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Case Report

Successful Management of Repeated Oligometastatic Squamous Cell Carcinoma of the Mouth Floor with Metastasectomy and Maintenance Tegafur-plus-uracil: A Case Report

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Abstract

This case report describes a patient with poorly differentiated squamous cell carcinoma (PD SqCC) of the mouth floor, staged as pT4aN0M0. The initial treatment comprised surgical resection followed by adjuvant concurrent chemoradiotherapy. The patient subsequently experienced metastatic recurrence of poorly differentiated carcinoma, first in the lung and later in the pancreas. Two rounds of metastasectomy were performed. Despite the complexity of multiagent systemic therapies, the patient was maintained on tegafur-plus-uracil therapy following the two metastasectomies, leading to long-term disease-free survival. This case illustrates that with careful recognition of oligorelapse and oligoprogression, metastatic head-and-neck cancer can be effectively managed with a more simplified therapeutic approach.

Keywords: Head-and-neck cancer, maintenance therapy, oligometastasis, squamous cell carcinoma, tegafur-plus-uracil

Introduction

Current guidelines for adjuvant concurrent chemoradiotherapy (CCRT) in high-risk, locally advanced head-and-neck squamous cell carcinoma (LA-HNSCC) with extranodal extension (ENE) and/or positive surgical margins indicate no notable benefit from reducing distant metastasis.[1-3] For recurrent or metastatic (RM) HNSCC, pembrolizumab, either alone or in combination with cisplatin and 5-fluorouracil (PF) is the current standard treatment.[4,5] For patients of RM HNSCC who are not eligible for immunotherapy, cetuximab

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with or without conventional chemotherapies is an alternative treatment option.[6,7] However, patients with RM HNSCC may present with varying tumor burdens and differing disease trajectories. The increasing recognition of oligometastasis has led to alternative strategies for treating metastatic disease. In contrast to conventional systemic therapies used in polymetastatic disease, metastasectomy, combined with local ablation therapies and metronomic antiangiogenesis, may play a more crucial role in managing patients with oligometastatic disease. Herein, we report a case of RM HNSCC with repeated oligometastatic disease, successfully treated with metastasectomy and maintenance therapy using tegafur-plus-uracil (UFUR; TTY Biopharm Co., Ltd.).

Case Report

A 61-year-old Taiwanese man presented with a toothache that persisted for 1–2 years. On October 2, 2017, a biopsy of a lesion on the left floor of the mouth revealed poorly differentiated squamous cell carcinoma (PD SqCC). Based on magnetic resonance images of the head and neck, clinical staging was cT4aN0, whereas positron emission tomography–computed tomography (PET-CT) indicated that clinical staging was TxN0M0. Additional examinations including a chest X-ray and bone scan revealed no discernible findings. The patient had tobacco smoking with 1 pack/day for 30 years, social drinking, but no betel quid chewing. He had comorbidities including diabetes mellitus, hypertension, gastroesophageal reflux disease grade A, gastric ulcers, and duodenal ulcers.

On October 26, 2017, the patient underwent a wide excision of the tumor with neck dissection. The pathological staging was pT4aN0M0, with a closest surgical margin of 1 mm, a depth of invasion of 20 mm, and tumor involvement in the skin, skeletal muscle, and bone cortex as well as perineural invasion. Although no major risk factors such as ENE or positive margins were present, adjuvant CCRT was administered due to the presence of multiple minor risk factors. The patient received 3 Arc IMAT, which was delivered in 6600 cGy/33 fractions over 44 days concurrently with weekly cisplatin 40 mg/m² for four cycles, from December 5, 2017, to January 19, 2018.

On October 15, 2018, PET-CT revealed a small nodule in the right upper lung, with progressive enlargement found on February 26, 2019. Based on the CT scan findings [Figure 1], the patient underwent thoracoscopic lobectomy and lymph node dissection on March 25, 2019. Pathological evaluation confirmed poorly differentiated carcinoma, with the lung lesion identified as metastatic from the original HNSCC [Figure 2c and d].

