Synchronous triple squamous cell carcinomas of the stomach, skin and gingiva with liver, lung, spleen, kidney, bone and brain metastases: A case report

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Abstract. Synchronous multiple squamous cell carcinomas (SCCs) of the stomach, skin and gingiva are very rare. A 67-year-old male patient was admitted to hospital with progressive chest tightness and fatigue, accompanied by melena. Gastric and dermal biopsies revealed SCCs, and it was considered that triple primary SCCs of the skin, stomach and gingiva had metastasized to the cerebrum, liver, lung, spleen, kidney, bone and subcutaneous tissue. The patient received one cycle of camrelizumab, carboplatin and nab-paclitaxel, followed by two cycles of camrelizumab monotherapy and best supporting care. However, his performance status deteriorated, and he had a very poor survival outcome, succumbing 3 months after diagnosis. Discriminating pathologically between synchronous SCCs in individual organs as metastases or primaries is challenging. In the present case, a diagnosis of triple primary SCCs of the skin, stomach and gingiva with multiple organ metastases was made based on epidemiologic features and clinical presentation. The results of the present case report suggested that anti-programmed death 1 antibodies combined with platinum-based chemotherapy may be a treatment option for metastatic SCC.

Introduction

Due to increases in lifespans and advancements in diagnostic techniques, the incidence of multiple primary malignancies is increasing. Depending on the criteria used, the reported frequency of multiple primary malignancies ranges from 2.4 to 17% (1). Aetiological factors that may predispose patients to multiple primary malignancies can be grouped into host related, lifestyle factors and environmental influences. The International Agency for Research on Cancer defines synchronous multiple primary malignancies as two or more malignant tumors diagnosed within the same individual concurrently or within 6 months of each other (2). Commonly occurring combinations include head and neck with lung cancer (3), skin with head and neck cancer (4), skin with lung cancer (5), breast with ovarian cancer (6) and breast with endometrial cancer (7). The malignancies can share the same histology or be completely different entities. Long-term survival with multiple primary malignancies is variable and is influenced by cancer type and stage at diagnosis (1). The present report described a case of synchronous multiple squamous cell carcinomas (SCCs) of the stomach, skin and gingiva with metastases to the liver, lung, spleen, kidney, bone and brain. These results may provide valuable data on the treatment of multiple primary malignancies, which could potentially be used to develop future treatments for these patients.

Case report

Case presentation. A 67-year-old male patient was referred to Zhuji People's Hospital of Zhejiang Province (Zhuji, China) in December 2023 with progressive chest tightness and fatigue, accompanied by melena persisting for almost 1 week. His history included heavy smoking (~60 cigarettes/day), alcohol consumption (75 ml/day) for 35 years and betelnut chewing for several years. He also had a 3-year history of hypertension and type 2 diabetes mellitus, but no family history of cancer. A comprehensive medical history was obtained, and physical examination, laboratory blood analyses and pulmonary and cardiac function tests were performed. Physical examination revealed an anemic appearance, multiple nodules on the scalp (Fig. 1A), forehead (Fig. 1B), nasal cavity (Fig. 1C) and right forearm (Fig. 1D), as well as multiple subcutaneous lumps on the right chest (Fig. 1E) and left calf. In addition, a large mass was observed on the right gingiva (Fig. 1F).

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Laboratory examinations revealed severe hypochromia with a hemoglobin level of 50 g/l (normal range, 130-175 g/l), a positive fecal occult blood test, a high serum creatinine level (125 μmol/l; normal range, 57-111 μmol/l), high levels of cytokeratin 19 fragment (cyfra 21-1; 55.1 ng/ml; normal range, 0.0-3.3 ng/ml), neuron specific enolase (26.2 ng/ml; normal range, 0.0-20.0 ng/ml) and SCC antigen (26.7 μg/l; normal range, 0.0-1.5 μg/l), normal levels of carcinoembryonic antigen (1.9 μg/l; normal range, 0.0-5.0 μg/l), α-fetoprotein (1.8 μg/l; normal range, 0.0-7.0 μg/l), carbohydrate antigen 19-9 (19.3 KIU/l; normal range, 0.0-30.0 KIU/l) and pro-gastrin releasing peptide (59.4 pg/ml; normal range, 0.0-65.0 pg/ml). The results of pulmonary and cardiac function tests were normal.

