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Case Report

Hepatocellular carcinoma metastasis to the mandibular ramus: a case report

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Abstract: Hepatocellular carcinoma (HCC) is one of the most commonly reported cancers worldwide. Although the extrahepatic metastasis of this carcinoma has been reported frequently, the mandible is a rare site for HCC metastasis. Here we have presented a rare case of mandibular metastatic HCC in a 37-year-old man presenting with painless swelling over his right parotid gland for the previous 3 months. This patient had a history of HCC caused by a hepatitis C viral infection. The tumor cells exhibited eosinophilic and rich cytoplasm, and they appeared to be trabecular (similar to hepatic cells), with sinusoids between the tumor cells. Moreover, the tumor cells were positive for Hep Par-1 and Glypican-3 in the cytoplasm. A 64-multidetector-row computed tomography scan was performed, and it showed pathological tracer uptake in the right mandible. Therefore, an excisional biopsy was performed, and with the support of an immunohistochemical analysis, an HCC mandibular metastasis diagnosis was made. The patient was treated with radiotherapy and chemotherapy. This patient was followed up in the oncology department for 1 year, and he was still alive at the time this report was written. This extremely rare case highlights the differential diagnosis difficulties that can be encountered, and the importance of diagnostic clues, such as the clinical history, histopathology, and immunohistochemistry, in the establishment of a definitive diagnosis. Clinicians should be aware of the possibility of encountering HCC metastasis in the mandible, and take this into consideration in order to prevent a misdiagnosis.

Keywords: Mandibular ramus, metastasis, hepatocellular carcinoma, hepatitis C, immunohistochemistry

Introduction

Hepatocellular carcinoma (HCC) is the 3rd most commonly diagnosed carcinoma worldwide. In China, it accounts for approximately 12.9% of all tumors [1]. HCC with extrahepatic metastasis has been reported in approximately 50% of the cases. In the literature, the most frequently reported HCC metastatic sites include the colon, kidneys, lungs, and skeleton [2]. HCC bone metastasis has been reported in 1.6-16% of the patients, with the ribs being the most frequently affected bones, followed by the humeri, femurs, iliac bones, and vertebral bodies [3, 4]. The mandible is a rare site for HCC metastasis; therefore, this study describes the case of a patient with HCC extrahepatic metastasis to the mandibular ramus.

Case report

A 37-year-old man was referred to the Jining First People's Hospital in Jining, China in May of 2016 with a history of painless swelling over his right parotid gland for the previous 3 months. The swelling had increased gradually in size during that period of time. This patient did not have a history of trauma or pain, but he first noticed occasional symptoms of numbness in his right lower lip over the last month. The rest of his examination was normal, and an assessment of the other clinical parameters showed nothing unusual. However, less than one year ago, he was diagnosed with HCC caused by a hepatitis C viral infection, and he has been undergoing treatment. It was not necessary to obtain ethical approval for this case report; however, this patient did provide informed consent for the publication of his case.

The extraoral examination of this patient showed diffuse, fixed, painless swelling in the right parotid gland region, and his maximum mouth opening was 2.5 cm. The intraoral examination revealed a swollen area of approximate-

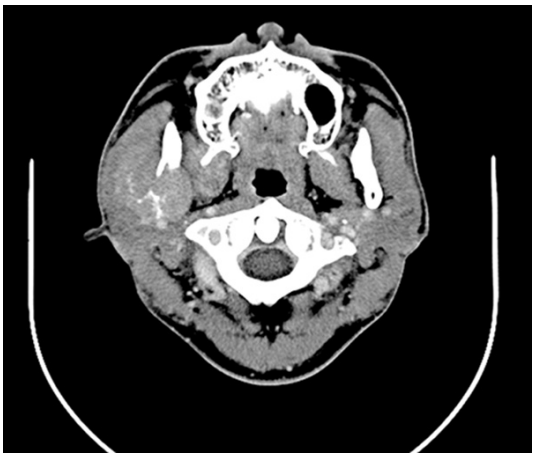

Figure 1. Computed tomography scan revealing bone destruction in the medullary and cortical portions of the right mandible.

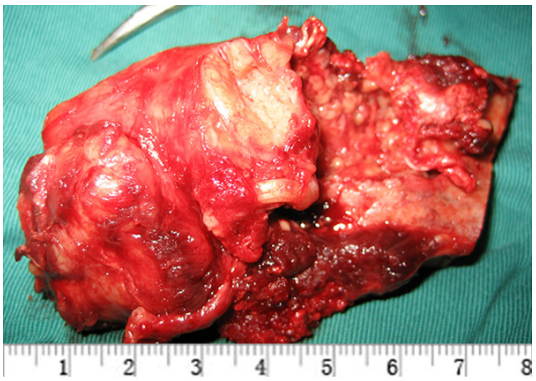

Figure 2. Macroscopic appearance of the resected segmented mandibulectomy in the right posterior mandibular body and mandibular ramus.

