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Metastatic gastric adenocarcinoma of the tongue with initial symptoms of glossodynia

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ABSTRACT

A 60-year-old woman presented to our department with severe tongue pain. On initial examination, the mucosal surface of the tongue was intact but a hard submucosal mass on the dorsum of the tongue was detected on palpation. Magnetic resonance imaging demonstrated an ill-defined tumor in the intrinsic tongue muscles. Sequential whole-body positron emission tomography/computed tomography revealed a tumor of the pancreas apart from the tongue lesion, and upper gastrointestinal endoscopy revealed gastric mucosa ulceration. On biopsy, the tongue lesion was confirmed to be metastatic gastric adenocarcinoma, and the gastric ulcer was simultaneously diagnosed as poorly differentiated gastric adenocarcinoma. The definitive diagnosis was thus gastric adenocarcinoma and synchronous pancreatic cancer, with gastric carcinoma metastases to the tongue. We administered FOLFIRINOX treatment for pancreatic cancer and FLTAX treatment for gastric cancer. Because of difficulty with oral intake due to the growth of the tongue lesion, we administered palliative radiation therapy at a dose of 30 Gy in 10 fractions following which the patient was able to resume oral intake and was satisfied with this outcome. She died 8 months after her first visit to our department.

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Introduction

Metastatic cancer to the oral cavity accounts for 1%-3.2%[1] of all cancers. The most common primary sites for oral metastases are the lung, kidney, liver, and prostate for men; and the breast, reproductive organs, kidney, and colon/rectum for women.[1,2] Here, we report a case of metastatic gastric adenocarcinoma of the tongue.

Case presentation

A 60-year-old woman felt discomfort in the upper abdomen 2 months before visiting our department and was prescribed famotidine at a peripheral clinic. She also had increasingly worsening severe sore throat and tongue pain and as a result, she visited our department in October 2015. At her first visit to our clinic, examination revealed an intact mucosal surface of the tongue (Fig. 1), but on palpation, a hard submucosal mass was detected on the dorsum of the tongue. No significant cervical lymphadenopathy was observed.

Magnetic resonance imaging (MRI) demonstrated an ill-defined tumor measuring $1.5 \times 2.3 \times 2.0$ cm within the intrinsic tongue muscles. The tumor had low signal intensity on T1-weighted images and nonuniform heterogeneous high intensity on T2-weighted images (Fig. 2). Because the lesion was suspected to be malignant and the patient had developed severe abdominal pain originating from the back after the MRI examination, we performed positron emission tomography/computed tomography (PET/CT), which revealed a tumor of the tongue; a tumor of the pancreatic body widely invading from the splenic vein to the anterior pararenal space; multiple liver tumors; lung tumors; a peritoneal mass in the pelvic space