The patient subsequently underwent a chest computed tomography (CT) plain scan, upper abdominal and pelvic CT scan with contrast enhancement, brain magnetic resonance imaging with contrast enhancement and diffusion-weighted imaging. Imaging revealed the presence of multiple nodules in the frontal, parietal and temporal lobes of the brain with associated edema (Fig. 2A), a nodule in the left pulmonary upper lobe invading the pleura (Fig. 2B), local thickening and enhancement of the gastric wall in the lower part of the gastric corpus and multiple enlarged lymph nodes around the lesser curvature (Fig. 2C). The endoscopic examination revealed the presence of a large ulcer with an uneven base in the lesser curvature of the stomach (Fig. 2C). In addition, bone of the right superior ramus of the pubis was degraded (Fig. 2D) and multiple nodules were observed in the liver (Fig. 2E), left kidney (Fig. 2F) and spleen (Fig. 2G). Finally, the patient underwent an electronic gastroduodenoscopy with biopsy (Fig. 3A) and a biopsy of the subcutaneous mass of the right forearm (Fig. 3B). However, he declined biopsies of other sites. Histological analysis of the two biopsy specimens revealed moderately differentiated SCC. No *Helicobacter pylori* was detected in the gastric biopsy specimens. Immunohistochemical staining of the biopsy specimens revealed the positive expression of pan-cytokeratin (panCK; Fig. 3C and D), P63 (Fig. 3E and F) and P40 (Fig. 3G and H), while the expression of CK20 and CD56 was negative. In addition, the specimen from the gastric biopsy was classified as programmed death ligand 1 (PD-L1) negative, with a combined positive score (CPS) of 0 (Fig. 3I), P16 expression was negative, and P53 overexpression indicated a mutational phenotype. Furthermore, the immunohistochemistry (IHC) of Epstein-Barr virus (EBV) was negative (Fig. 3J).

Based on these findings, the patient was diagnosed with SCC of the stomach, skin and gingiva with brain, lung, liver, spleen, kidney, superior ramus of the pubis and subcutaneous metastases, and an Eastern Cooperative Oncology Group (ECOG) performance status of 2.

After 15 days, treatment was initiated with intravenous camrelizumab (200 mg over 60 min) on day 1, intravenous carboplatin (area under the concentration-time curve 5 mg/ml/min for 30 min) on day 1, and intravenous nab-paclitaxel (100 mg/m^2 over 30 min) on days 1 and 8, repeated every 3 weeks. However, the patient suffered from an anaphylactic reaction to carboplatin, presenting as generalized skin eruption and chest tightness. Therefore, carboplatin was discontinued and replaced with cisplatin (25 mg/m^2 over 6-8 h) on days 1-3 of the 21-day cycle. After one cycle of camrelizumab plus the nab-paclitaxel and platinum-based (AP) regimen, physical examination revealed a marked reduction in the size of the cutaneous and subcutaneous lesions. However, the performance status of the patient deteriorated to an ECOG score of 3. Following discussions with the patient and his family, camrelizumab was administered alone for the second and third treatment cycle, after which a palliative approach was pursued. The patient succumbed 3 months after his initial diagnosis.

