 1A). Computed tomography (CT) and magnetic resonance imaging (MRI) revealed a non-homogeneous enhancing mass in the left side of the sublingual region, extending through the mylohyoid muscle (Figure 1B,C). Neck CT detected several enlarged lymph nodes in unilateral level I–II, suggesting the presence of lymph node metastases. No other specific findings were observed on chest or abdominal CT. Biopsy revealed features of invasive squamous cell carcinoma. The tumor on the floor of the mouth was clinically classified...
as stage IVA (T3N2bM0) based on the UICC TNM classification criteria of oral cavity cancer. The patient initially received definitive concurrent chemoradiotherapy (CCRT) at 70 Gy/35 fr with triweekly cisplatin (CDDP 100 mg/m²) and subsequently underwent post-CCRT unilateral planned neck dissection. Locoregional recurrence was observed 2 months after CCRT and salvage surgery with subtotal glossectomy, partial mandibulectomy, and radical neck dissection was performed, along with reconstruction with a vascularized scapula and latissimus dorsi flap. However, the patient developed multiple lung metastases at 6 months after salvage surgery (Figure 2A,B); this histopathological diagnosis was obtained through bronchofiberscopy, and nivolumab immunotherapy was decided in accordance with the suggestion of an institutional tumor board meeting. His clinical condition was good (ECOG performance status 0), PD-L1 expression in the tumor was 5% on immunohistochemistry, and the neutrophil-lymphocyte ratio (NLR) on blood examination was 4.1. Nivolumab administration was initiated at 240 mg every 2 weeks. CT after nine cycles of nivolumab administration revealed complete remission of the metastatic lesions (Figure 3). After 15 cycles of nivolumab administration, he developed hypothyroidism as a thyroid immune-related adverse event (irAE) for which he received levothyroxine, whereas the nivolumab treatment regimen remained unaltered. After 33 cycles, he developed interstitial lung disease as a pulmonary irAE for which he was treated with prednisone, and nivolumab treatment was interrupted. Thereafter, CT revealed no evidence of lung metastases or other metastatic diseases. Nivolumab was then discontinued owing to complete remission observed on follow-up CT, which lasted 6 months after discontinuation of nivolumab administration, and his clinical condition was good for >2 years after the discovery of lung metastases.

### DISCUSSION

Here, we describe the case of a patient with oral squamous cell carcinoma presenting with lung metastasis, wherein radiological complete remission was achieved after immunotherapy with anti-PD-1 antibody nivolumab.

Although the continuous advancements in multimodal therapies have revealed improvements in the control of metastatic oral cancer, overall survival, and disease-specific survival were not significantly enhanced. Therefore, distant metastasis remains one of the most critical causes of unfavorable outcomes in oral cancer, and therapeutic intervention with a novel strategy would be desired to markedly enhance survival benefits.

Conventional treatment modalities including surgery, chemotherapy, and radiotherapy may exert limited treatment benefits among patients with metastatic oral cancer. Surgical intervention has a limited indication only for solitary metastatic disease, and palliative local radiotherapy is also administered for treating single metastases to relieve symptoms. Palliative chemotherapy has been more commonly used for treating metastatic oral cancer and has prolonged the median survival of patients with metastatic diseases in several studies. Molecular-targeted therapy directed to epidermal growth factor receptor (EGFR), which is aberrantly overexpressed in head and neck squamous cell carcinoma cells, has also been used for treating metastatic diseases in combination with other chemotherapeutic agents and reportedly enhances

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**FIGURE 2** A lung metastatic lesion detected through computed tomography (A) and positron emission tomography (B)

**FIGURE 3** No recurrence of lung metastases after 9 cycles of nivolumab administration
overall survival. However, primary or acquired biological resistance to chemotherapy or molecular-targeted therapy is common, and long-term survival benefits of these therapies remain limited.

The emerging role of the immune system in cancer and its potential effect as a novel alternative for cancer treatment has received increasing attention. In particular, the emergence of immune checkpoint inhibitors (ICIs) has revolutionized the treatment of recurrent and/or metastatic oral cancer, resulting in a better overall survival than that of conventional therapies. However, the overall response rate of ICIs among patients with advanced oral cancer is <20%, with numerous patients displaying primary or acquired resistance. Hence, prognostic indicators for patients receiving nivolumab need to be urgently identified, along with the causes of this resistance and strategies to overcome them.

Various mechanisms underlying impaired antigen presentation and T-cell activation have been suggested to be associated with resistance to immunotherapy.

A lower tumor mutation burden and insufficient neoantigens, which are associated with decreased tumor immunogenicity, reportedly predict a poor response to ICIs in different cancers, indicating that the tumor mutation burden is an emerging biomarker for predicting the response to immunotherapy. PD-L1 expression in tumors has also been considered a predictive biomarker in the clinical setting for ICI treatment in different cancers. Higher levels of PD-L1 expression have been reported to be associated with better outcomes for ICI therapy in various cancers, including head and neck cancers. Moreover, systemic inflammatory markers, such as the neutrophil-to-lymphocyte ratio (NLR) and lymphocyte-to-monocyte ratio (LMR), which are considered pivotal markers of inflammation, have also been suggested as potential indicators of responses to ICIs in different cancers, suggesting that a higher baseline NLR is associated with a worse response to ICIs, although the NLR of the present patient was relatively high at 4.1 on initiation of nivolumab.

**4 | CONCLUSION**

This case study is the first, to our knowledge, to elucidate complete remissions of lung metastases in oral cancer upon treatment with anti-PD-1 antibody among Japanese patients. Although this is only a single case report, our case suggests that immunotherapy is a potentially promising alternative for metastatic oral cancer in which other therapies are no longer effective. Studies on the prediction of responses to ICIs are continuously evolving, more suitable biomarkers urgently need to be identified to better facilitate patient selection. Moreover, a novel strategy combined with chemotherapeutic agents or molecular-targeted therapies is required to overcome treatment resistance.

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**CONFLICT OF INTEREST**
None declared.

**AUTHOR CONTRIBUTION**
KS, SI, KT, HT, and MN contributed to the manuscript preparation. KS, SI, KT, HT, AI, KF, and MN contributed to the patient management. KY is a radiological oncologist who contributed to the patient's radiation therapy. SO is a pulmonologist who contributed to the patient's management of pulmonary toxicity. All authors read and approved the final manuscript.

**ETHICAL APPROVAL AND CONSENT TO PARTICIPATE**
Because this report involves no experiment, ethics approval is waived.

**CONSENT FOR PUBLICATION**
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

**DATA AVAILABILITY STATEMENT**
Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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