ly 2.0 × 2.0 × 2.0 cm in size in the right buccal region. Otherwise, complete dentition and normal mucous membranes were observed. A 64-multidetector-row computed tomography (CT) examination (Somatom Definition AS; Siemens Medical Solutions, Forchheim, Germany) showed a low-density area approximately 3.5 × 3.0 cm in size that had destroyed the medullary and cortical portions of the right mandible (**Figure 1**). A radiographic examination of his chest showed no abnormal changes. The laboratory testing showed positive results for the hepatitis B antigen, hepatitis B antibodies, and hepatitis B virus S1 antigen; however, his liver and kidney function tests showed no abnormal changes. The single photon emission CT scan (Infinia Hawkeye 4; GE Healthcare, Fairfield, CT, USA) using ^{99m}Tc-methylene diphosphonic acid (MDP) (HTA Co., Ltd., Beijing, China) revealed an isolated focus of ^{99m}Tc-MDP uptake in the right mandibular ramus.

Based on the preoperative examination, we determined that the swelling was destructive to the surrounding tissue in an invasive growth pattern that was consistent with the characteristics of malignancy. Therefore, this patient was preoperatively diagnosed with a malignant tumor. Given his history of liver cancer, we considered the possibility of HCC metastasis. This patient was recommended for surgery, and the swelling was resected via a segmented mandibulectomy of the right posterior mandibular body and mandibular ramus (**Figure 2**). This revealed metastatic carcinoma by virtue of a rapid intraoperative pathological diagnosis.

The resected tissue specimens were formalin-fixed, paraffin-embedded, cut into 4-μm sections, dewaxed in xylene, and rehydrated in a series of graded alcohols. Subsequently, the slides were submerged for 10 min in a peroxidase quenching solution containing one part 30% hydrogen peroxide to nine parts absolute methanol. After rinsing the slides in phosphate buffered saline, antigen retrieval was carried out by autoclaving the tissue in a 0.01 M sodium citrate buffer (pH 6.0) at 120°C for 3 min. Then, the sections were blocked in 10% normal goat serum for 10 min at room temperature, and they were incubated overnight at 4°C with the primary antibodies. The polyclonal anti-hepatocyte specific antigen antibody (MAB-0249; Fuzhou Maixin Biotech. Co., Ltd., Fuzhou, China) and the anti-Glypican-3 antibody (Kit-0036; Fuzhou Maixin Biotech. Co., Ltd.) were used for the immunohistochemical analysis. Subsequently, the sections were stained using a 2-step plus poly-HRP anti-mouse/rabbit immunoglobulin G detection system (PV-9000; ZSGB-BIO, Beijing, China) and a liquid 3,3'-diaminobenzidine substrate kit (Invitrogen, Shanghai, China). The samples were rinsed well with distilled water, and then they were counterstained with Mayer's hematoxylin solution, dehydrated, and mounted.

The growth patterns of the tumor cells appeared to be trabecular, solid, and pseudoglandular. The tumor cells showed extensive pleomorphism and bizarre mitotic figures. The nuclei and nucleoli of the tumor cells were prominent, and the cytoplasm was rich and eosinophilic.

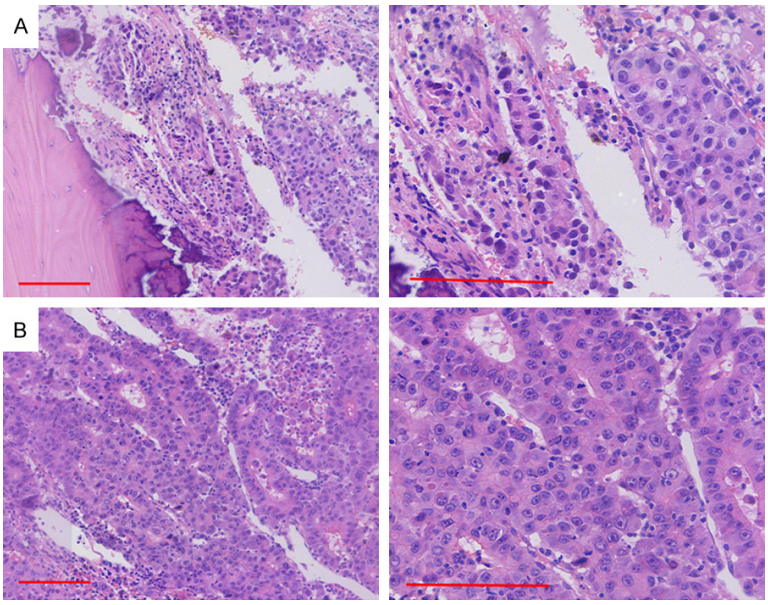

Figure 3. Histological examination of mandibular metastatic carcinoma. Different views with hematoxylin and eosin staining. Scale bars: 60 μm.

