Hepatocellular carcinoma metastasis to the gingival soft tissues: A case report and review of the literature

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Abstract. Metastases to the gingival soft tissues are rare in hepatocellular carcinoma (HCC). To the best of our knowledge, only 13 cases have been reported in English literature to date. The present study described the case of a 43-year-old Chinese man who was admitted to Tangdu Hospital (Xi'an, China) due to the presence of a gingival tumor that was initially diagnosed as granulation tissue by a dental surgeon. Examination of the patient's medical history revealed that a solid mass, measuring 1.5 cm in diameter, was identified in the right lobe of the liver 2 years prior to presentation at the current hospital; however, no biopsy was performed. Thus, the tumor was resected and histological examination resulted in an initial diagnosis of atypical squamous cell carcinoma. However, the histopathological characteristics, immunohistochemical features and serum α-fetoprotein expression levels supported a diagnosis of metastatic HCC. In conclusion, the present case study highlights the difficulties in diagnosing metastatic HCC without a history of primary HCC, and the importance of excluding a diagnosis of metastatic tumor when a lesion is identified in the gingival. Furthermore, it was determined that a final diagnosis of gingival metastasis of HCC predominantly depends on pathological characteristics and immunohistochemical features.

Introduction

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-associated mortality worldwide. The prognosis for patients with HCC is poor, due to the high possibility of recurrence, and intrahepatic and extrahepatic metastasis following surgical resection (1). Extrahepatic metastasis of HCC occurs in ~30-50% of patients (2-5), and the most common metastatic sites are the lungs, abdominal lymph nodes and bones (2-5). Metastasis to the gingiva is rare and, to the best of our knowledge, only 13 such cases have been reported in English literature thus far (6-17). The age range of these patients was 46-78 years and the average age was 61 years. The presentation typically imitates other conditions, such as pyogenic granuloma affecting the oral cavity (16). Gingival tumor may be the first and only manifestation of HCC (17). Furthermore, the disease has a high incidence rate in male patients in Asia, possibly due to the incidence of HCC (15). A final diagnosis of HCC with metastasis to the gingiva primarily depends on the histopathological characteristics and immunohistochemical features of the tumor (18). Microscopically, the tumor cells may be trabecular, solid or tubular. Intranuclear pseudoinclusions caused by cytoplasmic invaginations may be present, and the cytoplasm may contain Mallory's hyaline, copper, pale bodies or bile pigment (19). In addition, an important diagnostic feature is the network of sinusoidal vessels that surrounds the tumor cells. Immunohistochemically, the tumor cells are positive for α-fetoprotein (AFP), cytokeratin (CK)18, glypican 3 (GPC3) and hepatocyte paraffin 1 (HepPar-1), and of these, GPC3, AFP and/or HepPar-1 are relatively specific to the diagnosis of HCC.

Patient histories must be considered when establishing a diagnosis. The prognosis is poor for patients with extrahepatic metastases and predominantly depends on the metastatic site at the time of diagnosis. It has been reported that the time between appearance of the gingival metastasis and mortality is no more than a few weeks. However, the survival of individual patients may reach 8 months (15). The current study presented a case of metastatic HCC to the gingival, and investigated its histopathological characteristics and immunohistochemical features. In addition, the current study highlighted the importance of obtaining a comprehensive patient history following the diagnosis of a metastatic malignant tumor of the gingival.Written informed consent was obtained from the patient's family.