Histopathological examination. Samples were stained with hematoxylin (room temperature for 10 min) and eosin (room temperature for 1 min), before being observed using a light microscope. IHC was performed as follows: The tissue samples were fixed in 10% neutral buffered formalin (Zhejiang Jinhua Tonghe Biotechnology Co., Ltd.) at 25˚C for 12 h and then embedded in paraffin. The tissue paraffin block was cut into 3-μm sections, which were heated at 60˚C for 30 min, and then deparaffinized in three xylene baths successively for 5 min each, and rinsed thrice with anhydrous alcohol, ethanol (95 and 75%) and water for 2 min each. Antigen retrieval was performed using the DAKO PT Link instrument (Agilent Technologies, Inc.) at 97˚C for 20 min. Staining was performed using the DAKO Autostainer Link 48 system (Agilent Technologies, Inc.). The following primary antibodies (prediluted by the manufacturer, Guangzhou Anbiping Medical Laboratory Co., Ltd.) were used: CK (cat. no. IM067; clone: AE1/AE3), P63 (cat. no. IR383; clone: LBP2-P63), P40 (cat. no. IR345; clone: LBP2-P40), CK20 (cat. no. IR385; clone: LBP2-CK20), CD56 (cat. no. IR040; clone: MRQ-42), P16 (cat. no. IM342; clone: LBP1-P16), P53 (cat. no. IM123; clone: LBP1-P53), EBV (cat. no. IM077; clone: CS1-4) and PD-L122C3 (cat. no. DAKO SK006). For detection, an EnVision FLEX+, Mouse, High pH (Link) kit (cat. no. K8002; DAKO; Agilent Technologies, Inc.), which included blocking reagent, EnVision FLEX/HRP secondary antibodies and DAB+ chromogen, was used. Blocking was performed with peroxidase blocking reagent (cat. no. DAKO SM801) at 25˚C for 5 min and all primary antibodies were incubated with the samples at 25˚C for 30 min, followed by incubation with the prediluted EnVision FLEX/HRP secondary antibodies (cat. no. DAKO SM802) at 25˚C for 20 min and, finally, staining with DAB+ chromogen (cat. no. DAKO DM827) at 25˚C for 5 min. Images were captured using a light microscope.

Discussion

Among invasive forms of non-melanoma skin cancer (NMSC), cutaneous SCC (CSCC) is the second most prevalent among White individuals (8,9). It constitutes ~30% of all NMSC cases (10), demonstrates a sex disparity, with a higher prevalence in male (9-14%) compared with female individuals (4-9%) (8,11), and accounts for 20% of all cutaneous malignancies (9,12). Established risk factors include chronic inflammation, cicatricial lesions, lighter skin tone, high cumulative sun exposure and human papillomavirus (HPV) infection (13-15). The majority of lesions (80-90%) develop on sun-exposed areas of the head and neck in older White male individuals (16). Metastasis is rare in CSCC, and the disease generally follows a favorable clinical course with local surgical

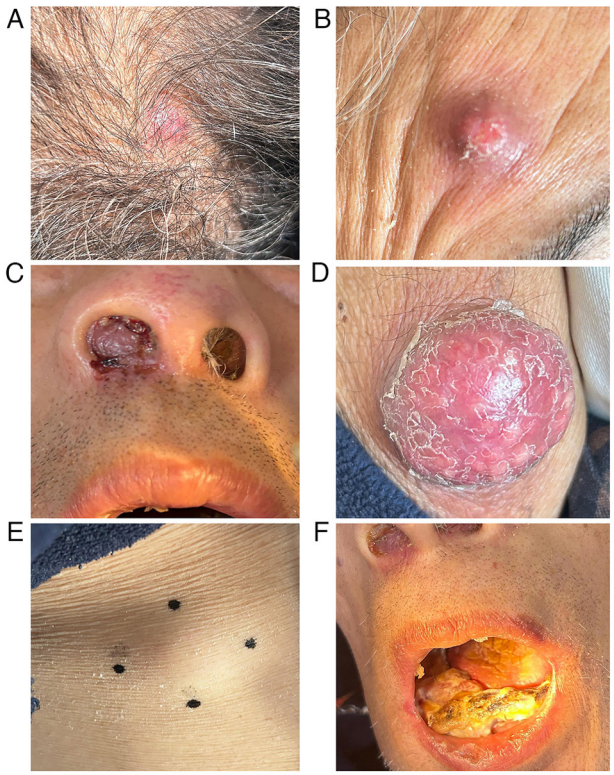

Figure 1. Physical examination findings of the patient on hospital admission showing various nodules and masses. (A) Nodule on the scalp, (B) nodule on the forehead, (C) mass in the nasal cavity, (D) nodule on the right forearm, (E) subcutaneous lump on the right chest and (F) a right gingival mass.