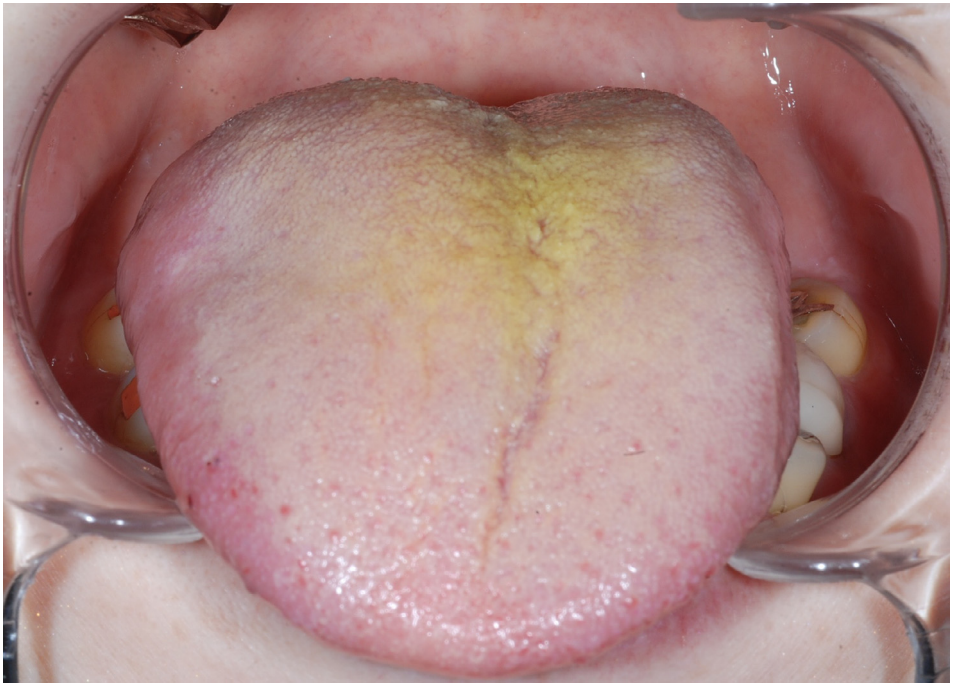

Fig. 1. Oral photograph at the first visit.
There was no lesion on the tongue mucosa.

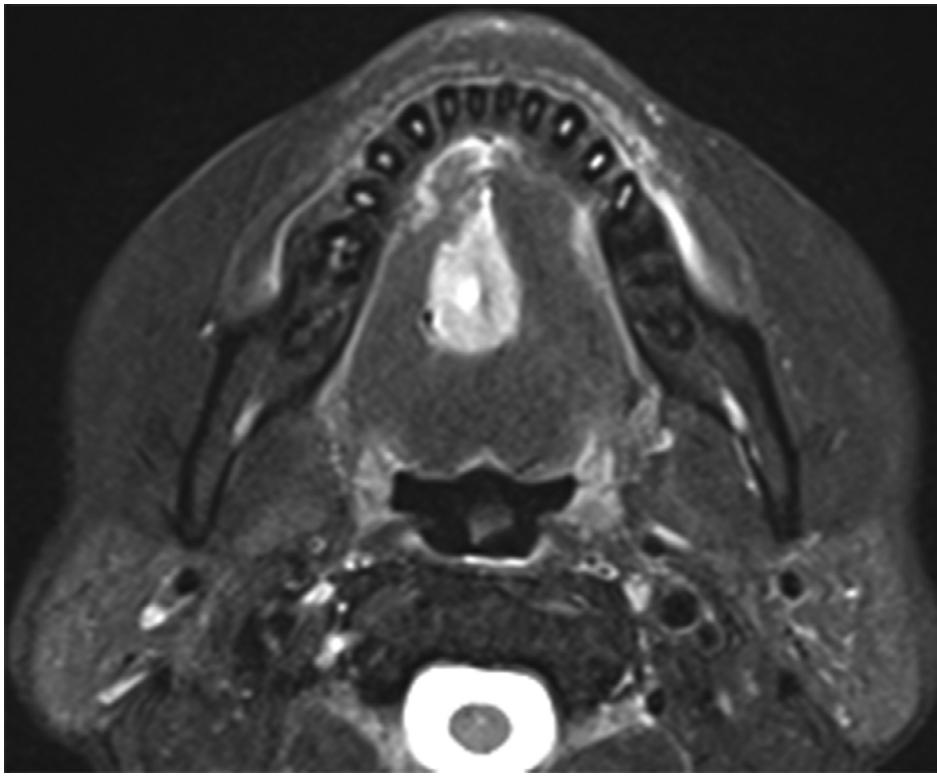

Fig. 2. MRI axial view on T2-weighed image.
MRI axial view on T2-weighed image shows a nonuniform heterogeneous lesion with high intensity. The tumor was adherent to the right sublingual gland.

considered a dissemination; and FDG uptake in lymph nodes along the left gastric artery (Fig. 3A and B). Contrast-enhanced CT (computed tomography) showed tumor of pancreatic body widely invaded from the spleen sinus vein to anterior pararenal space. The serosal layer of the stomach attached to the pancreas tumor was destructed and tumor invaded into to the stomach cavity wall (Fig. 4). Because the most anatomical form of the stomach kept in shape (Fig. 4) it was considered to be the possibility of invaded stomach by pancreas cancer rather than invaded pancreas by stomach cancer. From the radiological findings there was a possibility of synchronous pancreatic cancer with gastric cancer, the possibility of invaded stomach by pancreas cancer.