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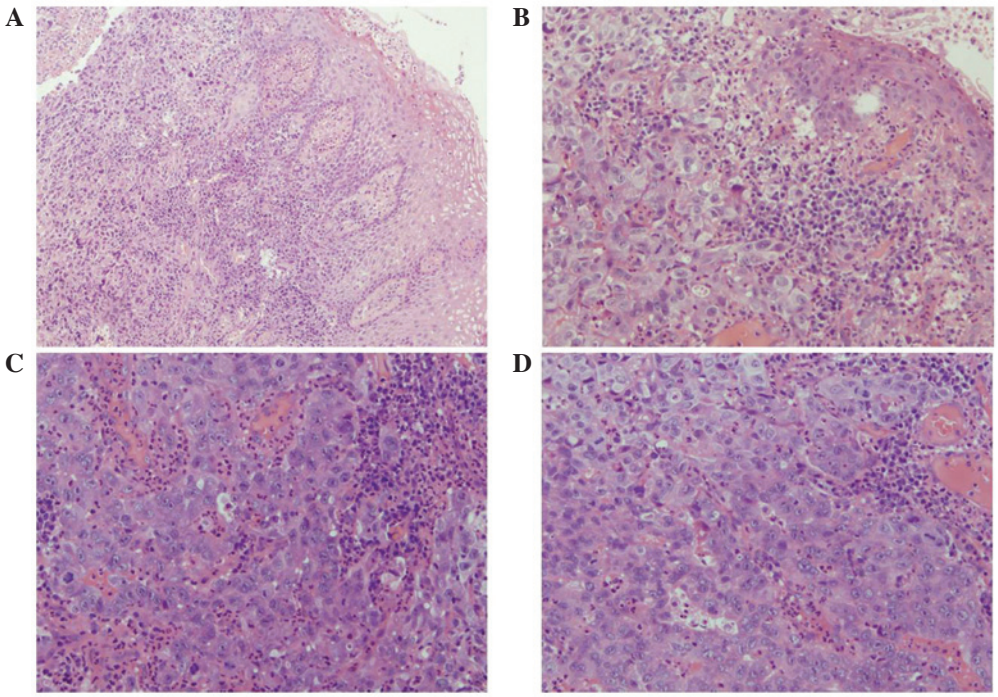

Figure 1. Microscopic analysis of the gingival soft tissue tumor cells, revealing tumor cells (A) located in the submucosa (magnification, x100), and (B and C) arranged in trabecular, solid growth patterns (magnification, x200). (B) Inflammatory exudates and necrosis were identified on the surface of the mucosa, and (C) numerous tumor cells were arranged in pseudoglandular patterns. (D) The tumor cells were almost uniform in size and the nuclei were prominent (magnification, x200; hematoxylin and eosin staining).

Case report

A 43-year-old male was admitted to Tangdu Hospital (Xi'an, China) on April 26, 2014 due to the presence of a lesion in the gingiva, which had been identified >1 year prior to admission, but the patient did not seek medical advice. Examination of the patient's medical history revealed that a solid mass, measuring 1.5 cm in diameter, was identified in the right liver 2 years prior to presentation at the hospital; however, no biopsy was performed as the patient did not agree to perform the biopsy. An oral examination confirmed the presence of a 2x1.5x1-cm irregular mass located in the right upper gingival soft tissue. The mass was subsequently resected, fixed in 10% neutral formaldehyde and embedded in paraffin. Serial sections were cut at a thickness of 4-μm and stained with hematoxylin and eosin. Microscopically, the tumor cells were located in the submucosa (Fig. 1A) and predominantly arranged in a solid, trabecular growth pattern (Fig. 1B). Furthermore, the cells were arranged in pseudoglandular patterns in the focal area (Fig. 1C) and were uniform in size with prominent nuclei (Fig. 1D). Inflammatory exudates and necrosis were observed in the surface of the mucosa (Fig. 1C). Initial observations indicated that the histological morphology was similar to an atypical squamous cell carcinoma. Thus, immunostaining was performed to clarify this diagnosis using a streptavidin-labeled peroxidase kit (Maixin Biotech. Co., Ltd, Fuzhou, China), according to the manufacturer's instructions. The following primary rat anti-human monoclonal antibodies were used in the current study: Anti-high molecular weight CK, anti-epithelial membrane antigen (EMA), anti-p63, anti-CK5/6 and anti-vimentin. All reagents were supplied by Fuzhou Maxin Biotechnology Co., Ltd. (Fuzhou, China).

