

Metastatic hepatocellular carcinoma of the oral cavity - A report of two cases

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Abstract

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide that is etiologically linked to a previous hepatitis B infection. We describe two cases of HCC metastasis to the oral cavity in 60- and 67-year-old male patients. The first case was a diffuse, hard swelling in the left body of the mandible. Histopathologic and immunohistochemical analysis was done, and a positive for CK7, CK19, HEPPAR and TTF and a negative for NAPSIN were found to be diagnostic of metastatic HCC. Subsequent examination of the serum alfa- fetoprotein (AFP) level showed a high value of 450 ng/ml, confirmatory of HCC. The second case was a pedunculated, reddish, mobile soft tissue growth on the retromolar region. Its macroscopic and histopathologic features themselves were confirmatory of HCC, and the elicited history was corroborant of metastasis.

Keywords: CK7, CK19, hepatocellular carcinoma, HEPPAR, metastasis, NAPSIN, TTF

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer, with a worldwide incidence of 500,000 to 1 million new cases per year. It is the second-leading cause of cancer mortality worldwide.^[1] The most common etiologic factor is described as chronic hepatitis B infection.^[1] HCC has a tendency to metastasise to other organs such as bone and soft tissues at the advanced stage, the most frequent sites of metastasis being the colon, kidneys, lungs, and skeleton.^[2] Bone metastasis has been reported in 1.6–16% of the patients, with the ribs being the most frequently affected bones.^[3] HCC metastasis to the oral cavity and jaws is uncommon, with only 71 cases being reported in the literature. Along with its low incidence rate, the easily ignored clinical symptoms and signs also contribute to

the rarity of pathologically confirmed cases of metastatic hepatocellular carcinoma of the oral cavity. Here we report two cases of metastatic hepatocellular carcinoma of the oral cavity in two male patients, one with a silent primary malignancy.

Case 1

A 60-year-old male reported to our institution with the complaint of rapidly increasing swelling in the left lower jaw for the past 2 months. A detailed clinical history revealed that he was apparently healthy except for a dull pain and swelling in the left lower jaw for a couple of weeks. There was no significant medical history, and a physical examination disclosed a well nourished man in no acute distress, and his family history was non-contributory.

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On intraoral examination, a diffuse hard swelling of size $3 \times 3 \text{ cm}^2$ with a smooth surface obliterating the mucobuccal sulcus was seen in the left side of the body of the mandible [Figure 1]. The swelling extended from 36 to the pterygomandibular raphe. Third molar (38) was tender on percussion and showed grade 1 mobility. Level 1B lymph nodes were palpable.

A panoramic radiograph displayed a well defined radiolucent lesion in the left posterior body of the mandible extending mesiodistally from the distal aspect of the distal root of 36 to 6.03 mm distal to 38, and super inferiorly from the alveolar crest to 4.21 mm superior to the inferior border of the mandible of size approximately $30.42 \times 24.62 \text{ mm}$. Borders appeared well defined and non-corticated [Figure 2]. Magnetic resonance imaging (MRI) suggested an expansile lytic lesion in the left hemimandible in relation to the roots of the last two molar teeth.

The patient was sent for routine blood and biochemical investigations to rule out any systemic diseases. Haematological reports revealed that he was anaemic, with an elevated erythrocyte sedimentation rate and an absolute monocyte count. His serum creatinine level was low, whereas other biochemical parameters were well within the normal limits.

With clinical and radiographic features, differential diagnoses of central giant cell granuloma, odontogenic and metastatic neoplasms were considered. The mandibular mass was biopsied, and microscopic sections showed a malignant epithelial neoplasm composed of tumour cells arranged in a glandular pattern and in nests. Tumour cells lining the glandular structure were cuboidal to short columnar, with granular cytoplasm and a round basophilic nucleus. Some areas showed a cribriform arrangement of tumour cells. Intervening connective tissue was oedematous and showed moderate cellularity [Figure 3]. Based on microscopic findings, an overall diagnosis of “cribriform adenocarcinoma” was rendered.

