



Hepatocellular Carcinoma Presenting as Retromolar Swelling- A Rare Case Report with Review of Literature

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Abstract

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and represents a significant global health concern. The incidence of HCC varies with geographic regions and is influenced by factors such as the prevalence of chronic liver diseases, hepatitis B and C infections, exposure to aflatoxins, alcohol consumption and changes in lifestyle. Distant metastasis of HCC is uncommon and oral hepatic metastatic hepatocellular carcinoma is very rare. We hereby present a case of HCC metastasis to the retro-molar trigone in a 77 year old who presented with ulcer over the inner aspect of the right cheek with associated burning sensation which turned out to be a metastatic Hepatocellular carcinoma as the initial presenting features of the malignancy even before the detection of the primary malignancy.

Keywords: Hepatocellular Carcinoma (HCC); Immunohistochemistry (IHC)

Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignant neoplasm of the liver accounting for 70-90% of the hepatocellular malignancies and commonly encountered in the setting of chronic liver disease and cirrhosis [1]. HCC is more common in men than women and is the second leading cause of cancer mortality worldwide and in developing countries [2]. Clinically, patient with HCC usually present with mass effects or features of underlying disease such as upper abdominal pain, weight loss, hepatomegaly with or without palpable mass. Patients can also seldom present with distant metastasis. The commonest sites of HCC metastases are the lungs, followed by lymph nodes, bones and adrenal glands [3]. The unusual sites of HCC metastases include rectum, spleen, diaphragm, esophagus, pancreas and urinary bladder. Very rarely, HCC can present with metastasis to

the oral cavity. The extra-hepatic metastases generally correlate with the advancing intra-hepatic tumor stage but occasionally, the extrahepatic metastatic site may be the initial presenting feature.

Metastatic neoplasms of the oral cavity indicate a disseminated disease and are rare, accounting for approximately 1% of all oral malignant neoplasms [4]. The metastases can involve most commonly the gingiva and alveolar mucosa followed by buccal mucosa and soft palatal mucosa [5]. The prevalence of oral metastases differs in view of the differences in the primary sites and between various geographic areas [4]. Studies have found that the liver is the most common primary site and gingiva being the most commonly affected metastatic site in such patients [4,5]. In about one third of the patients with oral metastasis, the oral manifestation is the first clinical sign of an unrecognized primary malignancy [6].

Case Report

A 77 years old, a known case of systemic hypertension, interstitial lung disease-UIP pattern, type 2 Diabetes mellitus, Chronic lymphocytic leukemia and an old treated case of pulmonary tuberculosis, presented with complaints of ulcer over the right retromolar trigone of a week duration with associated burning sensation. He also complained of pain over the ulcer site which was aggravated by mastication. The patient also gave history of loose stools, about 8-10 episodes per day, watery in consistency and associated with abdominal pain and low-grade fever. On evaluation, Hb-9.1g/d, Total leukocyte count- 32,600/cmm, Platelet count- 2.74 lakh/cmm, serum urea/creatinine- 32/0.9 and total bilirubin- 0.59 mg/dl.

Patient later developed melena and oral bleed. In view of the recurrent oral bleed, dental consultation was sought and he underwent right tooth extraction for the same. However, with the patient’s persistent bleeding problem and painful non-healing ulcer over the right retromolar trigone despite the tooth extraction, the patient was taken up for the biopsy of the ulcer site.

The patient underwent an incisional biopsy and the specimen was sent for histopathology. Haematoxylin and Eosin stained section revealed the biopsy being lined by hyperplastic stratified squamous epithelium. The subepithelium revealed the presence of an invasive tumor arranged predominantly in trabeculae separated by thin capillary channels. The individual tumor cells are polygonal, moderately pleomorphic with round to oval nuclei, vesicular chromatin, conspicuous nucleoli and moderate amount of eosinophilic to pale cytoplasm. Bile pigment is noted in the tumor cells. Mitotic figures are present in the range of 5-6/10 hpf. Scattered bizarre tumor giant cells are also seen. The surrounding stroma shows marked desmoplastic reaction with foci of mild to

moderate lymphoplasmacytic inflammatory infiltrate. Areas of haemorrhage and necrosis are also seen.

Ancillary studies were conducted including immunohistochemistry (IHC). The tumor cells were highlighted by antibodies against Hepar1 and CK7. Fouchet’s stain highlighted the presence of bile pigment in the tumor cells. The morphological and immunohistochemical features are those of metastatic hepatocellular carcinoma.

In view of the above findings, the patient was advised to undergo further investigations including PET-CT scan which revealed presence of FDG avid lesions in the right mandible showing expansile destruction of the bone with soft tissue component. The scan also revealed the presence of FDG avid soft lesion in the right retromolar fossa with the lytic changes in the right mandibular ramus. There were also FDG avid lesions in the liver segments VIII and IVA along with enlarged necrotic periportal, portocaval and paracaval lymph nodes. The USG abdomen revealed an enlarged nodular liver with multiple variably sized, hyperechoic lesions scattered in both lobes, likely metastatic.