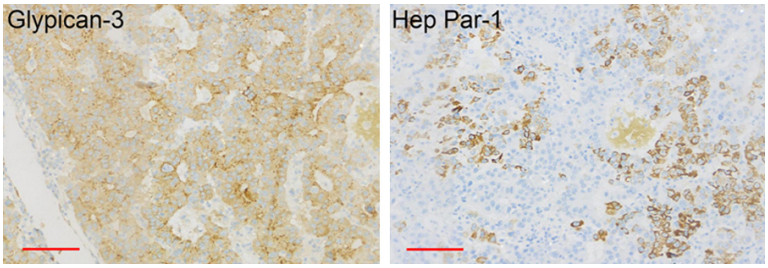

Figure 4. Immunohistochemical analysis of mandibular metastatic carcinoma. Glypican-3 and Hep Par-1 are two biomarkers that are helpful for determining the metastatic hepatocellular carcinoma origin. These two markers react positively in the cytoplasm. Scale bars: 60 μm.

Sinusoids could be seen between the tumor cells (**Figure 3**). The immunocytochemistry showed that the cytoplasm was Hep Par-1 and Glypican-3 positive (**Figure 4**). The histological examination and tumor history of the patient revealed that the source of the metastatic epithelial tumor was HCC. The immunohistochemical analysis confirmed the hepatocellular origin.

Based on the above results, this patient underwent CT scans of his brain, chest, abdomen, and pelvis, which revealed no other evidence of metastatic disease. Therefore, he was treated with radiotherapy (2 Gy/day for 3 weeks) and chemotherapy (300 mg/m^2/day of tegafur and uracil and 20 mg of cisplatin twice a week for 2 weeks). The patient was followed up in the oncology department for 1 year, and he was still alive at the time that this report was written.

Discussion

An accurate diagnosis is the first step in optimal cancer care. However, distant metastases of HCC are being seen more frequently after a patient is diagnosed with the primary disease [5]. The most common HCC metastasis sites are the lungs and bones. The incidence of HCC bone metastasis is approximately 1.6-16%, with the most common sites being the vertebrae, pelvis, and ribs [6, 7]. The occurrence of HCC bone metastasis to the mandibular ramus is rare. Therefore, these patients could be misdiagnosed, and they may not receive the appropriate treatment in a timely manner. Moreover, distinguishing primary cancer from a secondary metastatic lesion can be challenging. HCC metastasis to the mandibular ramus is characterized by the presence of diffuse, firm, and painless swelling in the temporal region, and a destroyed mandibular ramus in the radiographic examination of a hepatitis B virus carrier. This has been proven by many previous studies in the literature.

The mode of extrahepatic HCC spread is usually hematogenous metastasis, and the metastatic dissemination reaches the maxillofacial area later through the communication between the hepatic artery and portal vein [8]. There is free communication between the neck, thorax, abdomen, and pelvis venous systems with the valveless vertebral venous plexus that extends from the cranial base to the coccyx. It has been postulated that there is a connection between the azygos and hemiazygos veins and the vertebral venous plexus (Batson's venous plexus) [9, 10].

Additionally, it has been proposed that metastatic deposits have a predilection for bone

marrow spaces [9]. The mandibular ramus has less bone marrow than the mandibular body; however, the blood supply to the mandibular ramus comes from the branches of the maxillary artery and superficial temporal artery. These anatomical peculiarities might be the related mechanism.

Radiographically, mandibular metastatic carcinoma exhibits a range of features consistent with its malignant nature. In general, the lesion margins are ill-defined, with a destructive lesion on the mandible appearing as a large soft-tissue mass. The radiographic findings can provide a certain amount of evidence for the diagnosis.

A noninvasive approach to the diagnosis of this disease may not be sufficiently precise. Undoubtedly, a clinicopathologic diagnosis, which has been regarded as the gold standard, is the best diagnosis of HCC mandibular metastasis. The cellular morphology and growth pattern appear to be trabecular, solid, and pseudoglandular, which are similar to those of the liver cells. Sinusoids can be seen between the tumor cells. Hep Par-1 is one of the most reliable biomarkers of hepatocytic differentiation, with Glypican-3 being the latest marker that has been added to the hepatocellular phenotype listing. Glypican-3 is a member of the heparin sulfate proteoglycan family, and it plays roles in cell growth, differentiation, and migration. These two markers react positively in the cytoplasm. We detected positive staining in the tissues, and we confirmed the source of the tumor using hematoxylin and eosin staining, as well the immunohistochemical analysis.

The radical resection of metastatic HCC is controversial, because the prognosis of patients with extrahepatic metastases is poor [11]. However, the resection of an oral metastatic neoplasm could help to improve the quality of life and survival for certain patients, although it does seem to be palliative in most cases [11-13]. For this patient, it was necessary to remove the metastatic neoplasm in order to improve his quality of life. A diagnosed case of oral metastasis with synchronic HCC was excluded, because the survival might have been markedly influenced by the metastatic tumor [14]. The literature highlights the importance of a complete medical evaluation of the patient in order to identify the possible oral repercussions of primary diseases.

The prognosis of mandibular metastatic HCC is not entirely clear. However, recently developed management options can prolong the life expectancy. Palliative treatments, such as radiotherapy, chemotherapy, and immunotherapy, can be used to relieve pain and extend the patient's life. In summary, we have reported a rare case of the mandibular metastasis of HCC. This has been done to alert clinicians to the possibility of encountering this disease, and encourage them to consider these various characteristics in order to prevent a misdiagnosis.

Disclosure of conflict of interest

None.

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