Immunohistochemical staining for CK7, CK20, CDX2, CK19, HEP PAR-1, TTF and NAPSIN was done. Tumour cells were positive for CK7 [Figure 4], CK19 [Figure 5], HEP PAR1 [Figure 6] and TTF [Figure 7] and were negative for CK20 [Figure 8], CDX2 [Figure 9] and NAPSIN [Figure 10]. Thus, a diagnosis of metastatic hepatocellular carcinoma was given. Serum AFP levels were analysed, and a value of 450 ng/ml was found diagnostic of HCC. Later, the patient was referred to the department of oncology and underwent two cycles of chemotherapy. Unfortunately, the patient succumbed to death in a couple of weeks.



Figure 1: Shows the clinical image of case 1, showing diffuse hard swelling of size $3 \times 3 \text{ cm}^2$ with a smooth surface obliterating the mucobuccal sulcus in the left body of the mandible



Figure 2: Shows OPG of case 1 displaying a well defined radiolucent lesion in the left posterior body of mandible

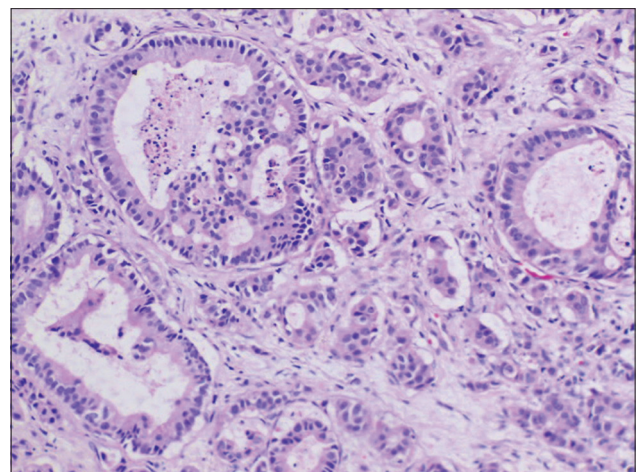


Figure 3: Shows the histopathologic image of case 1 (H&E stain, 40x)

Case 2

A 67-year-old male patient was reported with a pedunculated reddish mobile soft tissue growth of approximately size $2 \times 1 \text{ cm}^2$ in the retromolar region distal to the 48. The lesion was

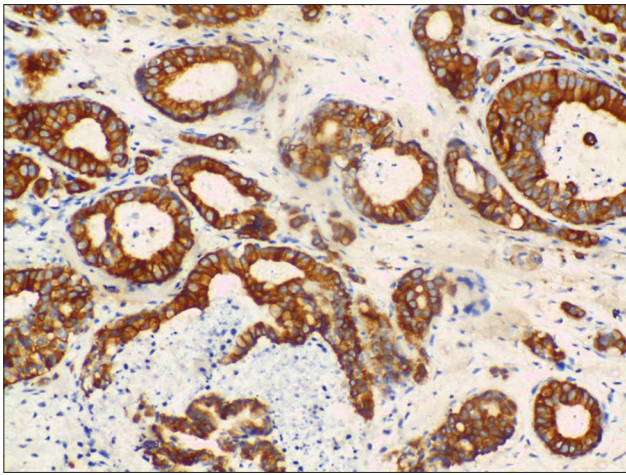


Figure 4: Shows CK7 positivity in case 1 (40x magnification)

