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A Case of Large Lymph-Node Metastasis from Tongue Cancer with a Complete Response Maintained Even After Discontinuation of Cetuximab Plus Paclitaxel Combination Therapy

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Keywords: Large lymph-node metastasis; Cetuximab; Paclitaxel; Oral cancer; Complete response.

Abbreviations: CR: Complete Response; MRI: Magnetic Resonance Imaging; PD: Progressive Disease; PR: Partial Response; SCC: Squamous Cell Carcinoma; SD:Stable Disease.

Abstract

The combination therapy of the epidermal growth factor receptor inhibitor, cetuximab (Cmab), and paclitaxel (PTX) can be possibility effective for treatment of large cervical lymph-node metastasis. Here, we report a case of a patient with large cervical lymph-node metastasis treated with Cmab+PTX in whom complete response (CR) was maintained even after treatment discontinuation at the request of the patient. The patient was a 55-year-old female with a chief complaint of left-tongue pain. At the consultation, an ulcerative lesion with induration was found on the left-tongue margin, and a diagnosis of poorly differentiated squamous cell carcinoma (T3N0M0: Stage III) was made on the basis of tissue biopsy findings. Under general anesthesia, hemilateral resection of the left tongue, left-neck dissection, and reconstruction with a forearm flap were performed. Two months after discharge, she declined a consultation, and 5 months after the operation, she visited the hospital due to sudden swelling on the right side of her neck. Contrast-enhanced CT (e-CT) was performed, which appeared to indicate late metastasis of the right-cervical region. A diagnosis of large metastatic lymph node in the level III region was made. Surgery was judged to be difficult, so we administered Cmab+PTX combination therapy. Based on imaging findings 7 months after start of therapy, CR was assessed. The Cmab+PTX therapy was continued as planned for 14 months (Once every 1-2 weeks), but after 21 months, the patient strongly desired to discontinue the treatment, and the treatment was completed after a total of 37 treatments. Four years have passed since the discontinuation of treatment, but CR has been maintained, and no recurrence or metastasis has been observed.

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Introduction

Cetuximab (Cmab), a molecular-targeted drug, was approved for head and neck cancer in Japan in December 2012, and its use in treatment has been reported [1–6]. Multidrug therapy, including Cmab and cisplatin (CDDP), is recommended for patients with unresectable recurrent or metastatic oral cancer. In our department, Cmab and Paclitaxel (PTX) combination therapy is administered for platinum preparation refractory/intolerant cases, and an effect has been observed. However, Cmab+PTX therapy should be continued until Progressive Disease (PD) or unacceptable toxicity [1–3]. In the present case as well, it was essential to continue administration of Cmab and PTX even after a Complete Response (CR) was obtained. We report a case of a patient treated with Cmab+PTX for inoperable large lymph-node metastasis in which a CR was achieved and maintained even after the combination therapy was discontinued at the request of the patient.

Case report

A 55-year-old female with increasing left-tongue pain was referred to our institution. On initial examination, the patient had an ulcerative mass with induration at the left tongue of 42 × 21 mm (Figure 1). A biopsy specimen was obtained, and the tongue mass was diagnosed as a poorly differentiated Squamous Cell Carcinoma (SCC). Magnetic resonance imaging (MRI) showed that the tumor extended to near the center of the tongue (Figure 2A). We then performed ^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) demonstrated high FDG uptake at the left tongue (maximum standardized uptake value=15.1) (Figure 2B). Contrast-enhanced CT (e-CT) showed an enhanced mass on the left-tongue margin (Figure 2C) and no metastases in the bilateral cervical lymph nodes (Figure 2D). Results of the distant metastasis of FDG-PET/CT were negative. Based on these findings, the SCC of the left tongue was diagnosed as T3N0M0, Stage III.

With the patient under general anesthesia, hemilateral resection of the left tongue, left-neck dissection, and reconstruction with a forearm flap were performed. The resected margin of the resected tissue was negative, and no metastatic lymph nodes were found in the resected lymphoid tissue. Two months after discharge, the patient missed a scheduled consultation. Five months after the operation, she visited the hospital because of sudden swelling of her right neck (Figure 3A). From e-CT, lymph nodes with diameters of 60 × 51 mm and internal non-uniform pericontrast were observed in the level III region (Figure 3B). FDG-PET/CT demonstrated high FDG uptake at the right lymph nodes. A cervical mass was diagnosed as postoperative metastasis of the cervical lymph nodes from her tongue cancer.