To get a more detailed diagnosis we performed tongue biopsy and biopsy of ulcerative lesions of the gastric mucosa.

Pathologic findings

Hematoxylin and eosin (H&E) staining of the specimens from the stomach demonstrated adenocarcinoma. Immunohistochemical staining revealed tumor cells positive for MUC5AC and MUC6 and negative for MUC1 and MUC2. These immunohistochemical findings indicated that the tumor was of gastric but not pancreatic origin because pancreatic carcinomas are generally negative for MUC6 and positive for MUC1.[3] These histopathologic features of gastric specimens led to a diagnosis of poorly differentiated gastric adenocarcinoma. The tongue biopsy revealed

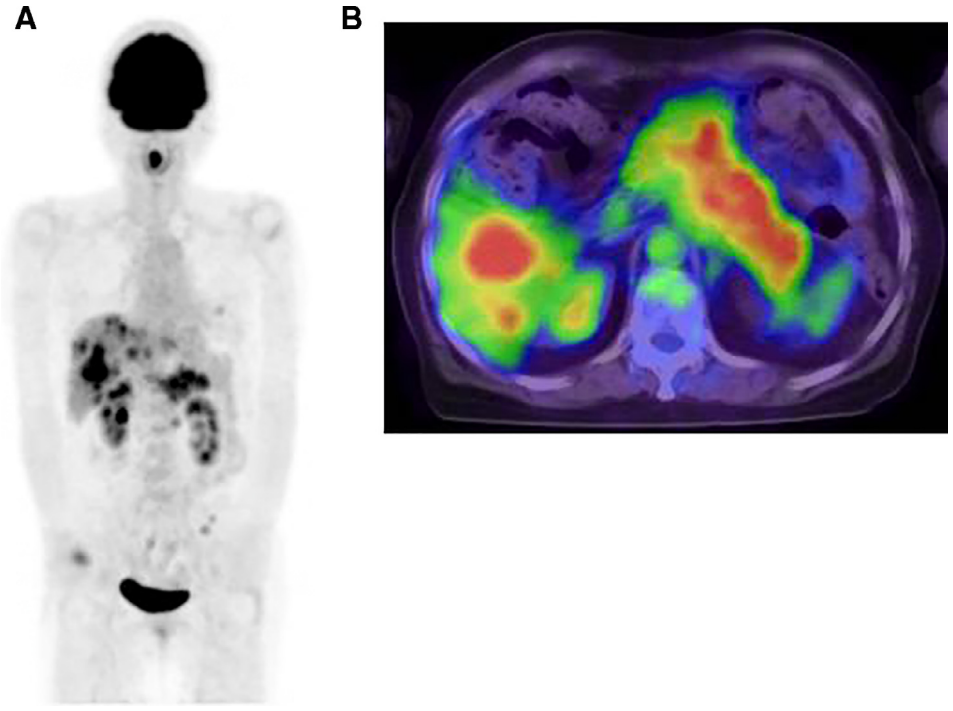

Fig. 3. **(A)** Three-dimensional maximum intensity projection of PET/CT imaging.
Three-dimensional maximum intensity projection of PET/CT imaging shows tumors with high ^{18}F-FDG accumulation occupying the tongue, pancreas, lymph nodes along the left gastric artery, lymph nodes of the lung, and multiple sites in the liver. (**B**) PET/CT axial view. The lesion in the pancreas was attached to the serosal layer of the stomach. ^{18}F-FDG high accumulative lesion in the pancreas spanned from the splenic vein to the anterior pararenal space.

similar features to the stomach lesion on H&E; immunohistochemistry also revealed tumor cells positive for MUC5AC and MUC6 and negative for MUC1 and MUC2. The final diagnosis was metastatic gastric adenocarcinoma. The pathologic images are shown in Figure 5A-C.

Additional tissue biopsies of the metastatic lesions of the liver were planned for, but the patient declined and consent was not obtained.

