Treatment strategy for maxillary gingival metastasis arising from gastric adenocarcinoma: A case report and literature review

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Abstract. Gastric cancer metastasizing to the gingiva is rare. The present study reports a case of maxillary gingival metastasis arising from gastric cancer treated with chemotherapy, surgical excision and radiotherapy. A 55-year-old male, who received chemotherapy with trifluridine/tipiracil for treatment of refractory gastric cancer with multiple metastasis, was admitted to the Department of Dentistry and Oral Surgery, Tohoku Medical and Pharmaceutical University Hospital (Sendai, Japan) in December 2023 because of the right side of the maxillary gingival mass presenting with protruding growth. The size of the tumor was ~20 mm. Tumor excision was performed followed by histopathological diagnosis which revealed a metastatic gingival tumor originating from gastric adenocarcinoma. Consequently, the patient underwent a palliative Radiation Therapy Oncology Group 8502 'QUAD shot' regimen. Although there was no progression of oral lesion, the patient died 3 months after diagnosis of gingival metastasis. The present study reviewed previous case records of gingival metastasis originating from gastric cancer and summarized treatment modalities along with clinicopathological association. In conclusion, the prognosis of patients with metastases to the oral region (MOR) is usually unfavorable. For the management of MOR, a multidisciplinary team approach is necessary to develop appropriate treatment strategies. If there are possibilities to improve prognosis or quality of life, the consideration of combination therapy with radical or palliative intent is warranted.

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Abbreviations: RT, radiotherapy; FTD/TPI, trifluridine/tipiracil; MOR, metastases to oral region; QOL, quality of life; RAM, ramucirumab; ECOG-PS, Eastern Cooperative Oncology Group-performance status; CT, computed tomography; SUV, standardized uptake value; HNC, head and neck cancer

Key words: MOR, maxillary gingiva, gastric cancer, combination therapy, QUAD shot

Introduction

Metastases to the oral region (MOR) are rare and represent 1-3% of all oral malignancies (1,2). The occurrence of MOR is associated with unfavorable prognosis and diminished overall survival (1-6). The anatomical regions most affected by MOR are the posterior mandible and, when it is in soft tissue, the gingiva (1-6). The clinical symptoms of MOR include pain, swelling, local bleeding due to ulceration and mass formation (4-7). The predominant primary sites of MOR are the lung, breast and kidney (1,4-6,8-11). Although gastric cancer is the fourth leading cause of cancer-associated mortality (12), the stomach counts for only ~2.5% of all primary cancer sites discovered in patients with MOR (5,6). There is currently no effective treatment for cases of gastric cancer metastasizing to the gingiva. To the best of our knowledge, including the present case, 23 cases (13-34) with gingival metastases from gastric cancer have been reported in English and Japanese literature. The present study, which was created based on the Surgical Case Report 2023 guideline (35), presents a rare case of gastric adenocarcinoma metastasizing to the maxillary gingiva treated with combination therapy comprising chemotherapy, tumor excision and Radiation Therapy Oncology Group 8502 'QUAD shot' radiotherapy (RT).

Case report

A 55-year-old male was referred to the Department of Dentistry and Oral Surgery, Tohoku Medical and Pharmaceutical University Hospital (Sendai, Japan) to examine the gingival swelling and the mobility of the right maxillary second molar in December 2023. In September 2021, the patient had been diagnosed with gastric

adenocarcinoma with multiple regional lymph nodes and liver metastases. According to the Japanese Classification of Gastric Carcinoma 2017 (15th edition) (36), the clinical diagnosis was cT4aN2M1, stage IVB. Although the patient exhibited hepatic dysfunction that appeared to be associated with liver metastases, there was no other remarkable medical history. Serum levels of carcinoembryonic antigen (normal range, <5 ng/ml) and carbohydrate antigen 19-9 (normal range: <37 U/ml) were 2.5 ng/ml and <2 U/ml, respectively.