Surgery was judged to be difficult, so chemotherapy was planned. She completely refused inpatient treatment and chose Cmab + PTX therapy, which can be treated on an outpatient basis. A combination therapy of Cmab+PTX (Cmab: 400 mg/m^2 at the first administration, 250 mg/m^2 weekly after the second administration, PTX: 80 mg/m^2 weekly) was started. The treatment effect of chemotherapy was confirmed with the Response Evaluation Criteria in Solid Tumors (RECIST) guideline version 1.1 [7]. On the basis of the imaging findings of e-CT 3 months after the start of administration, a Partial Response (PR) was achieved (Figure 4A). Furthermore, the imaging findings of e-CT 7 months after the start of administration showed that a CR had been achieved (Figure 4B). Subsequently, the treatment was continued as planned for 14 months, but after 21 months, there was a strong desire from the patient to discontinue the treatment, and the treatment was completed after a total of 37 treatments. Acute adverse events (classified according to the National Cancer Institute Common Toxicity Criteria for Adverse Events v. 4.0) included grade 1 oral mucositis, grade 2 neutropenia and acneiform rash, and grade 1 paronychia, which were observed during and until 1 month after receiving treatment. No major complications, such as other neurological complications, were observed. Four years after discontinuation of treatment, however, her CR has been maintained, and there has been no recurrence or metastasis (Figure 5 A,B).

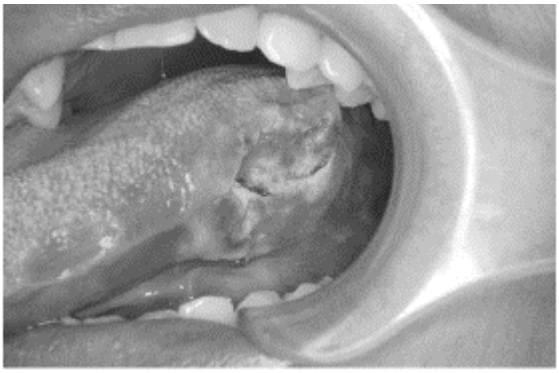

Figure 1: At the initial clinical presentation, an ulcerative mass with a 33×17-mm induration was observed on the left-tongue margin.

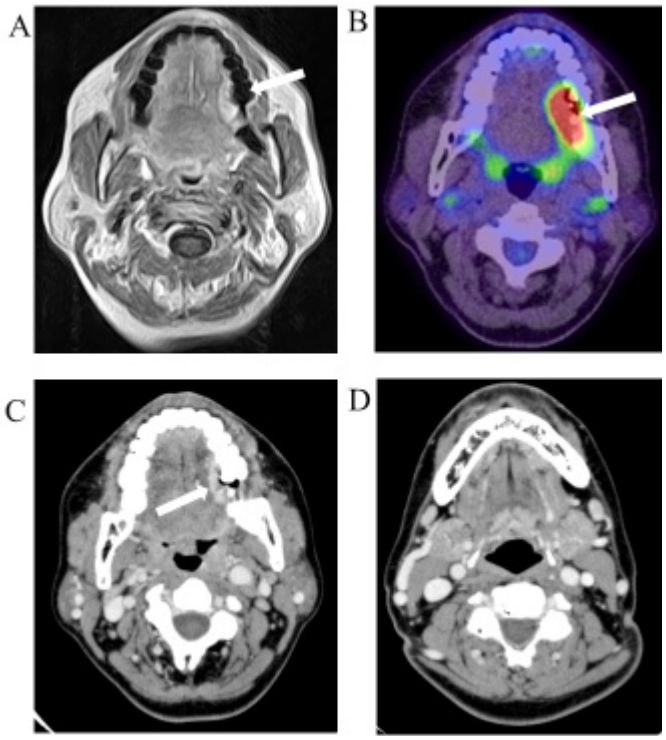

Figure 2: Magnetic resonance imaging showing a mass of tumor that has spread to the left tongue near the center (A, arrow). ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography–computed tomography imaging revealed abnormal uptake of FDG (maximum standardized uptake value = 15.1) of the left tongue (B, arrow). Enhanced computed tomography image showing a tumor mass that has spread to the left tongue near the center (C, arrow). Intensified computed tomography image showing no metastases to the cervical lymph nodes (D).