resection (17). However, CSCC has the potential to spread to regional lymph nodes and distant organs, with the incidence of systemic metastases ranging from 1 to 7% (18). Distant metastases most commonly occur in the lungs, liver, brain, bones and skin (18,19). Therapeutic outcomes for stage IV CSCC remain suboptimal, with a reported median progression-free survival (PFS) of 8 months and overall survival (OS) of 26 months, resulting in a 5-year survival rate of only 26% (20). Systemic therapy is recommended for patients with metastatic CSCC who are not candidates for surgery or radiotherapy (21). The management modalities include platinum-based chemotherapy, epidermal growth factor receptor inhibitors and immune checkpoint inhibitors (ICIs) (21). ICIs, particularly anti-PD-1 antibodies such as cemiplimab and pembrolizumab, are emerging as first-line options, demonstrating objective response rates (ORR) of 50% in phase II trials (22,23). Preliminary data have led to the National Comprehensive Cancer Network Panel suggesting that other anti-PD-1 inhibitors may also be effective in this setting (21).

Gastric SCC (GSCC) is rare, accounting for 0.04-0.07% of all gastric malignancies (24). The risk factors for GSCC have not been clearly identified. However, GSCC typically presents at an advanced stage, metastasizing to the liver, lymph nodes and other organs, generally leading to poor outcomes (25-28). No standard chemotherapy or chemotherapeutic regimen has been defined for GSCC. In addition, the stomach is a rare metastatic site for SCCs of all primary sites. The occurrence of gastric metastasis has only been reported in case studies involving individuals with lung and uterine cervical SCCs (29,30), as well as an immunodeficient patient diagnosed with CSCC and gastric metastasis (31).

SCC of the gingiva is uncommon, accounting for <6% of oral cavity SCCs (OCSCCs) (32). It most commonly occurs in middle-aged and older male individuals (33). Smoking, alcohol and betel quid chewing are well-established risk factors (33). SCCs of the mandibular gingiva are more common than those of the maxillary gingiva (34). ICIs combined with platinum-based chemotherapy are considered the preferred first-line systemic therapy for patients with unresectable and metastatic SCC of the head and neck (SCCHN) (35). However, metastatic lesions in the oral cavity are extremely rare, and account for ~3% of all malignancies in adults (36). The most common primary sources of oral cavity metastases are lung and breast carcinomas (37).

IHC is a powerful technique that uses specific antibody-antigen binding to detect the localization of specific antigens in cells and tissue (38). It is an essential ancillary technique in clinical diagnostics within anatomic pathology (39). IHC is an indispensable complement to an epidemiology- and morphology-driven approach to tumor diagnosis, helping to determine the site of origin of metastatic tumors and detect tiny tumor foci that may be inconspicuous on routine H&E staining (38,40). Guidelines for the standardization and analytic validation of immunohistochemical tests have been established by the College of American Pathologists (39,41). panCK is a useful biomarker for epithelial and epithelial-derived cells (42). SCCs are typically detected using CK5/6, P63 and P40, whereas CK7 and CK20 are commonly used as markers of adenocarcinoma, including gastric cancer (43,44). In the present case, the gastric and subcutaneous tumors were positive for panCK, P63 and P40, but negative for CK20. These immunostaining results supported a diagnosis of SCC. PD-L1 expression is an important biomarker for predicting the therapeutic effect of anti-PD-1 monoclonal antibodies. The KEYNOTE-055 study revealed that a higher CPS is associated with an increased ORR and improved survival outcomes (45). P16 expression as detected by IHC is a widely used surrogate biomarker that shows strong agreement with HPV status, as determined by the assessment of HPV E6/E7 mRNA expression (46). HPV infection is a predominant cause of SCC of the oropharynx, but is less common in OCSCCs (47). Patients with locally advanced HPV-positive SCCHN exhibit an improved treatment response, OS and PFS when compared with those with HPV-negative tumors (48). The wild-type P53 staining pattern is characterized by nuclear staining in 1-80% of tumor cells with varying intensities, while abnormal P53 expression includes overexpression, complete absence and cytoplasmic staining patterns. The overexpression pattern is associated with nonsynonymous missense mutations in the P53 gene, leading to excessive nuclear accumulation of P53 protein. This results in the detection of diffuse, strong nuclear positivity in >80% of tumor cells by IHC (49,50). Tumors with a complete absence of P53 staining are often associated with frameshift or nonsense mutations that result in a truncated P53 protein (51). The P53 cytoplasmic staining pattern is characterized by tumor cells showing distinct moderate or strong cytoplasmic staining, with variable or absent nuclear staining (50). In the present study, P53 IHC revealed an abnormal overexpression pattern, indicative of a mutational phenotype.