The patient underwent chemotherapy at the Outpatient Chemotherapy Center of the Department of Medical Oncology, Tohoku Medical and Pharmaceutical University Hospital (Sendai, Japan). Based on the Japanese Gastric Cancer Treatment Guidelines 2021 (6th edition) (37), two cycles of cisplatin (60 mg/m^2) + tegafur-gimeracil-oteraci (80 mg/m^2) was administrated as first-line treatment for gastric cancer over a period of two months. Subsequently, the patient received chemotherapy with second-line weekly paclitaxel (PTX; 80 mg/m^2) + ramucirumab (RAM; 8 mg/kg) for 16 cycles over a period of five months, followed by weekly administration of nanoparticle albumin-bound PTX (100 mg/m^2) + RAM (8 mg/kg) for 31 cycles for thirteen months, third-line nivolumab (240 mg) for two cycles for one month and fourth-line irinotecan (150 mg/m^2) for three cycles for four months. In each cycle of chemotherapy, doses were adjusted as appropriate based on the patient condition and white blood cell and platelet counts. However, these cancer chemotherapies were unsuccessful.

Upon admission, the patient received chemotherapy with trifluridine/tipiracil (FTD/TPI; 35 mg/m^2) for three cycles for 2 months. Eastern Cooperative Oncology Group-performance status (ECOG-PS) scale (ecog-acrin.org/resources/ecog-performance-status/) was grade 2. The swelling had grown rapidly for ~3 weeks since the patient noticed the localized lesion and tooth mobility in October 2023. The patient also complained of frequent gingival bleeding when eating and brushing teeth. No palpable enlarged cervical lymph node was observed. The maximal mouth opening was 35 mm. Intraoral examination revealed a partially necrotic tumor with exophytic growth, ~20 mm in size, on the gingiva of the right maxillary posterior (Fig. 1). The mobility of the right maxillary second molar was severe.

Panoramic radiography showed bone resorption around the maxillary molar region (Fig. 2A). Computed tomography (CT; tube voltage, 120 kVp; exposure time, 2.25 sec; scanning length, 225 s; slice thickness, 1 mm) showed a mass with irregular bony destruction of the right side of the posterior maxilla with soft tissue density in the maxillary sinus (Fig. 2B). There was no evidence of cervical lymphadenopathy. Fluorodeoxyglucose positron-emission tomography/CT in September 2021 showed increased accumulation in the stomach [standardized uptake value (SUV)max 6.2] with regional lymph nodes (SUVmax ~3.4) and liver (SUVmax 9.2 and 9). On the other hand, there was no accumulation in the oral region (Fig. 3).

Due to rapid growth of the gingival tumor, which was often accompanied by local hemorrhage, the patient underwent surgical excision of the gingival tumor with concomitant removal of the right maxillary second molar to decrease symptoms in December 2023. The procedure was performed while the patient was receiving chemotherapy with FTD/TPI.

The tissue samples of the gastric cancer and the gingival tumor were fixed in 10% formalin neutral buffer solution and

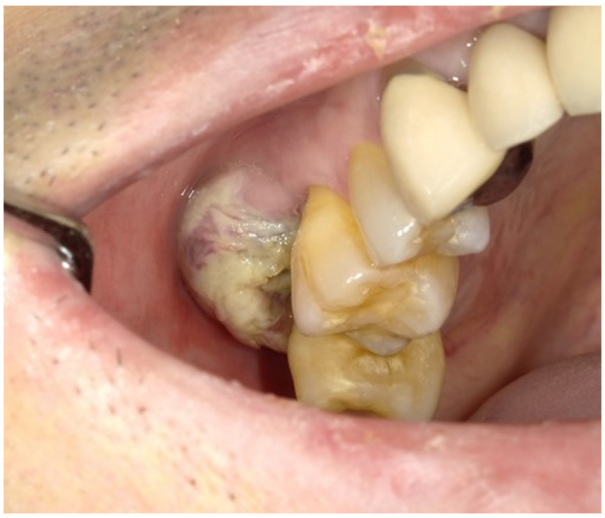

Figure 1. Metastatic tumor with an exophytic growth on the right side of maxillary gingiva.