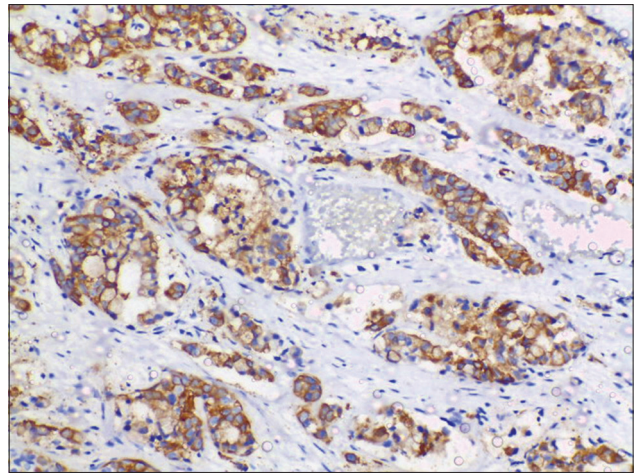


Figure 5: Shows CK19 positivity in case 1 under 40x magnification

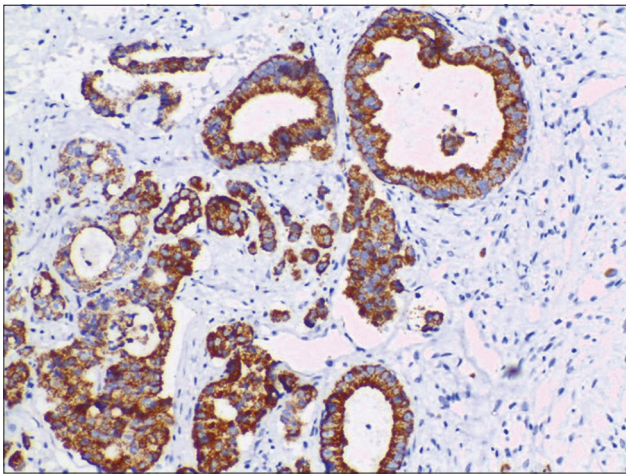


Figure 6: Shows HEPPAR positivity in case 1 under 40x magnification

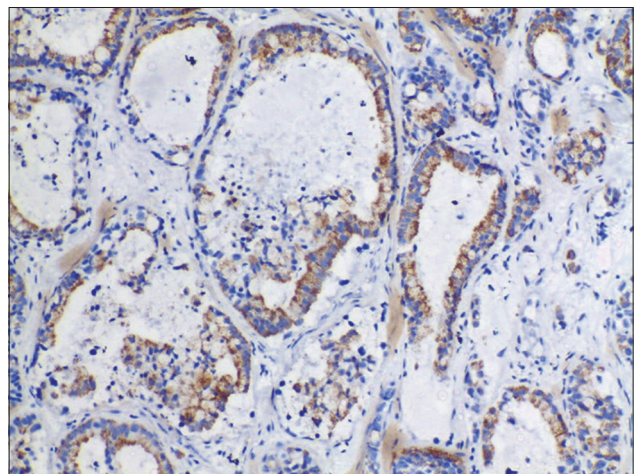


Figure 7: Shows TTF positivity in case 1 under 40x magnification

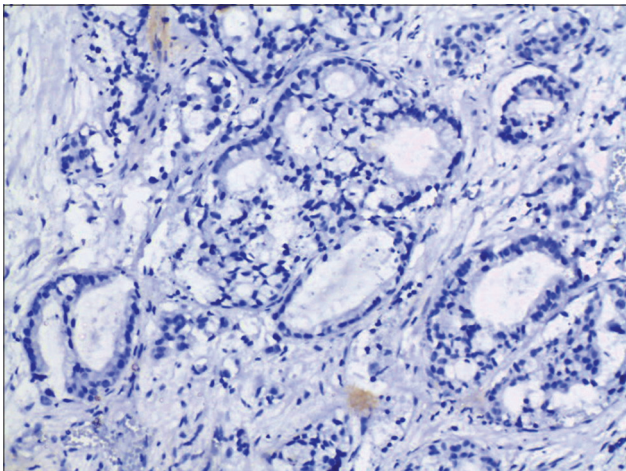


Figure 8: Shows CK20 negative in case 1 under 40x magnification

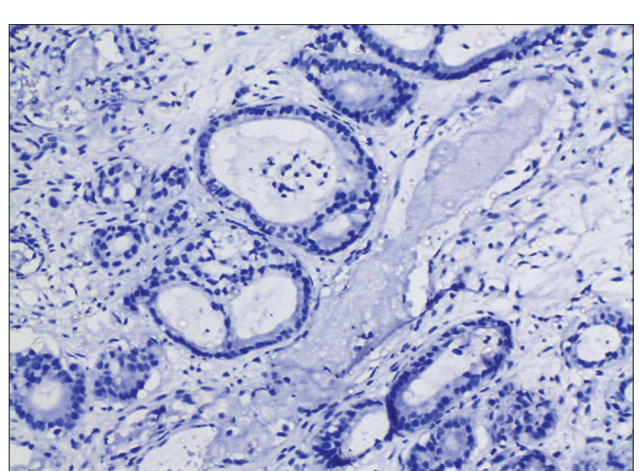


Figure 9: Shows CDX2 negative in case 1 under 40x magnification

tender and showed bleeding on palpation. His history revealed that he was a HCC patient and had undergone treatment. Ultrasonogram (USG) findings were given as a hypoechoic lesion with posterior echoic enhancement and evidence of increased vascularity suggestive of pyogenic granuloma.