Immunohistochemical analysis identified that the tumor cells were negative for all the aforementioned antibodies (Fig. 2). Combining the immunohistochemical analysis results and the patient history, a diagnosis of metastatic HCC was considered. Further immunohistochemical analysis for additional markers was performed to confirm this diagnosis, using rat anti-human monoclonal antibodies, such as GPC3 (MX005), CK18 (MX004), hepatocyte (OCH1E5), AFP, CD56 (56C04), and chromogranin A (LK2H10+PHE5), and a rabbit anti-human polyclonal antibody against synaptophysin. In addition, a physical examination on the liver was advised. The results demonstrated that the tumor cells were positive for GPC3, hepatocytes, CK and CK18, and negative for AFP, EMA, chromogranin A, synaptophysin and CD56 (Fig. 2). Serum AFP levels were high (5,860.00 ng/ml; normal range <20 ng/ml). Considering the observed immunohistochemical characteristics and the clinical history of the patient, metastatic HCC was diagnosed, despite the unconfirmed primary HCC. Thus, regular treatment for HCC was recommended, including chemotherapy and transcatheter arterial chemoembolization (TACE). However, the patient chose to end his own treatment and was lost in follow-up.

Discussion

HCC is one of the most common types of cancer worldwide, with high prevalence and mortality rates. High mortality rates are in part attributed to rapid recurrence and the development of intra- and extrahepatic metastasis following surgical intervention (1). Extrahepatic metastasis occurs in 30-50% of HCC cases (2-5), and the most common metastatic sites are the lungs, regional lymph nodes and bones (2-5). However, metastatic

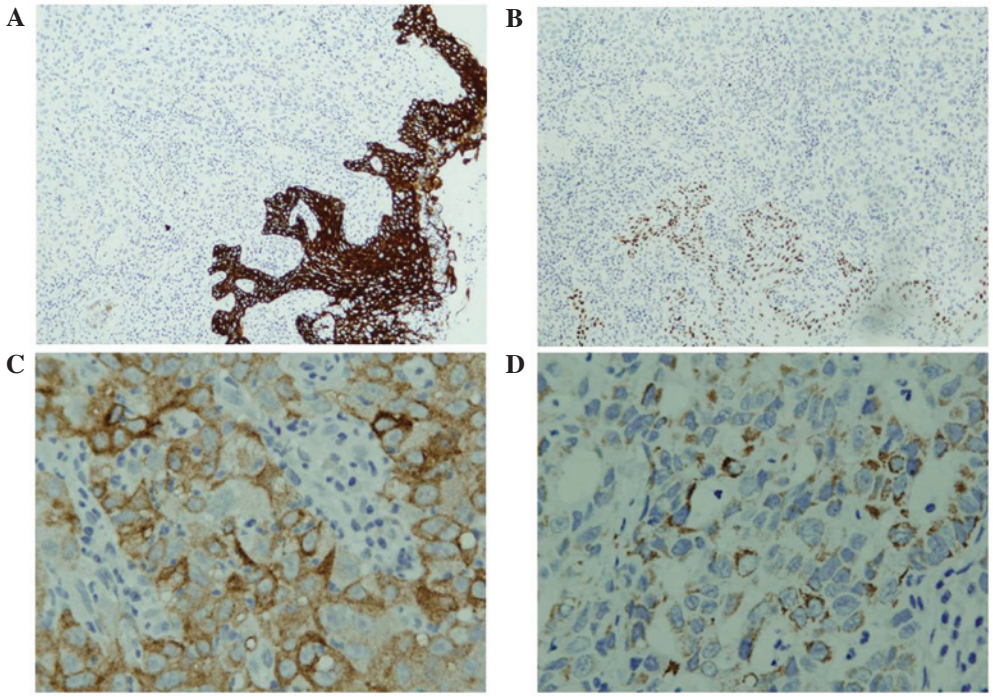

Figure 2. Immunohistochemical analysis of the gingival soft tissue tumor cells, revealing negative (A) high molecular weight cytokeratin and (B) p63 (magnification, x100), and positive for (C) glypican 3 and (D) hepatocytes (magnification, x200).