embedded in paraffin. Histological sections with a thickness of 4 μm were stained with hematoxylin and eosin (H&E) and immunohistochemistry using Tissue-Tek Prisma Plus Automated Slide Stainer (Sakura Finetek Japan Co., Ltd.) and VENTANA BenchMark ULTRA system (Roche Diagnostics K.K), respectively. The sections were incubated with rabbit antibody against CD10, CK7 and CK20 and with mouse antibody against MUC (mucin) 2, MUC5AC and MUC6. H&E staining of the specimens from gingival tumors (Fig. 4A) and gastric cancer (Fig. 4B) demonstrated poorly differentiated adenocarcinoma. Immunohistochemical expression of human epidermal growth factor receptor 2 in gastric cancer was negative. Immunohistochemistry showed that both specimens were positive for CD10 (Fig. 4C and D) and CK7 (Fig. 4E and F) but negative for CK20, MUC2, MUC5AC and MUC6. These pathological findings revealed metastatic adenocarcinoma of maxillary gingiva that was consistent with a gastric cancer origin.

Although no bleeding from the tumor was reported since the procedure was completed, RT was planned to inhibit tumor regrowth. At 2 weeks following the surgical excision, the gingival tumor showed growth and the patient was treated with one cycle of palliative QUAD shot RT immediately. A total of two daily fractions of 3.5 Gy was delivered with an interval of ≥6 h for 2 consecutive days, totaling 14 Gy over four fractions. After that, there was no progression of maxillary gingival metastatic lesion and the patient was capable of oral intake. However, the patient died of multiple organ failure caused by systemic metastases 3 months following the diagnosis of maxillary gingival metastasis originating from gastric cancer.

Discussion

The incidence of gingival metastasis originating from gastric cancer is rare. English literature in PubMed (pubmed.ncbi.nlm.nih.gov/), Scopus (https://www.scopus.com/) and Google Scholar(scholar.google.com/) and Japanese literature in J-Stage (jstage.jst.go.jp/) were searched without date limit. The keywords 'oral region', 'gastric cancer' and 'metastasis'

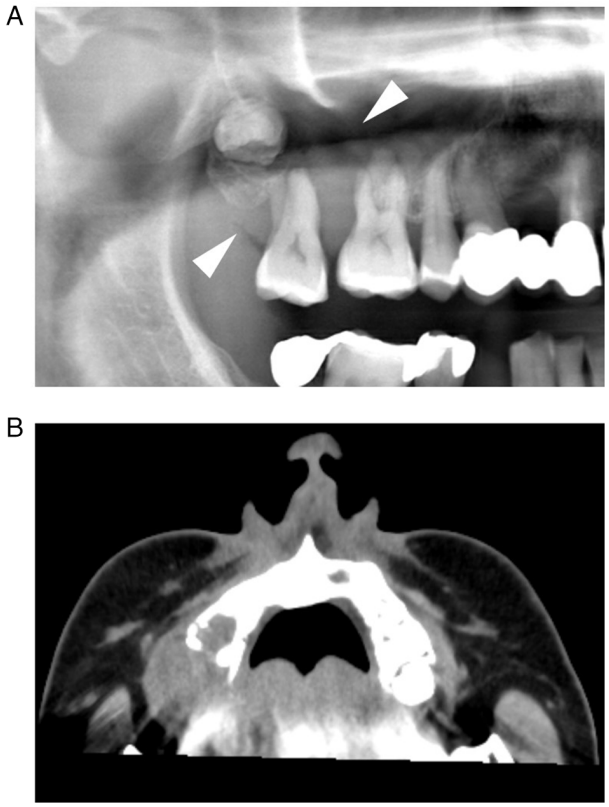

Figure 2. Radiographic appearance of metastatic maxillary gingival lesion. (A) Panoramic radiography showing bone resorption of the affected area (arrow head). (B) Computed tomography image showing bone destruction and a mass formation of the right side of maxilla.