Following the lung metastasectomy, maintenance therapy with UFUR was initiated for the patient at a dosage of 400 mg/day. However, a follow-up PET-CT on September 27, 2019, revealed a pancreatic lesion, retrospectively identified as present since the PET-CT on June 26, 2019, but without any notable changes [Figure 3]. The patient subsequently underwent distal pancreatectomy, and the pathological report

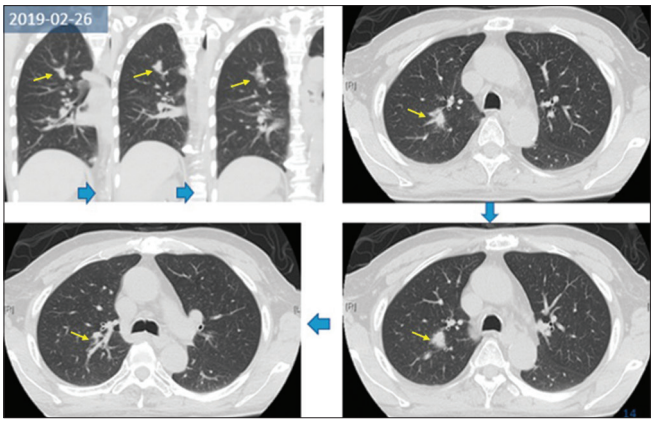

Figure 1: Chest computed tomography scan from February 26, 2019, favored primary lung cancer due to the lesion's location in the upper lung (where blood supply is less rich than in the lower lung) with spiculated border, contrast enhancement, presence of air bronchogram, punctate calcification, and bronchovascular invasion (arrow)

confirmed poorly differentiated carcinoma, consistent with the previous lung metastasis [Figure 2e and f]. A second independent pathologist reviewed the case and indicated that both the pulmonary and pancreatic lesions were metastatic from the original head-and-neck cancer. After the pancreatic tumor resection, the patient continued on maintenance UFUR for an additional 1.5 years until April 2021. The maximal adverse events associated with UFUR, as per the Common Terminology Criteria of Adverse Events, were grade 2 mucositis, grade 1 anemia, and grade 1 increased creatinine levels. At the most recent follow-up on April 19, 2024, the patient remained alive and free from tumor recurrence.

Discussion

Herein, we present a case of PD SqCC of the mouth floor, which was staged as pT4aN0M0, treated with surgery and adjuvant CCRT, followed by repeated oligometastases to the lung and pancreas. The patient was successfully treated with metastasectomy and maintenance therapy using metronomic UFUR.

Current guidelines recommend adjuvant CCRT for locally advanced HNSCC in patients with pathologic ENE and/or positive surgical margins.[1-3] However, as demonstrated in this case, adjuvant CCRT is frequently administered to patients with multiple pathological risk factors, aside from ENE and positive margins, who are at a high risk of therapeutic failure.[8] However, current adjuvant CCRT protocols have demonstrated no notable benefit in reducing the risk of distant metastasis.[1,2]

For patients with treated HNSCC who present with a single-lung SCC lesion, distinguishing between metastatic HNSCC and a second primary early-stage lung SCC is both critical and challenging. This differentiation typically requires the integration of clinical data, radiological findings, histopathological evaluation, immunohistochemistry, and in some cases, molecular testing. A multidisciplinary team,