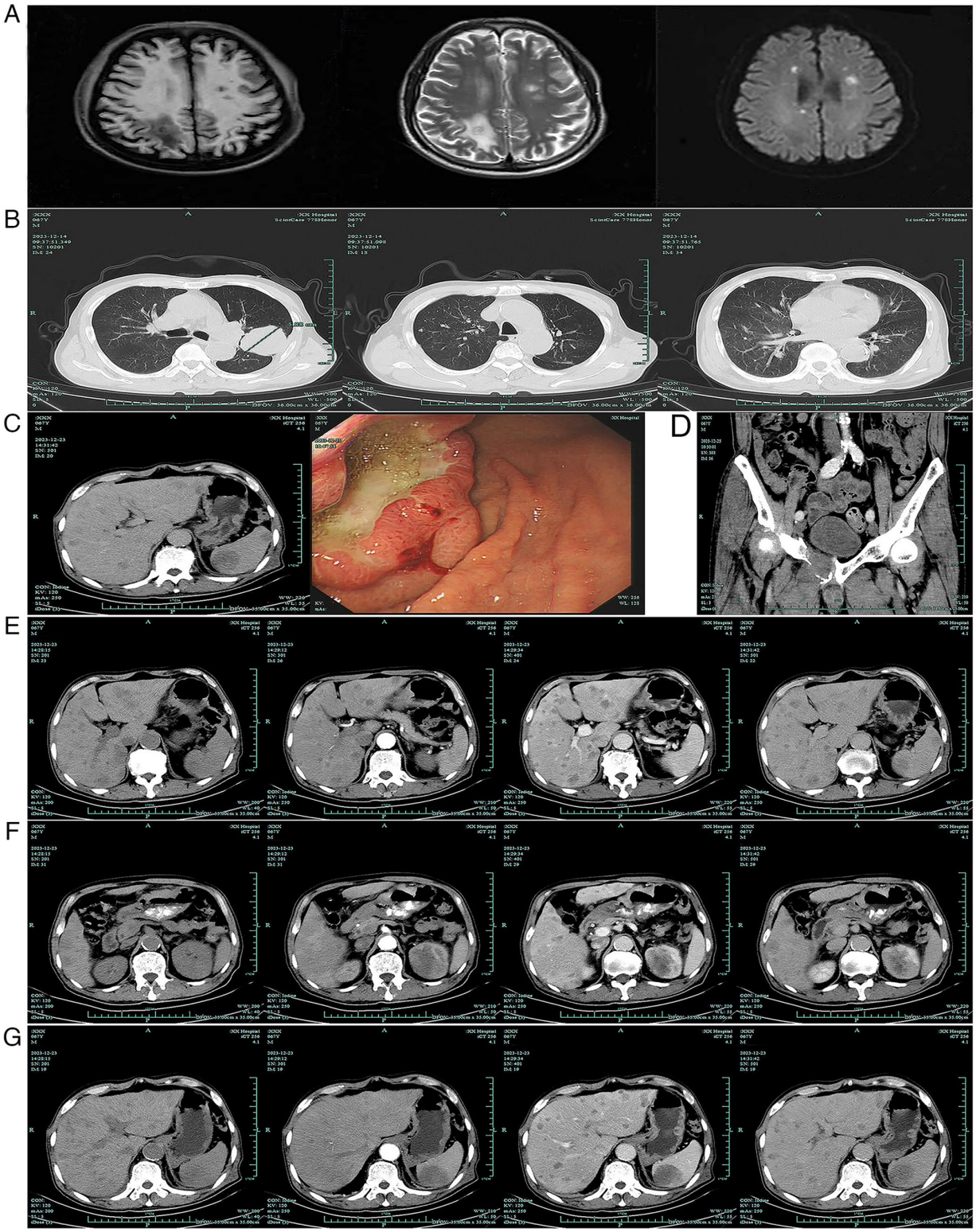

Figure 2. Imaging examinations of the patient on hospital admission. (A) Magnetic resonance imaging of the brain showing multiple nodules in the frontal, parietal and temporal lobes with edema. (B) CT plain scans of the chest showing a 5.88-cm node in the left pulmonary upper lobe invading the pleura and nodular lesions peripherally. (C) CT scan of the abdomen (left panel) showing a heterogeneously-enhanced lesion of the lower part of the gastric corpus and multiple enlarged lymph nodes, and endoscopy (right panel) revealing a huge ulcer located in the lesser curvature of the stomach. (D) CT scan of the pelvis showing bone destruction in the right superior ramus of the pubis. (E) CT scans of the abdomen showing the hepatic lesions, (F) nephritic lesions and (G) splenic lesions. CT, computed tomography.

Camrelizumab is a high-affinity PD-1 antibody that exerts antitumor activity with a favorable safety profile in various malignancies (52,53). Camrelizumab, in combination with docetaxel and cisplatin, may be also an option for recurrent/metastatic oral SCC (R/M OSCC), as suggested by the results of an open-label, single-arm, phase Ib trial (54). The trial indicated that the