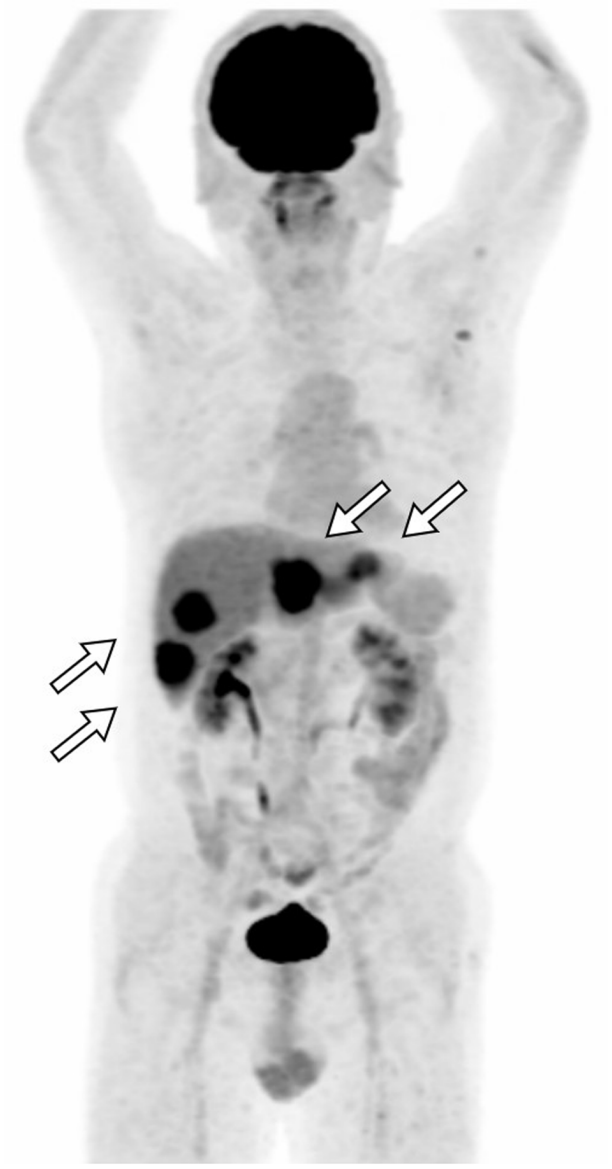

Figure 3. Fluorodeoxyglucose-Positron Emission Tomography/computed tomography mage in September 2021. The white arrows indicate hyper-accumulation in stomach (SUVmax 6.2), regional lymph nodes (SUVmax ~3.4) and liver (SUVmax 12 and 9.2), respectively (arrows). SUV, Standardized uptake value.

were searched in the title/abstract of publications. Studies cited by the review of Wu *et al* (32) and references of the included articles were also searched (Table I).

To the best of our knowledge, 23 cases including the present case have been reported to date in English and Japanese literature. Among these, ~43% (10/23 cases) were reported in Japan, indicating that such cases are more common compared with in other countries. This tendency may be due not only to advances in multimodal therapies globally but also from the progression of the Japanese super-aging society (5).

The present case exhibits features which align with those from previous reports: MOR is primarily observed in elderly patients, with a mean age of 57 years (5,6). The patient in the present case was 55-years-old, consistent with this age distribution. Secondly, the location of the MOR was the maxillary molar gingiva, a common site for gingival metastasis (4-6). In soft tissue, the attached gingiva is the most affected site because of chronic inflammation due to periodontitis (1,2,4,32). Allon *et al* (38) reported that in dentulous patients with gingival metastasis, metastatic foci were adjacent to teeth and the presence of teeth was significantly associated with gingival metastasis. When teeth are present, chronic inflammation may provide a niche for metastases (2,38,39). Shimono *et al* (5) suggested that chronic inflammation such as gingivitis causes MOR and gingival metastasis is likely to occur in the attached gingiva of remaining teeth. In the present case, the metastatic lesion was attached to the gingiva of the right maxillary molar. Thirdly, metastatic foci of the oral region sometimes show rapid growth (7,32). Here, gingival tumor presented as a nodule with local hemorrhage and enlarged rapidly within a month. Fourthly, MOR is typically accompanied by metastases of other sites (7,32,40). In the present case, gastric cancer was already accompanied by metastases of multiple lymph nodes and liver at first examination. Finally, prognosis of patients with MOR is poor and ~70% of patients die within 1 year of diagnosis of MOR (4). A review showed that the range of the mean time between the diagnosis of MOR and death is 7.5-9.8 months (5). In cases of gingival metastasis from gastric cancer, ~60% of patients die within 6 months of diagnosis (32). In the present case report, although the patient was treated with combination therapy, he died 3 months following diagnosis of maxillary gingival metastasis.

