Korean J Gastroenterol Vol. 68 No. 6, 321-325
https://doi.org/10.4166/kjg.2016.68.6.321
pISSN 1598-9992 eISSN 2233-6869

CASE REPORT

치은 종괴로 나타난 간세포암종 1예

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A Case of Hepatocellular Carcinoma Presenting as a Gingival Mass

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Oral metastatic tumor, which is uncommon and represents less than 1% of malignant oral neoplasms, usually arises from a primary mucosal or cutaneous cancer located in the head and neck regions. Metastasis of hepatocellular carcinoma (HCC) to the oral cavity, especially to gingiva, is extremely rare. A 50-year-old man, who was a chronic alcoholic and hepatitis B virus carrier, presented with abdominal distension and weight loss for the past 3 months. Three-phased contrast-enhanced abdominal CT revealed numerous conglomerated masses in the liver, suggesting huge HCCs arising in the background of liver cirrhosis with a large amount of ascites. He complained of recurrent profuse bleeding from the left upper gingival mass. A facial CT revealed an oral cavity mass destructing the left maxillary alveolar process and hard palate, which was diagnosed as metastatic HCC by an incisional biopsy. Herein, we report a case of metastatic HCC to the gingiva. **(Korean J Gastroenterol 2016;68:321-325)**

Key Words: Hepatocellular carcinoma; Neoplasm metastasis; Gingiva; Mouth

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world, especially in Southeast Asia.[1,2] HCC is a highly malignant cancer with frequent metastasis, primarily found in the lungs, bones, abdominal lymph nodes, and adrenal glands. Oral metastatic tumor is uncommon and represents less than 1% of malignant oral neoplasms; it usually arises from a primary mucosal or cutaneous cancer located in the head and neck region.[3-6] Metastasis of HCC to the oral cavity—especially to the gingiva—is extremely rare. Herein, we report a rare case of HCC presenting as a gingival mass.

CASE REPORT

A 50-year-old man was referred to our hospital due to abdominal distension and weight loss of 20 kg in a period of three months. Physical examination revealed a distended abdomen with an umbilical hernia, slightly icteric conjunctiva, and diffuse lower extremities edema. He was a heavy drinker. On arrival, his blood pressure, pulse rate, and temperature were 130/80 mmHg, 70 beats/min, and 36.7°C, respectively. The patient was conscious and orientated, but had been suffering from liver cirrhosis related to hepatitis B. He complained of pain from the left upper gingival mass. The lesion had been presented for approximately one month, which had been

Received July 8, 2016. **Revised** October 10, 2016. **Accepted** October 19, 2016.

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Financial support: None. Conflict of interest: None.

growing progressively. An oral examination showed bleeding and detaching necrotic tissue of the left upper gingival mass (Fig. 1).

Laboratory data revealed a platelet count of 95,000/mm^3, AST of 205 IU/L, ALT of 99 IU/L, total bilirubin of 2.9 mg/dL, albumin of 2.3 g/dL, PT of 16.1 sec (66%), and AFP of 5,870 ng/mL. The results of viral markers were HBsAg/anti-HBs (+/−), HBeAg/anti-HBe (+/−), anti-HBc IgG/IgM (−/−), and HBV DNA real time PCR of 4.45×10^9 copies/mL. Liver cirrhosis was classified as Child-Pugh class C. Three-phased contrast-enhanced abdominopelvic CT revealed numerous conglomerated masses throughout the liver in the background of cirrhosis with a large amount of ascites. These masses showed a heterogeneous enhancement in the arterial phase and typical wash-out pattern with heterogeneous low attenuation portal and delayed phase, which are relevant to the clinical diagnosis of HCC (Fig. 2). According to abdominopelvic CT, there was no evidence of metastasis to the vessels, lymphatics, or other solid organs. The whole body bone scan revealed slightly increased uptakes on the upper cervical spine according to the posterior view, which suggests metastasis or degenerative change. A facial CT demonstrated an oral cavity mass destructing the left maxillary alveolar process and hard palate (Fig. 3).