Taken together, the radiological and histopathologic findings led to a clinical diagnosis of synchronous double pancreatic and gastric cancers with peritoneal dissemination and accompanying metastases to the tongue.

Treatment course

Additional tissue biopsies of the metastatic lesions of the liver were planned, but the patient declined and consent was not obtained.

Treatment priority was given to the pancreatic cancer in terms of prognosis. As a first-line treatment, FOLFIRINOX therapy was instituted in 9 cycles according to the following regimen: oxaliplatin 85 mg/m^2 intravenous infusion over 2 hours, leucovorin 200 mg/m^2 over 2 hours, irinotecan 180 mg/m^2 intravenous infusion over 90 minutes, and 5-fluorouracil (5-FU) 400 mg/m^2 bolus then 2400 mg/m^2 continuous infusion over 46 hours in 1 cycle.

On CT evaluation after starting FOLFIRINOX, the pancreatic lesion and lymph nodes diminished in size and the multiple lung and liver metastatic lesions and peritoneal lesions showed no growth, but the gastric and tongue tumors increased in size as detected at 6 months (Fig. 6).

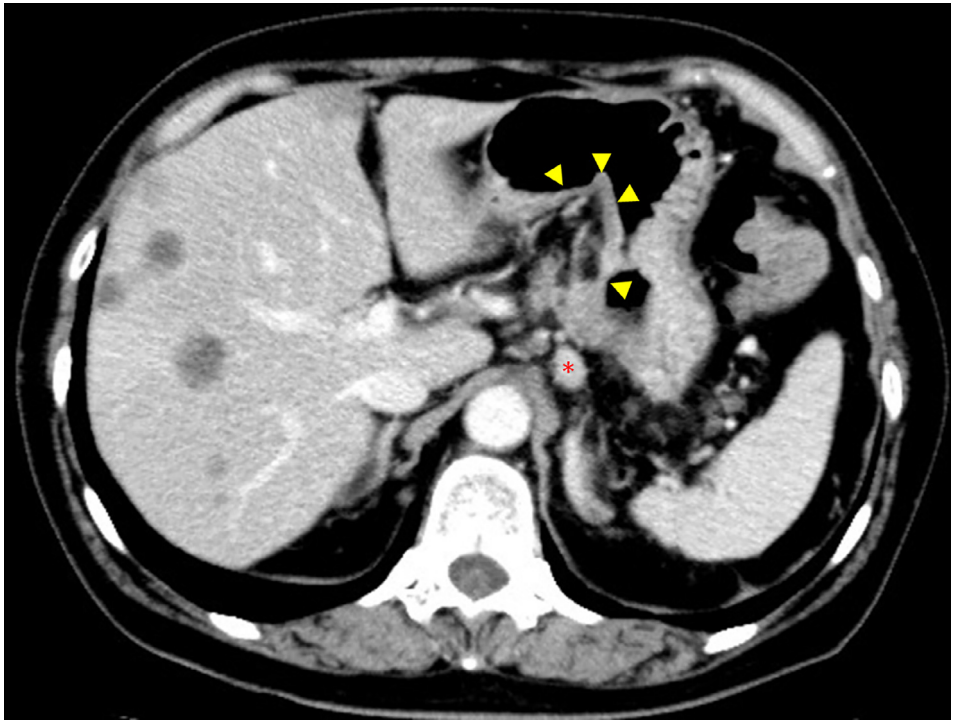

Fig. 4. Contrast-enhanced CT axial view at the first visit. Contrast-enhanced CT showed tumor of pancreatic body. The serosal layer of the stomach attached to the pancreas tumor was destructed and tumor invaded into the stomach cavity wall (yellow arrow). Lymph nodes in the left gastric artery lymph node were enlarged (red asterisk). However, most of the serosal layer of the stomach kept in shape.