The lesion was biopsied, and the gross specimen showed creamy bits of tissue with a peculiar greenish area underneath [Figure 11]. Histopathology disclosed proliferating tumour cells as sheets in a cellular connective

tissue stroma. Tumour cells were ovoid and showed granular eosinophilic cytoplasm with vesicular nuclei. Cells with dark eosinophilic cytoplasm and hyperchromatic nuclei were also seen. Tumour cells showed abnormal mitosis, an increased mitotic index and nuclear and cellular pleomorphism [Figure 12]. Immunohistochemical staining showed Pan-CK [Figure 13] and HEPPAR positivity. Based on history, macroscopy, histological features and immunological features, a diagnosis of metastatic hepatocellular carcinoma was disposed.

DISCUSSION

Hepatocellular carcinoma is defined as a malignant tumour developing from hepatocytes and/or showing hepatocellular differentiation. It is the second most common cancer in Asia and fourth in Africa. However, a lower incidence is observed in the United States and Western Europe.^[1] The male: female ratio for HCC in India is 4:1. The common age of presentation varies from 40 to 70 years.^[4]

HCC typically arises in the background of cirrhosis; however, about 20% of cases can develop it in a non-cirrhotic liver. In such cases, the disease is clinically silent in its early stages because of a lack of symptoms.^[5] Risk factors for HCC include liver cirrhosis independently of cause, chronic hepatitis B or C, alcohol consumption, non-alcoholic liver steatosis and mycotoxins.^[6] In the present series, one patient had no history of cirrhosis. Serum AFP is the most widely studied screening test for detecting HCC. The normal range is 10–20 ng/ml, and a level of 400 ng/ml or above is diagnostic of HCC, which was so in our case,^[7] whereas the other patient was a known HCC patient.

HCC frequently metastasises to extrahepatic sites like the lungs, regional lymph nodes and bones through a hematogenous route. In the oral region, metastatic tumour may occur in the soft tissues or jawbones. In jawbones, the

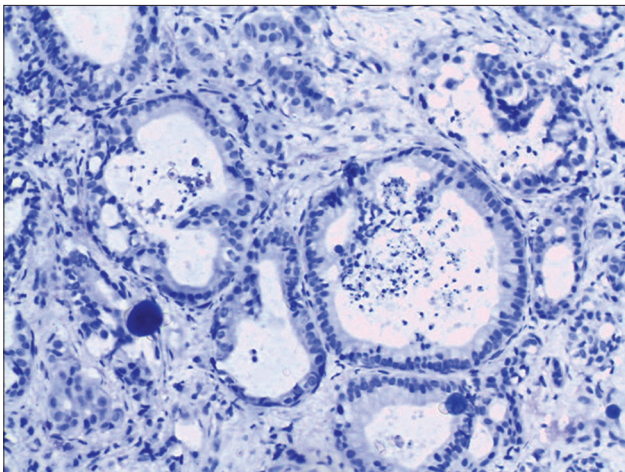


Figure 10: Shows NAPSIN negative in case 1 under 40x magnification



Figure 11: Shows gross image of case 2 showing greenish discoloration of the cut surface

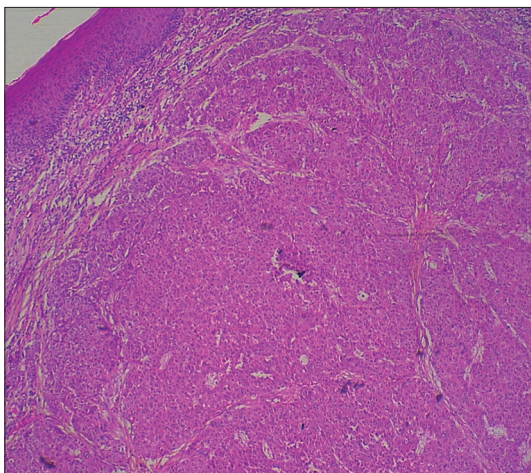


Figure 12: Shows H&E-stained histopathologic image of case 2 under 10x magnification

