Cancer of unknown primary site in the mandibular region: A case report

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Abstract. The diagnosis and treatment of cancer of unknown primary site (CUP) present with difficulties and produce a poor prognosis. The current study presents the case of a patient with CUP in the mandibular region was treated with docetaxel and lobaplatin chemotherapy, and vascular embolization of the tumor. The tumor size was markedly reduced and the patient's quality of life improved following radiotherapy. The present case report is accompanied by a discussion of the literature to contextualize the treatment regimen for patients with CUP. These findings will support current treatment practices, inform oncologists and benefit patients with cancer.

Introduction

Cancer of unknown primary site (CUP) is a rare heterogeneous clinical syndrome of metastatic cancer for which the primary site is difficult to determine. The pathogenesis of CUP remains unclear (1). CUP accounts for 2-5% of all cancer diagnoses (2-4). Most CUPs are associated with clinical signs and symptoms of metastatic tumors, such as weakness, loss of appetite, chest tightness and abdominal distension (4). The most commonly affected areas are the liver, lungs, bone and lymph nodes, followed by pleura and the brain (5). The diagnosis of CUP requires histopathological characterization, which is typically performed with immunohistochemistry (IHC) and, more recently, molecular analysis, which can detect the expression

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of specific genes in tumor cells of patients, and the tumor classification and subtype can be analyzed by comparing with the determined tumor classification database (4,6). As the primary features of CUP are unknown, most patients receive topical treatment or empiric systemic chemotherapy (7). Despite multiple combinations of chemotherapy, most patients have a poor prognosis, with a survival time of 3-6 months (8). In the present case report, a patient with a CUP of the mandible was successfully treated. The patient was admitted to our hospital for treatment in November 2021 and survived for nearly 1 year until October 2022, the patient is still healthy now.

Case report

A 1x1-cm mass was found in the right mandible of a 71-year-old female patient in November 2006. The patient had no obvious discomfort and was not treated. In November 2021, the patient presented at Jinshazhou Hospital of Guangzhou University of Chinese Medicine (Guangzhou, China) as the tumor had grown rapidly to 5x4x5 cm within 2 weeks, accompanied by pain, bleeding, salivation, a bad odour, and limited opening and closing of the mouth (Fig. 1). Results of a biopsy, achieved by scraping cells from the tumor surface, were consistent with ulceration. A pathological biopsy was performed subsequent to the initial superficial biopsy. MRI showed mandibular bone destruction and a soft-tissue mass lesion, with invasion of the bilateral sublingual glands, genioglossus muscle, right masseter muscle and lower lip soft tissue. Slightly larger lymph nodes were seen at the cervical Ia and bilateral Ib levels, indicating the possibility of lymph node metastasis (Fig. 2A).

Ultrasound-guided puncture biopsy of the mandibular tumor was performed and tumor bleeding was observed, which improved after symptomatic hemostasis. The biopsy tissue was soaked in 10% neutral formalin fixing solution for 8 h at 25°C (room temperature), embedded in Leica paraffin wax and sliced into 4- μ m unstained sections. Antigen repair was conducted with three 250 ml cylinders of xylene for 10 min each, two cylinders of 100 and 95% ethanol for 5 min each, and 90, 85 and 75% ethanol for 3 min per 250 ml cylinder hydration, at 100°C constant temperature, followed by TBS-T (0.05% Tween-20) washing for 3-8 min. After antigen repair, the