Nine cycles of FOLFIRINOX were completed and FLTAX therapy was started according to the following regimen: 5-FU 60 mg/m^2/day as a bolus infusion, l-leucovorin 250 mg/m^2/day as a 2-hours infusion, paclitaxel 80 mg/m^2/day as a 1-hour infusion on Days 1, 8, and 15 in 1 cycle repeated every 28 days. Because oral intake became extremely difficult, palliative irradiation at a dose of 30 Gy in 10 fractions was administered and the patient was able to resume oral intake thereafter.

On an enhanced MRI 1 month after palliative radiation therapy, metastases were observed in the right cerebellar hemisphere.

The patient died 8 months after the first visit to our department and after 2 cycles of FLTAX. Consent for autopsy could not be obtained.

Discussion

Metastatic tumors in the oral cavity are uncommon.[2] In 24% of cases of oral metastases, the oral lesion is usually detected first before the primary lesion is identified.[1] If an undiscovered malignancy at a distant site is suspected based on an oral lesion, a medical history and thorough physical examination is highly warranted. CT, PET, and scanning endoscopy are useful methods for diagnosis.

A literature search for reports on gastric carcinoma with distant metastasis to oral soft tissue revealed 30 cases.[2,4-6] Of these, 13 involved the lower gingival region; 8, the upper gingival region; 4, the tonsils; 3, other sites (soft palate, hard palate, and lip); and 2, the tongue. Chronic