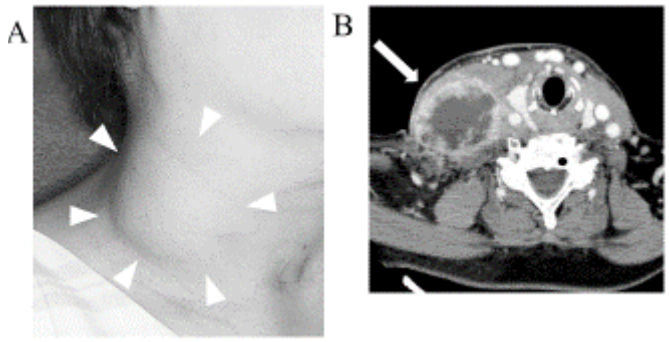

Figure 3: A large mass on the right side of the neck (A, arrowhead). Enhanced computed tomography image showing a ring-enhancing mass measuring 60×51 mm in the neck, level III on the right (B, arrow).

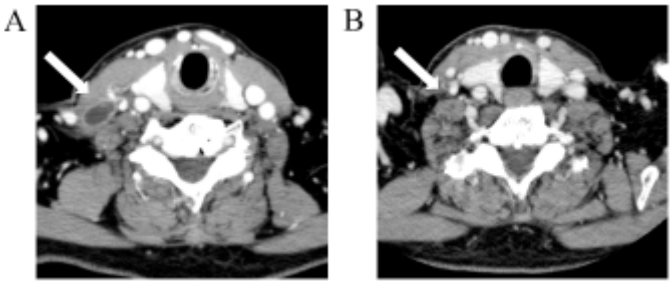

Figure 4: Contrast-enhanced computed tomography (e-CT) image 3 months after the start of administration showing that the metastatic lymph nodes are clearly reduced (A, arrow). Seven months after the start of administration, an e-CT image showing that the metastatic lymph nodes have disappeared (B, arrow).

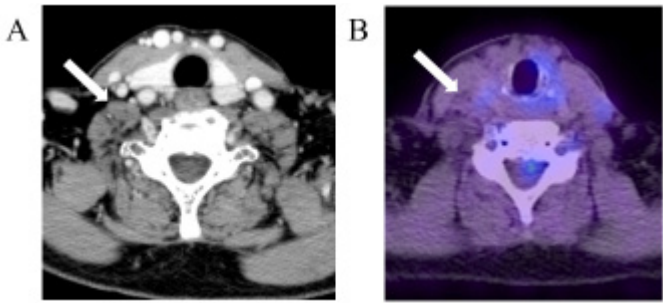

Figure 4: Contrast-enhanced computed tomography image showing improvement of the metastatic lymph node mass 2 years after discontinuation of chemotherapy (A, arrow). 18F-fluorodeoxyglucose (FDG)-positron emission tomography–computed tomography image showing disappearance of the FDG accumulation in the primary lesion and N3 cervical lymph node (B, arrow).

Discussion

The outcomes of patients treated for head and neck SCC with nodal metastases of >6 cm are variable and often poor. Nodal metastases with over 6 cm are generally considered unresectable owing to adhesions between the metastatic nodes and surrounding tissues, and patients treated for disease experience a very high rate of distant failure [8,9]. Therefore, oral SCC with N3 lymph-node metastasis is extremely difficult to treat, and the prognosis is generally poor [8-10]. In the present study, the large lymph-node metastasis was close to the internal and external carotid arteries before treatment and had rapidly increased in size.