Chemotherapy alone, with palliative intent, is utilized in ~40% of patients with MOR and ~30% of the cases are treated

Table I. Cases with gingival metastasis originated from gastric cancer.

First author, year	Age/sex	Gingival site	Duration between primary gastric cancer and gingival meta	Other metastasis	Treatment	Vital status, time	(Refs.)
Lund *et al*, 1968	63/F	Mand	Synchronous	+	S	Died, 2 months	(13)
Astacio *et al*, 1969	58/M	Mand	Synchronous	ND	C	Died, 4 months	(14)
Ohba *et al*, 1974	51/M	Mand	Synchronous	+	RT	Died, 7 months	(15)
Lopez *et al*, 1976	65/F	Maxi	Before primary, 3 weeks	+	-	Died, ND	(16)
Osaki *et al*, 1978	59/M	Maxi	ND	ND	S	ND	(17)
Tojo *et al*, 1989	69/M	Mand	ND	ND	C	Died, 5 months	(18)
Hamakawa *et al*, 1993	56/M	Mand	ND	+	S	Died, 4 months	(19)
Florio *et al*, 1995	66/M	Maxi	After primary, 3 months	-	RT	Died, ND	(20)
Makino *et al*, 1997	60/M	Mand	ND	ND	C	Died, 4 months	(21)
Yajima *et al*, 1999	65/M	Maxi	ND	-	S	ND	(22)
Shimoyama *et al*, 2004	56/M	Mand	After primary, 15 months	+	-	Died, 3 months	(23)
Colombo *et al*, 2005	61/F	Maxi	Before primary, 7 months	-	C, RT	Died, 15 months	(24)
Kwon *et al*, 2006	65/M	Mand	Synchronous	-	-	Died, 3 months	(25)
Nishide *et al*, 2006	82/F	Mand	After primary, 4 years	+	S	ND	(26)
Hwang *et al*, 2007	58/M	Maxi	After primary, 4 years	+	C	ND	(27)
Uchiyama *et al*, 2009	73/F	Mand	After primary, 10 months	+	C, RT	Died, 9 months	(28)
Suaerbom *et al*, 2011	70/M	Mand	After primary, 3 months	+	S	Died, 3 months	(29)
Guo *et al*, 2012	62/F	Mand	After primary, 2 years	+	-	Died, 6 months	(30)
Kalaitsidou *et al*, 2015	71/M	Mand	After primary, 2 years	ND	S	ND	(31)
Wu *et al*, 2017	75/M	Maxi	After primary, 2.5 years	+	C, RT	Alive, 9 months	(32)
Soares *et al*, 2018	43/M	Mand	Before primary, ND	ND	C, RT	Died, 3 months	(33)
Ayşegu *et al*, 2018	54/M	Maxi	Before primary, ND	+	S, C	Died, 5 months	(34)
Present case, 2023	55/M	Maxi	After primary, 2 years	+	C, S, RT	Died, 3 months	

F, female; M, male; Mand, mandible; Maxi, maxilla; ND, not defined; +, with other metastasis; -, without other metastasis; S, surgery; C, chemotherapy; RT, radiotherapy; Before primary, detection of gingival metastasis before primary gastric cancer; After primary, detection of gingival metastasis after primary gastric cancer.