HCC to the oral cavity, particularly the gingival soft tissues, is rare. To the best of our knowledge, only 13 such cases have been reported in the English literature to date (6-17).

The pathogenesis of the metastasis of malignant tumors to the gingiva is unclear. Following a comprehensive review of the literature, numerous studies were identified that discussed an association between HCC metastasis in particular and chronic periodontitis (20-23). The patient in the present study had chronic periodontitis before the gingival tumor was observed. From these studies, circulating reactive oxygen species (ROS), which are produced by host inflammatory cells upon stimulation by bacterial pathogens (24), were identified as a fundamental attributable factor to the association between HCC metastasis and chronic periodontitis. Furthermore, Severi *et al* identified that ROS were involved in the transcriptional activation of a large series of cytokines and growth factors that ultimately lead to malignant transformation (25). The results indicated that periodontitis may affect HCC by increasing the number of circulating ROS. Tamaki *et al* (23) recruited 64 patients with HCC, including 31 patients with chronic periodontitis and 33 periodontally healthy controls, and recorded the Japan Integrated Stage (JIS), which combines the tumor, lymph node, metastasis and Child-Turcotte-Pugh systems, and serum levels of reactive oxygen metabolites (ROM) in all patients. The results demonstrated that patients with HCC and periodontitis had higher JIS scores and circulating ROS levels compared with patients with HCC but without periodontitis (23). Therefore, the authors concluded that the stage of HCC may be associated with periodontitis, and increased ROS serum levels caused by periodontitis may be detrimental to hepatic health in patients with HCC (23). Another study proposed that inflammation may result in the migration of metastatic cells to the gingival soft tissues, as well as affecting where they invade, multiply and form a new tumor (26). However, metastatic spread to the gingiva from primary tumors is considered to primarily occur via the hematogenous route (26), the mechanism for which has yet to be fully determined. The ROM serum levels of the patient in the present study were not examined; therefore, an association with metastasis of HCC was not conclusive.

Metastatic malignant tumors of the oral cavity are rare. The most common malignancies are lung, breast and renal cell carcinomas (27,28). However, HCC metastases to the oral cavity are rarely observed. Therefore, it is difficult to diagnose gingival metastatic HCC without a history of primary HCC, particularly in cases of atypical histological morphology, such as the current patient. The patient's final diagnosis was primarily dependent on medical history, immunohistochemical analysis results and a physical examination of the liver. If a history of HCC was noted in advance in the current patient, the typical histopathological characteristics of HCC could have been identified according to the criteria described by Edmondson and Steiner (18,29). For instance, certain tumor cells were uniform in size with prominent nuclei and were arranged in pseudoglandular patterns, characteristic of HCC.

At present, in addition to surgical resection, the treatment strategies selected for patients with extrahepatic metastasis are typically TACE and/or administration of the targeted agent sorafenib, which is an inhibitor of tyrosine protein kinase. Furthermore, in patients with advanced HCC, concurrent treatment with sorafenib and TACE may increase the time to progression compared with TACE monotherapy (30). The prognosis is poor for patients with extrahepatic metastases and predominantly depends on the metastatic site at the time of diagnosis. In the present case, the gingival lesion was initially identified >1 year prior to presentation at the hospital; however,

the patient refused the proposed treatment regime due to poor economic conditions. Follow-up was not performed.

In conclusion, the present case illustrated the difficulties in diagnosing metastatic HCC without a prior history of primary HCC. The final diagnosis appears to predominantly depend on the pathological characteristics and immunohistochemical features of the lesion.

Acknowledgements

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