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biopsy tissue was treated with 3% hydrogen peroxide solution 25°C for 10 min for blocking. Pan-cytokeratin (CK) primary antibody (1:400; cat. no. MAB-0671; Fuzhou Maixin Biotech Co., Ltd.) was then added, and the biopsy tissue was incubated at room temperature for 50 min. The biopsy tissue was then incubated with secondary antibody linked to horseradish peroxidase diluted by TBS-T (1:2,500; cat. no. GK800711; Gene Tech Co., Ltd.) at room temperature for 30 min. DAB staining was used for visualization, which was conducted using an Olympus BX53 optical microscope. A pathological report was generated indicating the presence of a small round-cell malignant tumor and an immunohistochemical examination was recommended. The HE staining protocol of the $4-\mu m$ unstained sections was as follows (all steps were carried out at 25°C, room temperature): i) 10% neutral formalin fixing solution for 8 h; ii) xylene dewaxing I, II, III and IV (roman numerals represent a different number of 250 ml cylinders) for 6 min each; iii) rehydration in 100% (I and II), 95 and 75% ethanol for 1 min each, followed by rinsing with tap water for 2 min; iv) staining with hematoxylin for 5 min, followed by rinsing with tap water for 1 min; v) differentiation for 6 sec with 0.5% hydrochloric ethanol solution and rinsing with tap water; vi) incubation with saturated lithium carbonate solution for 5 sec, to prevent nuclei from being too light; vii) staining with eosin for 1 min; viii) 75% ethanol, two 250 ml cylinders of 95% ethanol, two 250 ml cylinders of 100% ethanol 1 min each; ix) xylene I, II and III 1 min each; and x) neutral gum sealing sheet to remove excess water and facilitate microscopic observation (Fig. 3A). The pathological diagnosis was of a malignant tumor.

Immunohistochemical analyses were not able to identify small cell carcinoma, small cell osteosarcoma or a primitive neuroectodermal tumor. The immunohistochemical results were as follows: Cytokeratin (-), vimentin (-), synaptophysin (-), chromogranin A (-), neural cell adhesion molecule 56 (-), Ki67 (5% +), special AT-rich 2 (-), thyroid transcription 1 (-), CD99 (-), desmin (-) and myoD1 (-). The tumor contained mostly necrotic material with little living tissue, making determination of the cancer type difficult and requiring further investigation. The IHC protocol was as follows: The undyed slide was placed in the oven at 60°C for 120 min, and then xylene I, II, III (roman numerals represent a different number of 250 ml cylinders)was added for dewaxing, 10 min for each cylinder. The slides were washed in 100% ethanol I, 100% ethanol II, 95% ethanol I, 95% ethanol II, 5 min per cylinder; 90, 85, 75% ethanol, 3 min per cylinder, and then rinsed with distilled water to complete the hydration. The slides were placed in a 100°C constant temperature machine for 3-8 min for antigen repair, washed with TBS-T (0.05% Tween-20), treated with 3% hydrogen peroxide solution for 10 min and then rinsed with TBS-T again. Primary CK antibody (1:400; cat. no. MAB-0671; Fuzhou Maixin Biotech Co., Ltd.) was added and the slides were incubated at room temperature for 50 min, before washing with TBS-T. Secondary antibody linked to horseradish peroxidase diluted with TBS-T (1:2,500; cat. no. GK800711; Shanghai GeneTech Co. Ltd.) was added and the slides were incubated at room temperature for 30 min. The slides were washed with TBS-T, DAB color developing solution was added and slides were incubated at 25°C for 5 min, and then washed with distilled water. The tissues were dyed with hematoxylin for 5 min, before washing with tap water for 1 min. Tissues were differentiated for 6 sec with 0.5% hydrochloric ethanol solution and washed with tap water. Saturated lithium carbonate solution was added for 5 sec to prevent nuclear staining being too light. Subsequently, the slides were washed with 75% ethanol, two 250 ml cylinders of 95% ethanol, two 250 ml cylinders of 100% ethanol 1 min each, two 250 ml cylinders of 95% ethanol, two 250 ml cylinders of 100% ethanol 1 min each to remove excess water and facilitate microscopic observation. The slides were then placed in 75% ethanol, two 250 ml cylinders of 95% ethanol and two 250 ml cylinders of 100% ethanol for 1 min each, and then in two 250 ml cylinders of 95% ethanol and two 250 ml cylinders of 100% ethanol for 1 min each. The above steps were conducted to remove excess water and facilitate microscopic observation. Finally, xylene solution I, II and III was added for 1 min each. A neutral gum sealing sheet was added (Fig. 3B). The tumor site was prone to bleeding and, given the extensive necrosis within the punctured tissue, the needle biopsy was not re-performed. Therefore, the pathological type of the tumor remained unknown, as did its site of origin, which may have been the mandible, tongue or gums.