with combination therapy (5). For the treatment of gingival metastasis from gastric cancer, ~30% (7/23) of cases underwent surgical excision only (13,17,19,21,26,29,31) and 17% (4/23) of cases received chemotherapy alone (14,18,21,27). On the other hand, 26% (6/23) of cases were treated with combination therapy: 17% (4/23) received chemotherapy and RT (24,28,32,33), 4% (1/23) underwent surgery and chemotherapy (34), and one patient (4%) case underwent chemotherapy, tumor excision and RT. However, 12/23 (52%) of cases resulted in patient death within 6 months (13-34). Despite treatment modalities, there is currently no effective treatment for patients with MOR. Treatment for MOR primarily focuses on improving patient quality of life (QOL) or prognosis through palliative care (2-5). Before treating MOR, it is necessary to evaluate the following factors: i) Patient prognosis; ii) patient condition, including ECOG-PS score; iii) existence of oral dysfunction or symptom; iv) whether the primary tumor is under control; v) progress of metastatic foci of the oral region and vi) patient will and intention in a multidisciplinary team approach.

Radiation Therapy Oncology Group 8502 'QUAD shot', which is a hypofractionated RT technique for palliative treatment, involves 2 days of twice-daily fractionation with a

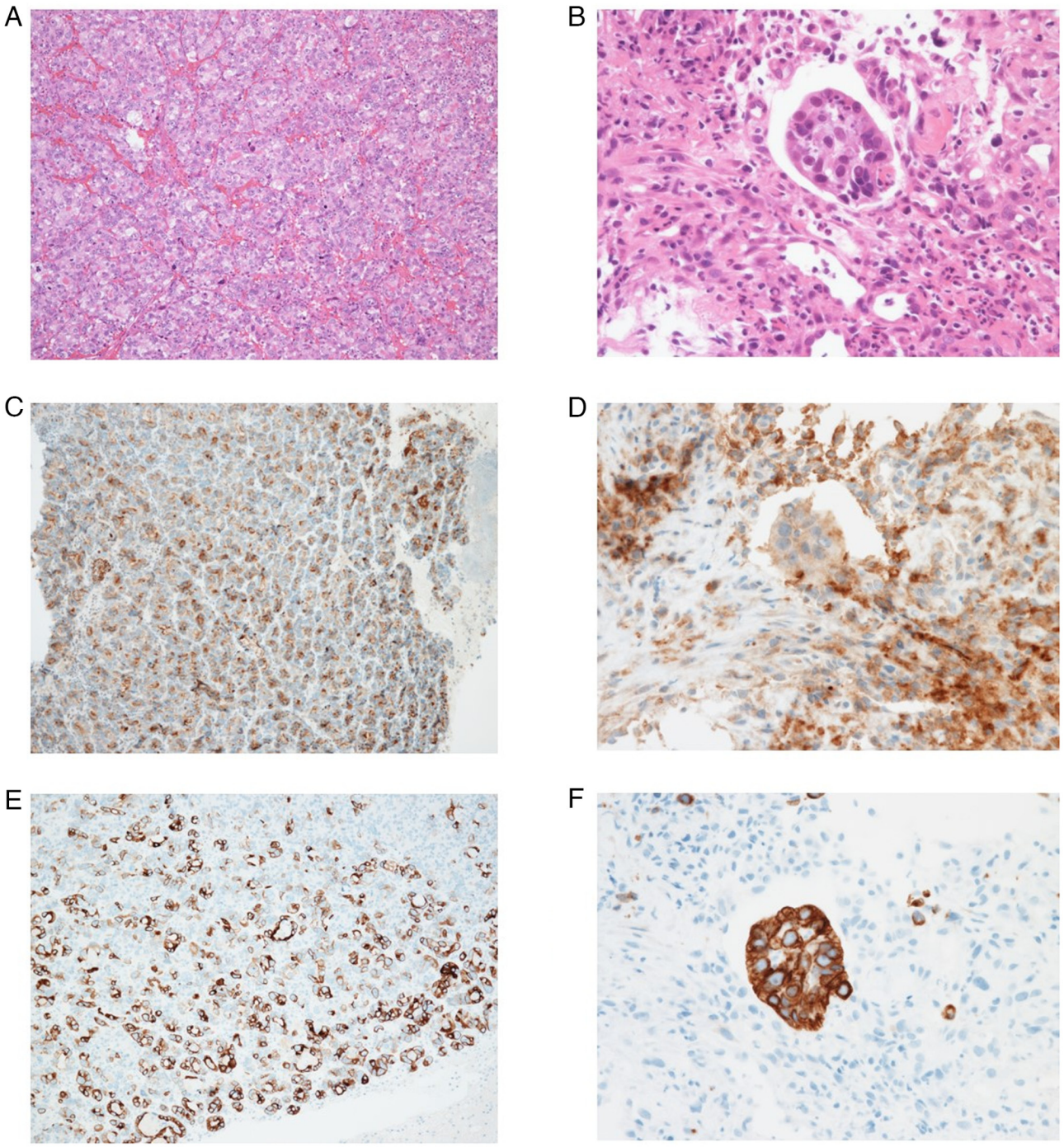

Figure 4. Histopathological examination. (A) Metastatic maxillary gingival tumor and (B) primary gastric cancer demonstrated poorly differentiated adenocarcinoma. Immunohistochemistry revealed that (C) gingival tumor and gastric cancer (D) were positive for CD10. CK7 was also positive in the gingival tumor (E) and gastric cancer (F) Magnification, x200.

fraction size of 3.0-3.7 Gy (14.0-14.8 Gy/cycle). If possible, this regimen is repeated at 3-6-week intervals for a total of three cycles with an RT dose of 44.4 Gy (41,42). QUAD shot has been widely adopted for palliative treatment in patients with head and neck cancer (HNC) due to superior response rate, palliation, mild adverse effects and minimizing physical and social burdens (41-43). The National Comprehensive Cancer Network guidelines recommend the QUAD shot regimen as a palliative RT care for HNC (44).

Due to rapid growth of the gingival tumor and associated local hemorrhage in the present case, tumor excision was performed in addition to chemotherapy. This approach was used to alleviate these symptoms rather than completely cure the gingival metastatic lesion. The patient received one cycle of palliative QUAD shot. After that, there was no tumor progression or local hemorrhage and the patient was capable of oral intake. However, the patient died of systemic metastasis after 3 months following diagnosis of maxillary gingival metastasis originating from gastric cancer.