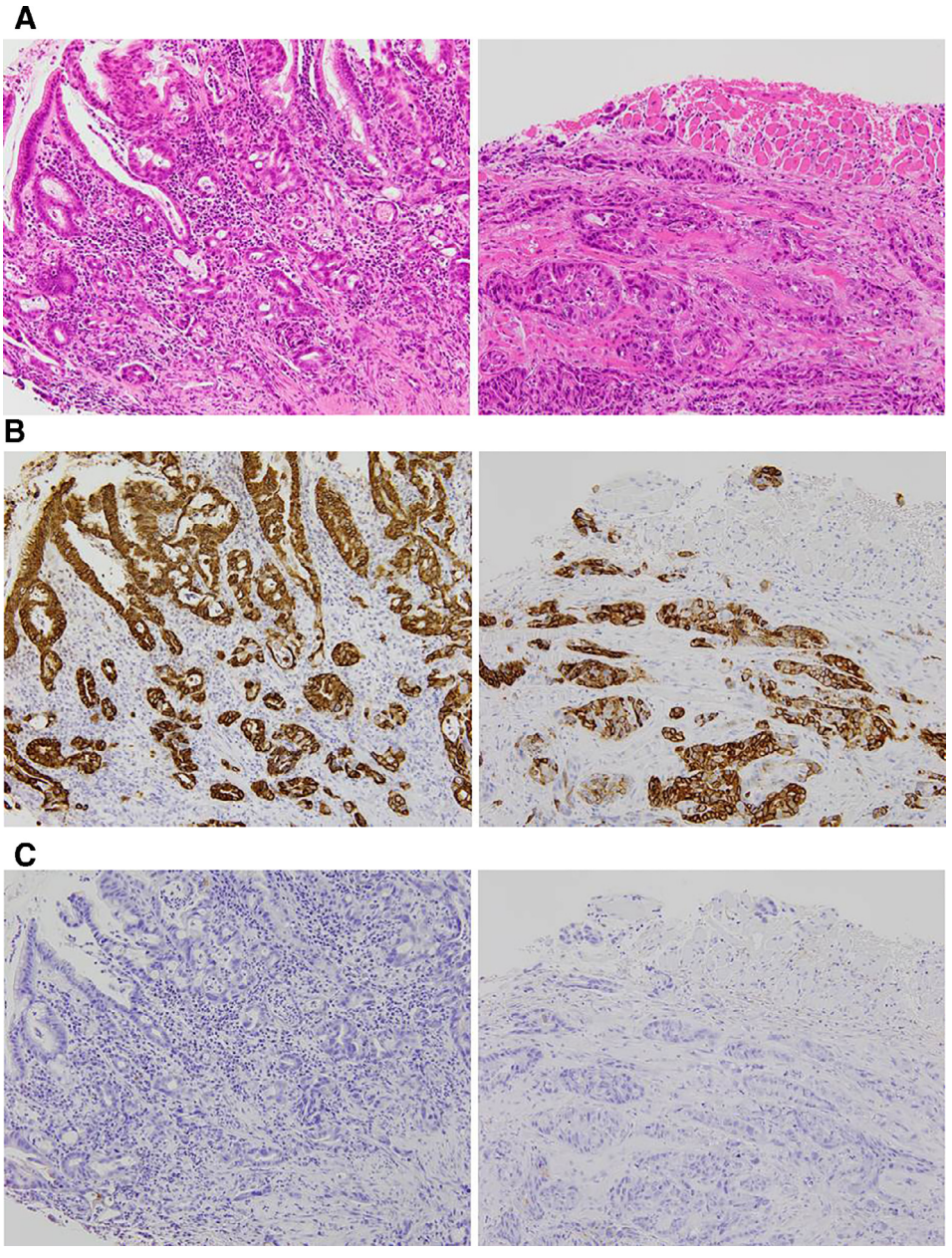

Fig. 5. Pathological images. **(A)** H&E staining. Left: the biopsy from the stomach was consistent with features of adenocarcinoma composed of tubules with varying diameter, irregular cords, and clusters. The adenocarcinoma spanned from the mucosal surface to the muscularis mucosa, mainly in the lamina propria. Well to poorly differentiated tubular adenocarcinoma with a signet ring cell component was observed (×200). Right: H&E staining of the tongue biopsy specimen revealed adenocarcinoma mainly composed of irregular cords and clusters with occasional ductal structures. The adenocarcinoma invaded the tongue muscle. Moderately to poorly differentiated adenocarcinoma with destruction of the tongue musculature (×200). **(B)** MUC5AC staining. Left: Tumor cells from the stomach: non-neoplastic foveolar epithelial cells were equally positive (×200). Right: Tumor of the tongue: cells were positive for MUC5AC staining (×200). **(C)** Images of MUC1 staining (×200). Left: Tumor cells of the stomach cavity and adjacent non-neoplastic cells were negative for MUC1 (×200). Right: Tumor cells of the tongue were negative for MUC1 (×200).

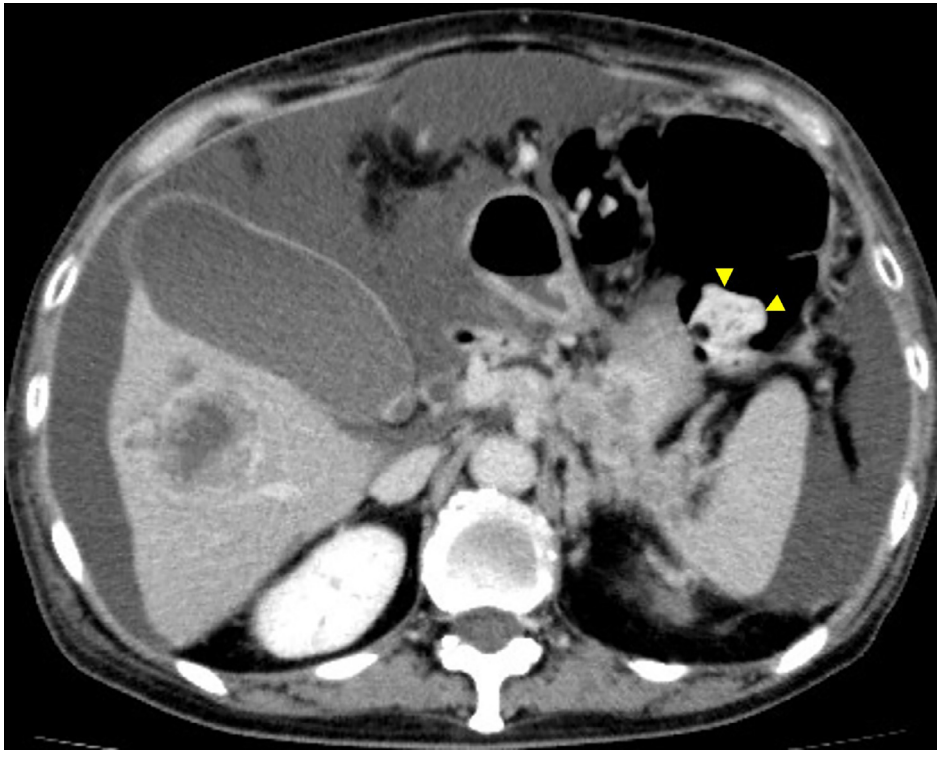

Fig. 6. Contrast-enhanced CT axial view at 6 months after starting FOLFIRINOX.
The gastric tumors increased in size (yellow arrow).