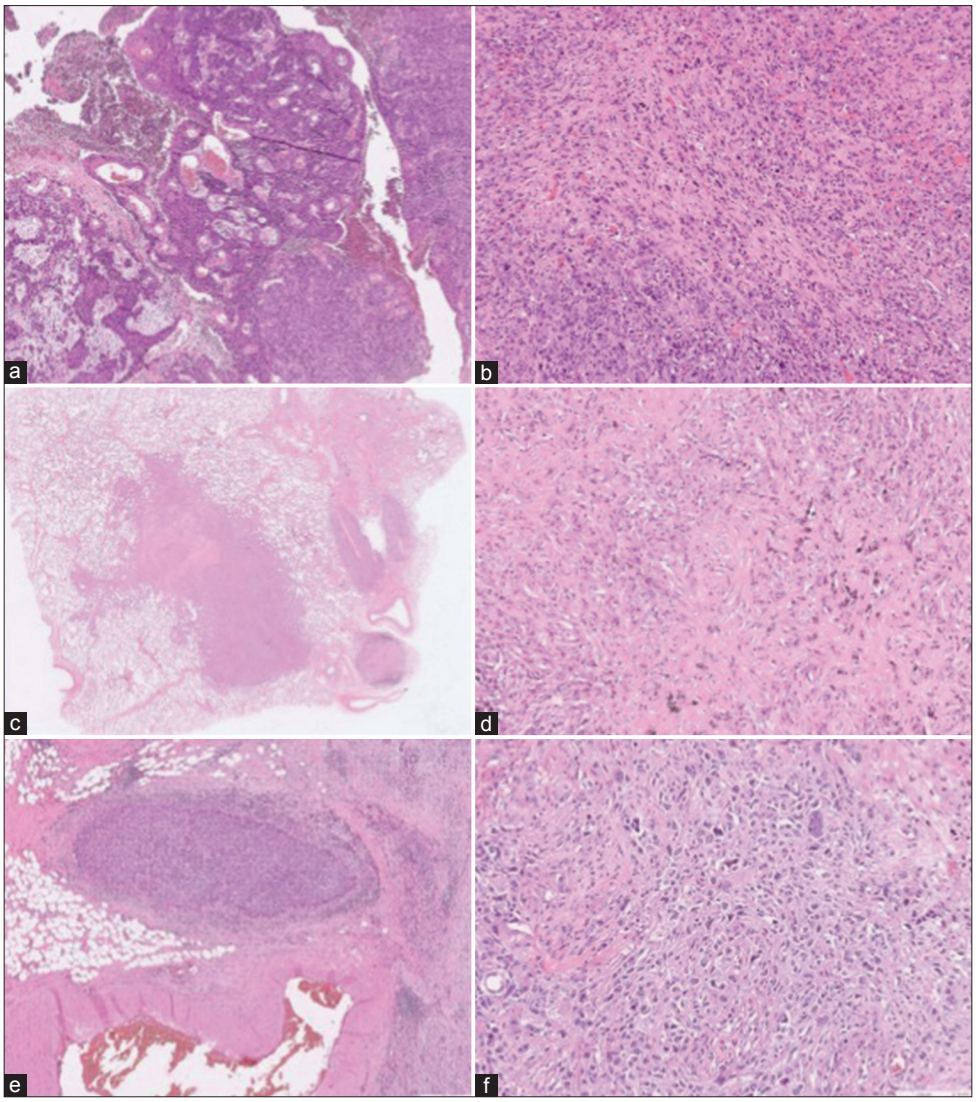

Figure 2: Pathology of tumors. (a) Poorly differentiated squamous cell carcinoma (PDSCC) of the mouth floor, October 26, 2017 (H and E, ×4). (b) Sclerotic stroma of the mouth floor PDSCC (H and E, ×10). (c) Poorly differentiated carcinoma of the lung, showing one main tumor mass and two satellite nodular lesions (H and E, ×2). (d) Similar sclerotic stroma within the lung lesions (H and E, ×10). (e) Poorly differentiated carcinoma of the pancreatic lesion (H and E, ×4). (f) Similar sclerotic stroma within the pancreatic lesions (H and E, ×20)

including oncologists, pathologists, and radiologists, is often essential for achieving the most accurate diagnosis, as demonstrated in this patient's case.