The lesions of MOR are treatment-resistant and often demonstrate rapid progression. Moreover, lesions frequently lead to various symptoms and dysfunctions such as local

hemorrhage, pain, hypoesthesia, difficulty in oral intake, dysphagia and airway compromise (5,8,45). Most lesions of MOR are reported as nodules, with ~64% of cases being symptomatic (5). For these reasons, MOR should be managed to alleviate symptoms and improve or maintain patient QOL.

In the future, the number of patients with MOR is expected to increase (4,6). The presence of MOR is rarely found while treating the primary tumor and clinical symptoms appear in advanced stages. Physicians should check the symptoms of the oral region and perform screening during cancer therapy. The present study reported a case of maxillary gingival metastasis originating from gastric cancer and summarized relevant literature. The prognosis of MOR is usually unfavorable. It is important to detect MOR as early as possible to facilitate appropriate treatment. If there are opportunities to improve patient QOL or prognosis, physicians should develop treatment strategies with interdisciplinary teams. Combination therapy, including chemotherapy, immunotherapy, surgery and RT, such as QUAD shot, should be considered.

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Availability of data and materials

The data generated in the present study are not publicly available due to patient confidentiality but may be requested from the corresponding author.

Authors' contributions

HM designed the study, wrote the manuscript and performed the literature review. HM, MS, and FS collected and analyzed the data and prepared figures and tables. HS, CK, MN, YI, ST and KM supervised the study, analyzed data and edited the manuscript. HM, HS, CK, MN, YI and ST confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

This case report was approved by Ethics Committee of Tohoku Medical and Pharmaceutical University Hospital (approval no. 2023-4-074).

Patient consent for publication

The patient provided written informed consent for publication of the case report and images.

Competing interests

The authors declare that they have no competing interests.

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