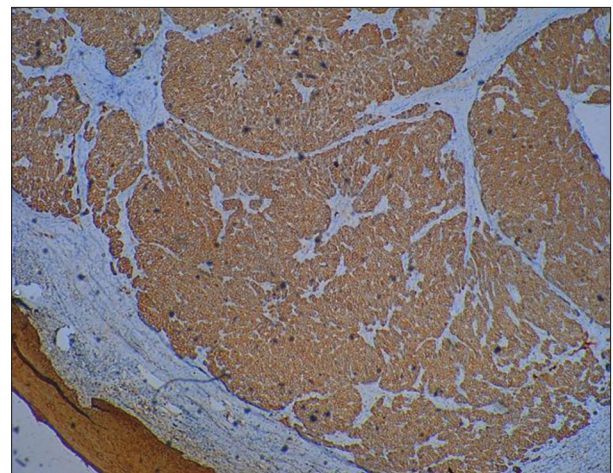


Figure 13: Shows Pan cytokeratin positivity in case 2 under 10x magnification

most common location is the mandible (81%), with the molar area being the most frequently affected site, followed by the premolar area. The metastatic dissemination reaches the maxillofacial area through the communication between the hepatic artery and portal vein.^[8]

Metastatic tumour of the jaw commonly present with clinical symptoms like progressive swelling, pain and paraesthesia. A proliferative mass, loss of teeth and ulceration may also occur if the lesion is in the oral mucosal tissues.^[9] In the first patient, intraoral examination revealed a diffuse swelling in his mandible, obliterating the mucobuccal sulcus. The second case showed a pedunculated reddish soft tissue growth over the retromolar region. Jaw lesions radiographically often display a radiolucent osteolytic lesion with ill-defined margins. In our case, in the mandible, both the panoramic radiograph and the cone beam computed tomography (CBCT) showed an osteolytic lesion in the left hemimandible. The second case exhibited no radiographic findings.

By microscopy, the typical patterns of hepatocellular carcinoma include trabecular, solid, acinar and ductular structures. The neoplastic cells in low-grade cases resemble hepatocytes by possessing wide eosinophilic cytoplasm and distinct cell borders. Increased nucleocytoplasmic ratio and nuclear atypia can be seen, although to a different degree. Atypical mitoses can be observed. The architecture shows unequivocal deviations from normal structure, such as thick trabeculae with more than two cell layers, solid areas, duct-like or gland-like structures.^[6] A glandular pattern and nest-like arrangement of cells were found in the first case, whereas sheets of proliferating tumour cells were found in the second case.

Immunohistochemical examinations help to identify both the nature and origin of neoplasms. In the first case, an initial panel of CK7/CK20 positive expression was suggestive of gastrointestinal origin. For the precise analysis of primary site, organ-specific antibodies were used. CDX2 is a highly sensitive and specific marker for the detection of intestinal-origin, which was negative in our case. The transcription factor TTF-1, expressed as intense granular cytoplasmic staining, was found in hepatocellular tumours with 60–70% sensitivity.^[6,10] Its expression in lung adenocarcinomas ranged from 54% to 86%. Napsin A, an enzyme expressed in type II pneumocytes and showing high specificity for lung adenocarcinomas, was negative in our case, thus excluding its diagnosis. The progenitor cell marker CK-19 was associated with poor survival in HCC patients, which was so in our case. Hep Par-1 positivity sensitively and

specifically determinates the hepatic origin, which was so in our case.^[6,11,12] In the second case, we obtained Pan-CK and HEPPAR positivity of the malignant cells.

According to Pires *et al.*^[11] in about two-thirds of oral metastatic HCC, the oral lesions were the initial presentation of the disease. A timely biopsy is therefore suggested to exclude a metastatic oral tumour in cancer sufferers, which is easily confused with odontogenic or reactive lesions. Also, patients with HCC with metastases have a very poor survival rate. Studies have shown a mean survival period of 6.1 months after discovering the jaw metastasis.^[9] In the first case, the patient underwent two cycles of chemotherapy (regimen: Injection IV gemcitabine 1.6 g day 1 and day 8 + Injection IV carboplatin 450 g day 1) but succumbed to death 2 weeks later. The second patient underwent chemotherapy (300 mg/m²/day of tegafur and uracil and 20 mg cisplatin twice a week for 2 weeks), and he is still alive.

CONCLUSION

Metastatic tumours in the jaws pose a significant challenge in diagnosis and are easily confused with odontogenic or reactive lesions. They constitute an already widespread disease with a grave prognosis. Thus, a timely histopathologic and immunohistochemical analysis along with a series of tests are key for a proper diagnosis and can thus help predict the survival and outcome of such patients.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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