inflammation has been linked to the various steps involved in tumorigenesis such as cellular transformation and metastasis.[1] Chronic inflammation is most frequently observed as gingivitis. Thus, it is considered that metastatic gastric adenocarcinoma to the gingiva is the most frequent. On the other hand, metastatic gastric adenocarcinoma to the tongue is uncommon.

Based on clinical features, an oral metastatic lesion may show different features from neoplasm of epithelial cell origin, thus an oral metastatic lesion can be misdiagnosed as a benign tumor, such as an epulis or an inflammatory lesion (eg, periodontitis). Furthermore, submucosal masses are difficult to detect.[1] In any case where the clinical presentation is unusual, especially where malignant disease is suspected, biopsy is mandatory.[1] In our case the mucosal surface of the tongue was intact but the submucosa contained a hard mass that was detected on palpation.

Metastases to the head and neck or brain are commonly associated with hematogenous spread from the lung.[1] However, the Batson venous plexus can provide a route for distant spread to the head and neck in the absence of pulmonary metastases.[7] In this case, pulmonary metastasis was detected radiologically, but the origin remained uncertain. If the pulmonary metastasis was of pancreatic cancer origin, the tongue metastasis of gastric cancer in this case could have spread by way of the Batson venous plexus.

The incidence of synchronous multiple primary pancreatic cancer has been reported at 4.5%-6.0%.[8] In the same study, analysis of autopsy cases indicated that the most common secondary multiple cancer associated with pancreatic cancer is gastric cancer, with an incidence of 20.5% of all synchronous multiple primary pancreatic cancers. The pancreas and mesocolon are the organs that are in close proximity to the stomach, and the pancreas is the most commonly invaded organ in gastric cancer.[9] Thus, the diagnosis whether the invasive cancer or synchronous

cancer, therapeutic strategy are considered to be difficult in synchronous multiple gastrointestinal cancer.[10] In our case, biopsy from metastasis lesion of the liver was not obtained patient's consent, however,biopsy from the tongue lesion could have performed. The histological diagnosis of the tongue lesion was considered to be important for establishing treatment for pancreatic and stomach cancer. Due to increasing in the aging population and advance in diagnostic technology for detection of cancer synchronous multiple primary cancers have increased recently.[11] Pooling of the cases of oral metastasis cancer may lead to further understanding the complex role of oncogenic signaling pathways, many factors influencing metastasis and developing the efficacious cancer therapy.

In our case, palliative radiation therapy with a dose of 30 Gy in 10 fractions was used and the patient was able to resume oral intake and was satisfied with this outcome of radiation.

The prognosis of cancer metastasis to the oral cavity is generally poor with an average survival time of 7 months after diagnosis.[1] Metastatic tumors to the oral cavity were reported to be treatment-resistant and tumor growth causes severe pain, disfigurement, and impairment of oral functions, such as oral intake, speech, and airway obstruction.[6,12] For these reasons, oral lesions should be managed conservatively to alleviate the symptoms and preserve quality of life.[6,12]

Further clinical studies and accumulation of case reports are needed to evaluate palliative treatment for metastatic cancer of the oral region.

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Ethics approval and consent to participate

All procedures were performed in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Declaration of Helsinki. This retrospective study was approved by the Medical Research Ethics Committee of Tokyo Medical and Dental University (D2015-600 (Previous number: No.1235)).

Patient consent

Written informed consent was obtained from the patient and uploaded as supplementary data.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.currproblcancer.2019.05.004.

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