Arterial infusion chemotherapy with 60 mg docetaxel and 40 mg lobaplatin was subsequently performed and the right facial artery was embolized. The tumor had decreased in size 3 days later, bleeding and salivation had decreased, and the opening and closing of the mouth were more flexible than previously. A second arterial infusion chemotherapy with the same drugs was performed 3 weeks later and the right facial artery was re-embolized. Visual examination (Fig. 4) and MRI (Fig. 2B) performed ~4 weeks after the second arterial infusion chemotherapy showed that the mandibular tumor had shrunk significantly and that the metastatic lymph nodes in the neck had decreased in number and size. A total of 4 cycles of chemotherapy according to the original scheme were administered and the tumor size remained stable.

After 12 rounds of radiotherapy (planning target volume 36 Gy/12 fractions) to the mandible, the tumor size had decreased and the tumor had almost disappeared. There was a little residual tumor on the CT scan, but the tumor was not active and was considered clinically cured. The patient was checked every 3 months and there has been no sign of recurrence since March 2022.

Discussion

Among CUP cases, 47% of patients suffer from highly to moderately differentiated adenocarcinoma, 44% from poorly differentiated or undifferentiated adenocarcinoma, 7% from squamous carcinoma and 2% from undifferentiated malignant tumors (9). Two-thirds of patients with cervical lymph node metastasis have squamous cell carcinoma (10). Melanoma of unknown primary site (MUP) comprises 3-4% of all melanomas, is typically present in the lymph nodes and more frequently involves the axillary lymph nodes, followed by the cervical, inguinal and parotid lymph nodes; the involvement of cervical metastatic lymph nodes is a negative prognostic factor for MUP (11). There are two hypotheses to explain the origins of CUP: i) A small, dormant or degenerative undetectable primary tumor means that a distinct primary lesion is the



Figure 1. Patient image before treatment. The tumor was protruding into the mandible, the surface was prone to bleeding and the patient had difficulty in opening and closing their mouth.



Figure 2. MRI images using T1 weighted imaging. (A) Before treatment, invasion of the bilateral sublingual glands, genioglossus muscle, right masseter muscle and lower lip soft tissue was observed. Red arrows indicate metastatic lymph nodes. (B) After treatment, the mandibular tumor was smaller and the metastatic lymph nodes in the neck were decreased in number and size.



Figure 3. Pathology. (A) First pathology report indicating a small round cell malignant tumor (HE staining). (B) Immunohistochemical result using a pancytokeratin antibody. Magnification, x200. The cytoplasm of the tumor cells was positive, indicating that the tumor originated from the epithelium.



Figure 4. Patient image after treatment. The mass in the mandibular region had disappeared and the mouth could be opened freely.

source; and ii) no primary tumor exists and the CUP is independent of a primary tumor mass and biologically different from other metastatic tumors (12). In support of the second hypothesis, a previous study has shown that head and neck CUP is associated with human papillomavirus (13).

At the time of CUP diagnosis, sufficient tissue for immunohistochemical examination is desirable (14), but sometimes unavailable, as with the present case study. Molecular tumor profiling (MTP) complements standard pathological assessment to allow determination of CUP tissue origin and is especially valuable when IHC produces uncertain results (1,14,15). These methods enable <87% of patients to receive a tissue-of-origin diagnosis, compared with 30% using conventional diagnostic tools (16). However, MTP does not always translate into survival benefits (17). Site-specific therapy based on accurate prediction using either reverse transcriptase polymerase chain reaction or gene microarray techniques (18-20) to determine the tissue of origin in patients with CUP, appears to improve the prognosis for some patients (21), but there is no curative effect in some tumor types, for example, breast, salivary gland, and adnexal skin cancers, as these neoplasms have overlapping gene expression, which may cause incorrect diagnosis of the tissue of origin (22,23). Moreover, the clinical benefit of MTP to CUP is not strongly supported (12).