After surgery for the patient's left-tongue cancer, we performed Cmab+PTX combination therapy to treat the large lymph-node metastasis. The standard treatment is the EXTREME regimen (FP+Cmab therapy), which combines CDDP+5-flurouracil with Cmab, and is the initial chemotherapy for head and neck cancer with recurrence or distant metastasis [11]. For locally advanced head and neck cancer that is inoperable, radiation therapy with Cmab combination therapy [12] is considered to be the first choice. However, because the patient eventually refused long-term inpatient treatment, Cmab+PTX combination therapy, which allows outpatient treatment, was selected. A report of Cmab+PTX combination therapy stated that the response rate was 54% [1], the median progression-free survival was 3.9 to 7.7 months [1–5,12], and the median overall survival was 7.6 to 16.8 months. When compared with the reports of FP+Cmab therapy cases, the median progression-free survival was 4.2 to 6.6 months, and the median overall survival was 7.3 to 12.6 months, which were similar [5,13–16]. In addition, Cmab+PTX therapy has been reported to achieve CR in a small number of cases [3,5]. Hitt et al. found that the CR rates for locally recurrent disease only, metastatic disease only, or both were 15%, 4%, and 2%, respectively, and the CR rates for metastatic disease were lower than those for patients with only local recurrence [1]. In addition, superselective intra-arterial infusion chemoradiotherapy (SSIACRT) has reportedly achieved CR for N3 patients who did not undergo surgical therapy [8,17]. There are some reports of combined use of hyperthermia for oral cancer cases with N3 lymph nodes [8], and treatment with Cmab combined with other drugs has also been reported [17]. In a paper by Robbins et al. [14], SSIACRT for N3 was reported, but the results for N3 alone was not described. However, SSIACRT was not applicable to our case because it requires long-term treatment with a catheter and long-term hospitalization because of to the presence of Grade 3 or higher oral mucositis.

The main side effect of Cmab+PTX therapy is neutropenia [1], but severe neutropenia makes it difficult to continue treatment, such as dose reduction or postponement or discontinuation of treatment. In this case, Cmab+PTX combination therapy was able to avoid serious complications, such as grade 3 or higher neutropenia, by temporarily discontinuing administration or reducing the dose of PTX, and continuous treatment was possible. It has been reported that Cmab+PTX therapy has a high frequency of adverse events of Grade 3 or higher and that sufficient caution is required, especially for febrile neutropenia [1,2,5,13].

The duration of maintenance therapy varies, but it should be determined on the basis of the balance between therapeutic effect and adverse events, long-term prognosis, and the patient's desire for continued treatment. The adverse events in this case were Grade 1 oral mucositis and Grade 2 neutropenia and acne-like eruption, which were within the expected range even during long-term administration and could be managed. However, 21 months after the start of treatment, the patient strongly desired that the treatment be stopped, so it was discontinued.

Regarding the duration of maintenance therapy, reports from the EXTREME trial [11] and Hitt et al. [1] have stated that Cmab should continue until PD or unacceptable side effects, but no definite duration was recommended. Regarding bioradiotherapy, Cmab maintenance therapy was not clearly stated in the Bonner study [12], and evidence has not been established. It has been reported that bioradiotherapy was performed for lymph-node metastasis from tongue cancer and that CR was

maintained even after maintenance therapy was discontinued [18]. However, our literature review showed that reports of discontinuation of treatment after CR of large lymph-node metastasis cases in Cmab+PTX therapy are rare.

In this case, Cmab+PTX combination therapy was effective and could be managed without serious adverse events. However, since there have been only a small number of reported cases involving patients treated with Cmab+PTX for inoperable large lymph-node metastasis, further accumulation of cases and study are needed. This therapy can be administered in outpatient clinics because adverse events can be predicted to some extent, and it should help maintain quality of life of patients.

Declarations

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Authors' contributions

KS and EK made substantial contributions to the conception and design, acquisition of data, and analysis and interpretation of data.

ST, AY, and AT were involved in drafting the manuscript and critically revising it for important intellectual content.

Ethics approval and consent to participate

The patient provided consent to participate in the study.

Patient consent for publication

Written consent to publish this case report was obtained from the patient.

Competing interests

The authors declare that they have no competing interests.

Authors' information (optional)

For additional information, please contact the Corresponding author.

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