Biopsy was performed for the left upper gingival mass, revealing malignant anaplastic and pleomorphic cell neoplasm, which was undifferentiated and had diffusely infiltrated the subepithelial stroma, without any evidence of transitioning to overlying, gingival, nonneoplastic, squamous epithelium. Tumor cells (Fig. 4) exhibited marked nuclear

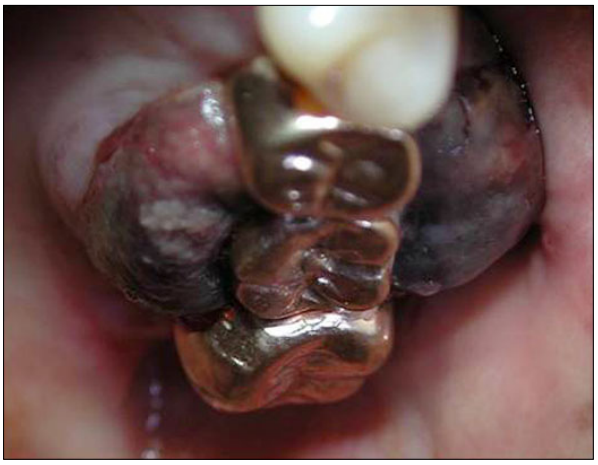

Fig. 1. A protruding mass suggesting metastatic hepatocellular carcinoma is noted at the left gingiva.

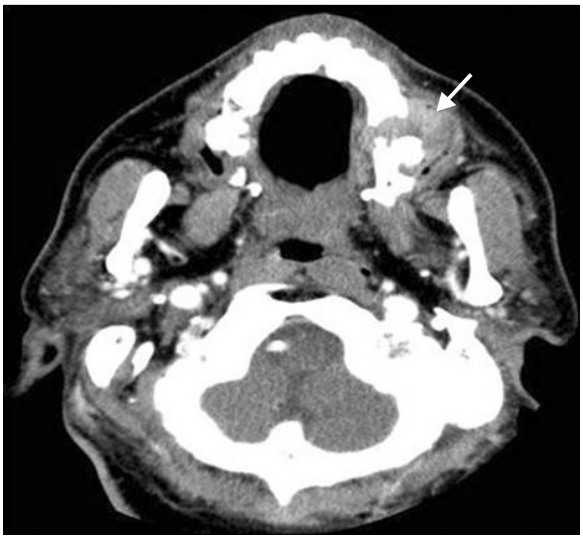

Fig. 3. Facial CT presents malignant tumor involving the alveolar process of the left maxilla and lateral aspect of the left side hard palate (arrow).

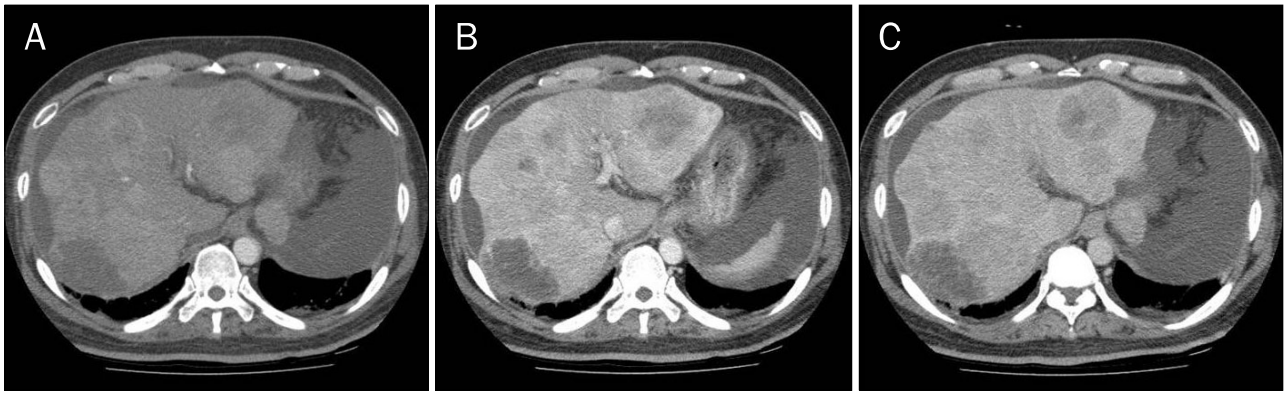

Fig. 2. (A) Arterial phase, (B) portal phase, (C) delayed phase. Numerous hepatocellular carcinomas are seen in the entire liver on abdominal CT. These masses show heterogeneous enhancement in arterial phase and typical wash-out pattern in portal and delayed phase.