Studies on pulmonary metastasectomy (PM) for patients with HNSCC with pulmonary metastasis have suggested that favorable candidates for PM, who demonstrate approximately 30%–40% 5-year overall survival after surgery, include those with a disease-free interval of >2 years, nonoral cancer origins, and resectable lung metastases. Conversely, patients with SCC histology, incomplete resection, a short disease-free interval, and oral cancer (especially originating from the mouth floor or tongue) tend to have a poorer prognosis after PM.[9] These findings align with the Gompertzian kinetics of tumor growth, which posits that after resection of the primary tumor mass, any remaining subclinical tumor cells or micrometastases may enter a rapid growth phase.[10] Research on circulating tumor cells (CTCs) further supports this finding, indicating that patients with oligometastatic lung cancer from HNSCC experience a more rapid postoperative increase in CTC numbers compared with patients with primary lung cancer after lung resection.[11] This implies that pulmonary SCC lesions appeared shortly after resection of the primary HNSCC are more likely to represent lung metastasis rather than a new primary lung cancer. In this case, the patient's disease-free interval was 14 months. However, no universally accepted cutoff point for disease-free interval exists to definitively distinguish between lung metastasis and a second primary lung cancer.

The CT scan of the present case initially displayed features suggestive of primary lung cancer, such as a solitary lesion <3 cm in diameter with spiculated border, contrast enhancement, air bronchogram, punctate calcification, and

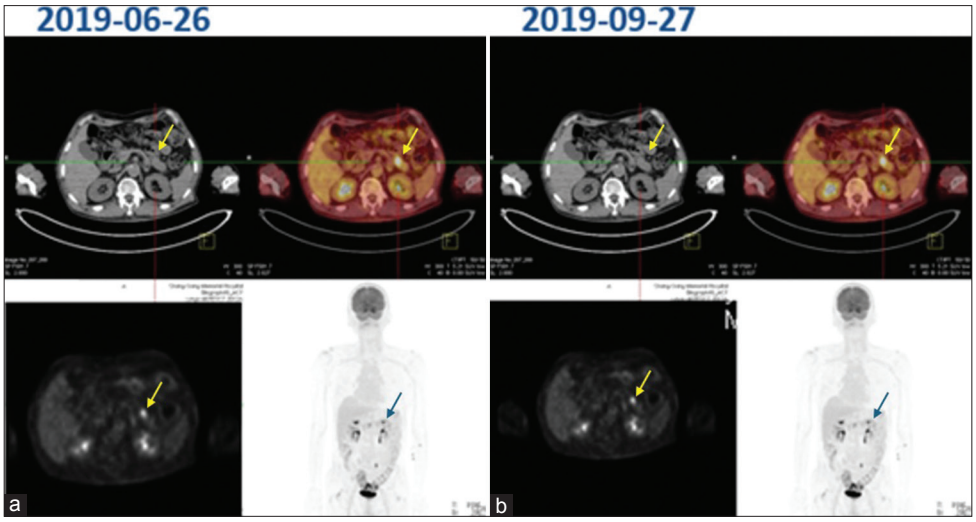

Figure 3: During the positron emission tomography–computed tomography (PET-CT) follow-up on September 27, 2019, a pancreatic lesion was detected (b, arrow). Retrospective analysis of the PET-CT from June 26, 2019, revealed the presence of the lesion, but it had undergone minimal change (a, arrow)

bronchovascular invasion. Consequently, the patient underwent thoracoscopic lobectomy and lymph node dissection under the presumption of primary lung SCC. However, upon review, two pathologists favored a diagnosis of metastatic cancer from HNSCC, citing similar pathologic characteristics between the lung lesion and the original head-and-neck tumor [Figure 2a-d]. The subsequent identification of similar pathological features in the pancreatic metastasis further supported the diagnosis of repeated oligometastases from the primary HNSCC [Figure 2e and f].