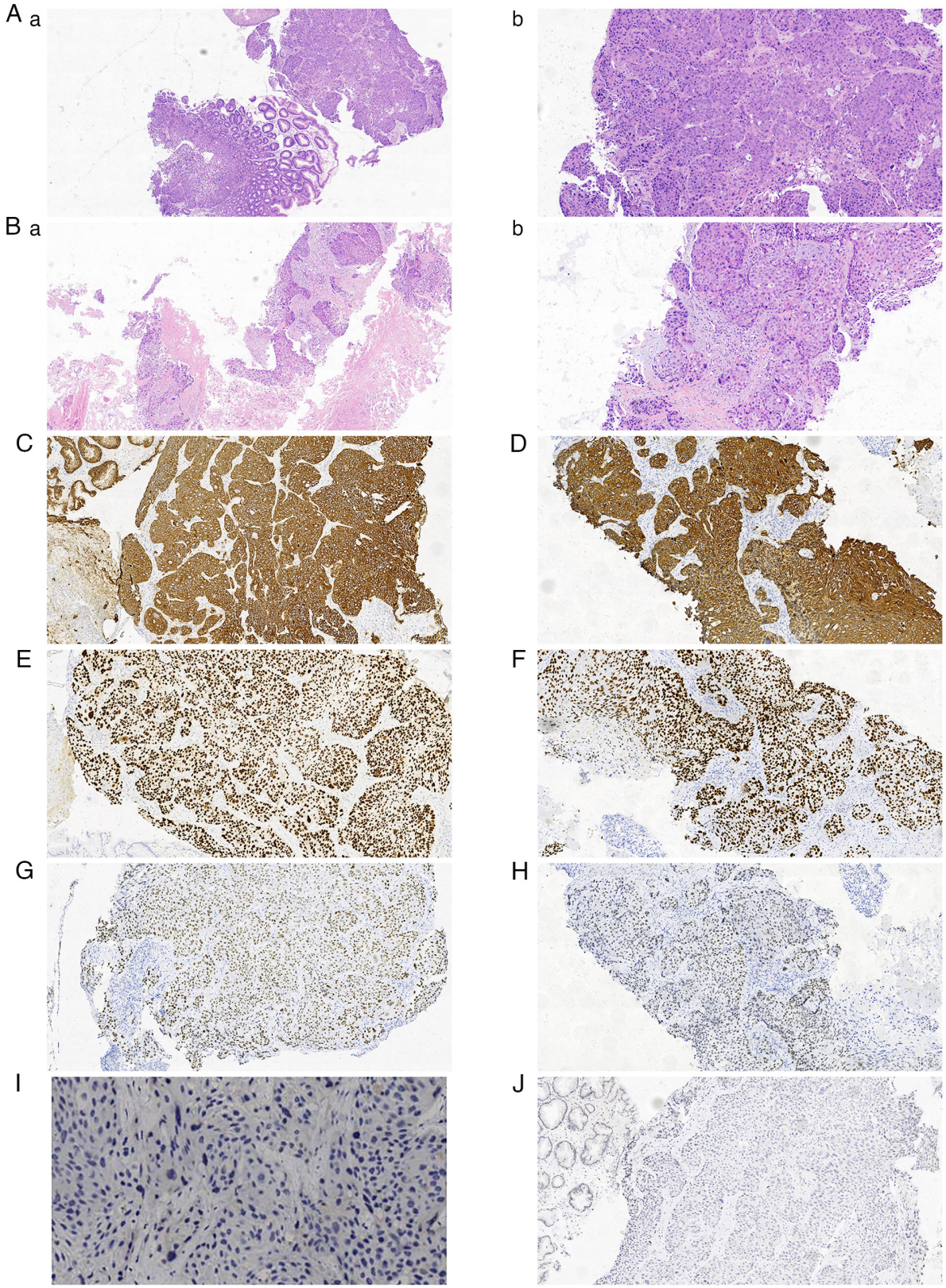

Figure 3. Histopathological images. Hematoxylin and eosin staining of (A) gastric and (B) dermal slices showing a moderately-differentiated squamous cell carcinoma [(a) magnification, x40 and (b) magnification, x100]. Immunohistochemical staining reveals that the gastric tumor cells were positive for (C) panCK, (E) P63 and (G) P40 and the dermal tumor cells were positive for (D) panCK, (F) P63 and (H) P40. In addition, the expression of (I) programmed death ligand 1 and (J) the immunohistochemistry of Epstein-Barr virus was negative in the gastric tissue (Envision staining; magnification, x100). panCK, pan-cytokeratin.

combination of camrelizumab and TP regimen chemotherapy was well tolerated and potentially improved the median OS, PFS and ORR in the first-line treatment of patients with R/M OSCC.

In the current case, the patient had a history of smoking, alcohol and betel quid chewing. Intraoral examination revealed a cauliflower-like mass on the right mandibular gingiva. Although, no

pathological biopsy was performed, given the clinical presentation and epidemiological features, a primary gingival malignancy was suspected. In addition, histopathological examination confirmed that the skin and stomach lesions were SCCs, as evidenced by the positive immunohistochemical expression of P40, P63 and panCK. The other lesions were considered secondary malignancies. Based on these findings, camrelizumab plus AP regimen chemotherapy was selected in accordance with systemic therapy guidelines for CSCC and SCCHN (21,35).

Notably, discriminating histologically between primary tumors and metastases in the present case was challenging, if not impossible. However, it may be hypothesized that triple primary skin, stomach and gingival tumors metastasized to the brain, liver, lung, spleen, kidney, bone and subcutaneous tissue. Anti-PD-1 antibodies combined with a nab-paclitaxel and carboplatin regimen may be an option for metastatic SCC in patients with a performance status of 0-1. However, in the present case, the patient had an unsatisfactory outcome due to multiple organ metastases and poor performance status.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

MT, XC and LL carried out data analyses and drafted the manuscript. BC, WH and XZ performed the follow-up. YC designed, coordinated and supervised the study and critically reviewed and discussed the manuscript. MT and YC confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Ethics Committee of Zhuji People's Hospital of Zhejiang Province (approval no. 20241109; Zhuji, China).

Patient consent for publication

Written informed consent was obtained from the patient for the publication of this paper.

Competing interests

The authors declare that they have no competing interests.

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