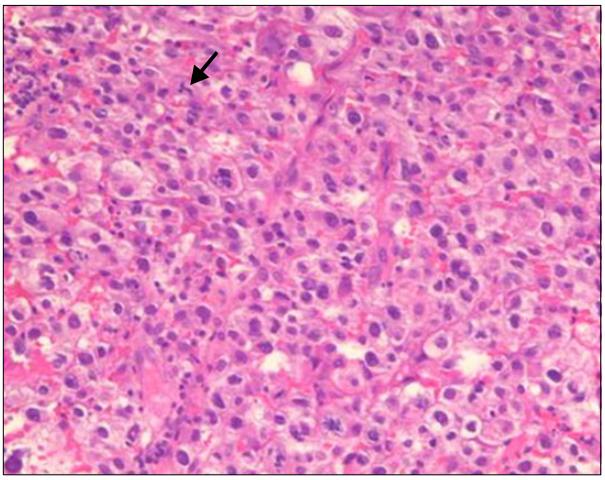

Fig. 4. Photomicrograph of oral mass exhibiting severe nuclear anaplasia and pleomorphism, frequent mitotic figures, including atypical tripolar mitotic spindle (arrow) and sheet to trabecular arrangement. H&E stain, ×200.

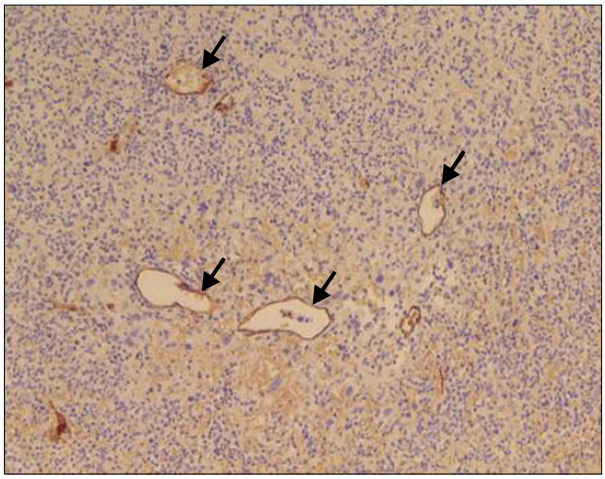

Fig. 5. Cellular tumor demonstrates vascular stroma (arrows), with distinct immunohistochemical expression for CD34 (×100).

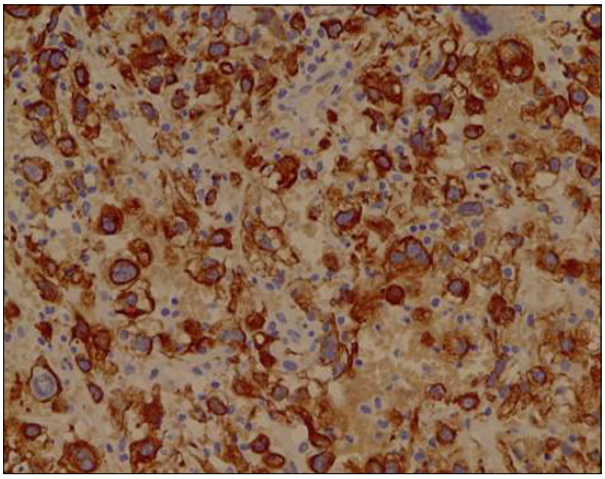

Fig. 6. Large anaplastic and pleomorphic tumor cells with bizarre multinucleated giant cells reveal diffuse cytoplasmic immunoreactivity for low molecular weight cytokeratin (Cam 5.2, ×400).

anaplasia and pleomorphism with some bizarre multinucleated giant cells, frequent mitoses, solid sheet to vague trabecular arrangement, and vascular stroma (CD 34 [+], Fig. 5), with an immunohistochemical reactivity for low molecular weight cytokeratin (Cam 5.2 [+], Fig. 6). Therefore, we suspected undifferentiated carcinoma. Tumor cells revealed neither biliary differentiation (CA 19-9 [−]) nor neuroendocrine differentiation (CD56 [−]).

These results suggest that cholangiocarcinoma or large cell neuroendocrine carcinoma could be excluded. The immunohistochemical markers supporting primary gingival squamous cell carcinoma (high molecular weight cytokeratin), malignant melanoma (HMB 45, S100 protein) or primary pulmonary carcinoma (thyroid transcription factor-1) were all negative. Therefore, in accordance with clinical reasoning, this undifferentiated carcinoma of gingiva may be metastatic carcinoma from huge HCCs.