Genomic evaluation was not available in the present case. Molecular profiling can sometimes help distinguish between primary lung SCC and metastatic HNSCC through the identification of specific mutations or alterations characteristic of either lung SCC or HNSCC. However, next-generation sequencing studies have revealed that SCCs originating from different organs may share common gene signatures. For instance, the "squamousness" gene signatures include the presence of TP53, PIK3CA, CCND1, CDKN2A, SOX2, NOTCH 1, and FBXW7 aberrations and the absence of KRAS alterations.[12] The overlap in molecular features across SCC tumor types may limit the clinical utility of molecular profiling in resolving such diagnostic dilemmas. The result of immunohistochemical study was cytokeratin (AE1/AE3)(+), CAM5.2(+), CK7(OV-TL)(−), CK5/6(−), TTF-1 (8G7G3/1) (−), p40(−), SOX10(−), and CD31(JC70A)(−). The above result is not specific to determine its origin by pathologist's opinion.

Conventionally, aggressive combined systemic therapies are employed for metastatic HNSCC due to its often devastating disease course. In this case, with cisplatin-sensitive RM HNSCC, pembrolizumab, either alone or in combination with the platinum/5-fluorouracil doublet (KEYNOTE-048) would be recommended as first-line treatment according to current guidelines.[5] However, patients with pulmonary oligometastasis from treated HNSCC may exhibit a distinct disease course and better prognosis compared with those with polymetastases.[9] In a study involving patients with resected oral cavity HNSCC and pathologic ENE, maintenance UFUR after adjuvant cisplatin-based CCRT was demonstrated to improve overall survival, disease-specific survival, and locoregional failure and reduce distant metastases.[13] Notably, UFUR maintenance was associated with a reduced incidence of therapeutic failure (35.9% vs. 56.4%, $P = 0.042$), and nearly half of the patients with metastatic failure in the UFUR maintenance cohort were oligometastatic (53% vs. 9%) and exhibited better survival (median 21.0 months vs. 11.0 months, $P < 0.001$). This implies that UFUR maintenance may alter the metastatic course of HNSCC through its potential dual effects on anticancer activity and antiangiogenesis.[13] Therefore, considering the possible better prognosis, the absence of residual targeted lesions after PM, the adverse events from aggressive systemic therapies, and the potential effect of UFUR maintenance, he received UFUR maintenance following the first PM.

However, the identification of a second pancreatic metastasis posed a challenge for subsequent systemic therapy. Although pancreatic metastases from head-and-neck and lung cancer were rare, the sequential histopathological evaluation per two pathologists suggested it is a metastasis originally from the head and neck. No immunohistochemical stain was done for the pancreatic lesion, and PET-CT scan revealed no other FDG-avid lesion. This implied that the patient might have a metastatic disease with indolent and oligometastatic behavior and possible benefit from the previous UFUR maintenance after PM. According to the consensus recommendations for defining and classifying oligometastases by the European Society of Radiotherapy and Oncology and the European Organization for Research and Treatment of Cancer,[14] the pancreatic metastasis was classified as oligoprogression during UFUR maintenance. Recommendations for managing

oligoprogression include switching to alternative systemic therapies or considering local ablative therapy while continuing the current systemic therapy regimen.[14] Therefore, after the local resection of the pancreatic tumor, UFUR maintenance was continued till April 2021. The patient remains disease-free at the follow-up in April 2024.

In summary, this case underscores the complexity and challenges in managing recurrent/metastatic HNSCC. Despite experiencing repeated metastatic failures, the patient achieved prolonged disease-free survival through a multidisciplinary approach that included surgical resection, adjuvant CCRT, metastasectomy for repeated oligometastasis, and maintenance therapy with UFUR.

Ethical approval

The study involving the human participant was reviewed and approved by the Chang Gung Medical Foundation Institutional Review Board (Approval No. 202401595B0, Approval Date October 14, 2024).

Declaration of patient consent

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and its amendments. The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

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Data availability statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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