Gene expression profiles can aid in the identification of primary tumor sites and targeted mutations (24). Liquid biopsy is a novel technique to aid CUP diagnosis via gene expression profiling and overcomes some limitations of tumor biopsy (12,25). The acquisition and interpretation of tumor biopsy have inherent limitations, and as a single tumor biopsy is typically very small, it is uncertain whether it can represent the whole tumor (26). Liquid biopsy can detect tumor cells and circulating tumor DNA fragments in bodily fluid specimens including blood, tissue fluid and cerebrospinal fluid, to aid in the diagnosis of CUP. However, to the best of our knowledge, large-scale clinical trials have not yet been conducted to confirm the benefits of gene sequencing (27). Such a clinical trial could involve a subgroup of patients with CUP undergoing site-specific therapy with or without a diagnosis from molecular cancer classifier assays, under the guidance of a classical immunohistochemical panel. The results of these trials could then be compared with those published in historical cases of CUP that received similar treatment at a known primary site. Despite the lack of prospective randomization, similar results will generate rapid progress in this field (28). Positron emission tomography/CT is also valuable for primary tumor diagnosis (29).

The prognosis of CUP is worse than that for most other tumors (9). There is currently no standard chemotherapy regimen for treatment (4,12), but empiric platinum or paclitaxel-based chemotherapy is often used (30-32), even though the level of evidence supporting this method recommendation is low (4,33,34). Combined chemotherapy with carboplatin and paclitaxel has been found to be effective in patients with

peritoneal carcinoma with lymph node/pleural metastasis from a CUP; however, in patients with liver, bone or multiple organ involvement, this regimen has limited benefits (35). Gemcitabine, alone or in combination with other drugs, may also be used (33). Most patients with metastatic squamous cell carcinoma of the neck are treated with radiotherapy (36). Notably, no significant difference in 5-year survival rates among patients administered radiotherapy or chemoradiotherapy alone and surgical treatment has been found (37). Whether immune checkpoint inhibitors (ICIs) are an effective CUP treatment option is also currently an open question (38). ICIs are actively being evaluated in CUP given their theoretical ability to mount an effective antitumor immune response. Chromosomal instability is infrequent in CUP but is a known driver of early dissemination and aggressive behavior, reducing the response to ICIs (39). A number of patients with chromosomal instability present with individual gene alterations with implications for immune-evasion and resistance to ICIs (39). A 60-case clinical trial involved treatment with carboplatin plus paclitaxel, followed by erlotinib targeted therapy plus chemotherapy, and the median survival time of patients was 13 months (40). Another trial of 47 patients treated with bevacizumab and erlotinib as second-line treatment had a median survival time of 7 months (41). Immunotherapy may also be a treatment option (12,42).

In conclusion, the diagnosis and treatment of CUP presents difficulties and results in a poor prognosis. The present case study is of the successful treatment of a patient with CUP. The relevant literature has been reviewed and a comprehensive treatment method including chemotherapy, interventional embolization and radiotherapy is described in order to inform treatment decisions for patients with CUP.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

XL, LXQ, YXC, JPG and JML were involved in the patient's treatment management process, BC participated in the pathological analysis, XJZ obtained medical images. All authors read and approved the final manuscript. XL, LXQ, BC and JML confirm the authenticity of all the raw data.

Ethics approval and consent to participate

This study was approved by The Ethics Committee of Jinshazhou Hospital of Guangzhou University of Chinese Medicine (Guangzhou, China).

Patient consent for publication

Written informed consent was obtained from the patient for publication of the present case report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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