Five days after admission, the patient complained of bleeding from the gingival mass. After consulting a radiation oncologist, palliative radiotherapy was recommended. However, his general condition gradually worsened, and after a week, he died due to hepatic and renal failure while waiting to receive radiation therapy for oral metastatic HCC.

DISCUSSION

Extrahepatic metastasis from HCC occurs in 37% of cases and it most frequently metastasizes to the lungs, regional lymph nodes, bones, and intra-abdominal organs.[3-8] Metastasis of primary HCC to the oral cavity is highly unusual, representing only in less than 1% of malignant oral neoplasms. The most common metastatic malignancies of the oral cavity are cancers in the lung, breast, colon or rectum, and renal cell with the exception of the metastasis from head and neck cancer.[9-12] In 2012, Shin et al.[13] reviewed patients with metastatic oral/oropahryngeal carcinoma diagnosed at the Asan Medical Center in Seoul, Korea, from 1995 to 2010. Among 1,445 patients with oral/oropharyngeal malignancy, only 29 cases (2%) were diagnosed as metastatic carcinomas; among them, eight cases were from HCC metastasis, and in

particular, metastasis to gingiva occurred in only three patients. The liver was one of the most common primary site in that study, suggesting it could be possible due to high incidence of HCC in Korea.[13]

In our patient, despite abnormal coagulation parameters, a biopsy of the oral mass was performed without any major complications. The growth of this oral mass was continuous with eventual aggravation of bleeding and pain.

In the present case, the gingival mass was undifferentiated and showed marked nuclear anaplasia and pleomorphism. There was no clear histologic and imunohisotochemical findings sufficient for a clear diagnosis of HCC metastasis to the gingiva. However, this gingival mass was more in line with metastatic carcinoma than with primary oral or maxillary sinus cancer because there was no transition between gingival mass and overlying squamous epithelial cells of oral cavity or maxillary sinus. Furthermore, the possibility of the diagnosis of primary gingival squamous cell carcinoma, malignant melanoma or metastatic pulmonary carcinoma can be excluded. Therefore, we concluded that HCC—the undifferentiated carcinoma variant—was metastasized to the gingiva. The limitation of our case report is that we were unable to provide a typical immunohistochemical evidence (such as AFP or hepatocyte) of HCC metastasizing to the gingiva.

The mechanism of oral metastasis from liver cancer is mostly hematogenous dissemination. There are two suggested routes of oral metastasis from the liver. The first route is via the portal hematogenous pathway, in which that major vessels of the liver, hepatic arteries, and portal veins can easily be invaded, with the lung being particularly vulnerable. The second route is via Batson's plexus of valveless paravertebral veins; due to its lack of valves, it can bypass other venous systems, such as caval, portal, and pulmonary, thereby leading to metastasis to the oral cavity.[13-15] Approximately 66% of oral tumor cases were detected prior to the identification of the primary hepatic lesion. Diagnosing metastatic HCC in the oral region may be challenging, especially without prior detection of HCC.[10]

In the case of gingival metastasis from HCC, surgical resection—whenever possible—should be considered as the first line of therapy for the symptomatic relief of oral discomfort, pain, and bleeding. However, severe bleeding may occur during surgical removal of metastases, especially in liver cirrhosis patients. Transarterial chemoembolization (TACE) and sorafenib can also be a useful treatment modality for extrahepatic metastasis.[16,17] Inaba et al.[18] reported that gingival bleeding due to metastatic HCC in an 80-year-old man was controlled successfully after TACE until his death, which was due to respiratory failure. In our case, surgical resection, TACE or sorafenib could not be performed due to poor liver function and unstable coagulation state. Radiation therapy with higher fractionated doses appeared useful in achieving partial control of gingival lesion with growth and hemorrhage. Three weeks after the diagnosis of gingival metastasis, our patient died due to hepatic failure while waiting for radiation therapy.

Solitary metastasis to the oral cavity presenting as a gingival mass in the setting of HCC is very rare. Oral metastatic HCC should be suspected in the differential diagnosis of rapidly growing oral lesions, particularly in patients with risk factors of HCC, including chronic hepatitis B.

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