Literature Review

Any searchable literature in the PubMed and Google Scholar databases related to the gingival metastases from HCC, published in English language, is included. The search terms used were “gingiva”, “metastasis”, “hepatocellular carcinoma”, “hepatocellular neoplasm”, “hepatic cancer” and “liver cancer”. The references to all such articles have been attached as secondary sources. A total of 35 case have been reported and published between 2000 and 2023 and these were analysed. The clinical and pathological data collected with respect to these cases have been summarized in table 1.

SI No.	Source	Age (in years)	Gender	Pre-existing liver disease	Location in oral cavity	Metastasis besides oral cavity	Oral cavity neoplasm as first sign
1.	Eugenio Maiorano, 2000 [26]	70	Male	None	Antero-inferior alveolar mucosa	None	Yes
2.	Ramrez JR, 2003 [23]	65	Male	Chronic decompensated hepatopathy	Incisor region of upper jaw	None	Yes
3.	Fabio Ramoa Pires, 2004 [13]	60	Male	Chronic Hepatitis B	Anterior mandibular gingiva	Lungs	No
4.	Hsueh-Hsin Huang, 2007 [27]	42	Male	Chronic Hepatitis B	Left maxillary sinus	Lungs	No

5.	Yoshiko Nagao, 2008 [28]	73	Male	Chronic Hepatitis C	Left tonsil	None	No
6.	Ryan Li, 2008 [29]	55	Male	Hepatocellular carcinoma	Right mandible	None	No
7.	Huang, Yung-Cheng, 2009 [30]	60	Male	Not described	Right upper gingiva	Lungs	Yes
8.	Sharada Rai, 2009 [20]	82	Male	Not described	Left mandible	None	Yes
9.	Reinhard E. Friedrich, 2010 [31]	72	Male	Not described	Upper jaw	None	No
10.	Thomas D Daley, 2011 [32]	76	Male	Hepatocellular carcinoma	Left posterior mandible	None	No
11.	Thomas D Daley 2011, [32]	78	Male	Cirrhosis, alcohol related	Right posterior mandible	None	Yes
12.	Tadashi Terada, 2011 [21]	55	Male	None	Left upper gingiva	None	Yes
13.	J Clinton Lasiter, 2011 [33]	76	Male	Chronic Hepatitis C	Left mandible	None	Yes
14.	Seung Yu, 2012 [34]	72	Male	Liver cirrhosis, alcohol related	Right posterior mandibular region	None	Yes
15.	Annie R Wang, 2013 [35]	74	Male	None	Right mandible molars	None	Yes
16.	Michael Pesis, 2014[36]	54	Male	Chronic Hepatitis C	Posterior mandibular area	None	Yes
17.	Marcos Martins Curi, 2015 [37]	58	Male	Chronic Hepatitis C	Left premolar and molar	Lungs	No
18.	SR Misra, 2015 [38]	50	Female	Not described	Left mandible	None	Yes
19.	Li Gong, 2015 [39]	43	Male	Not described	Right upper gingival soft tissue	None	No
20.	RA Alrumaih, 2015 [40]	73	Male	None	Upper gingiva	None	Yes
21.	Jian Lei, 2016 [41]	65	Male	Hepatocellular carcinoma	Right posterior wall of oral cavity	None	No
22.	Min Jung Kwon, 2016 [42]	50	Male	Chronic hepatitis B	Left upper gingiva	None	No
23.	Li-Jun Xue, 2017 [43]	60	Male	Chronic Hepatitis B	Alveolar mucosa of right upper first premolar	Lungs	No
24.	Yeon-Hee, Lee, 2017 [44]	45	Female	Not described	Maxilla	None	No
25.	Yeon-Hee, Lee, 2017 [44]	56	Female	Not described	Mandible	None	No
26.	Yeon-Hee, Lee, 2017 [44]	73	Male	Not described	Mandible	None	No

27.	Yeon-Hee, Lee, 2017 [44]	52	Male	Not described	Mandible	None	No
28.	Marcos Custodio, 2017 [45]	64	Male	Chronic Hepatitis C	Edentulous mandibular ridge	None	Yes
29.	J Adnot, 2018 [46]	56	Male	Cirrhosis, alcohol related	Left upper jaw	Lungs	No
30.	Ching Chang, 2020 [47]	53	Male	Hepatitis B related Cirrhosis with HCC	Left superior gingival line	None	No
31.	S Nadkarni, 2020 [25]	49	Male	Chronic Hepatitis B	Right upper alveolus	None	Yes
32.	Priscilla RP Lyon, 2022 [48]	32	Female	Cirrhosis	Hard palate	None	Yes
33.	Yuan Huang, 2022 [7]	68	Male	Chronic Hepatitis C	Left mandible	None	No
34.	Reesha K, 2023 [49]	60	Male	None	Mucobuccal sulcus in left body of mandible	None	Yes
35.	Reesha K, 2023 [49]	67	Male	Hepatocellular carcinoma	Retromolar region distal to 48	None	No

Table 1

Age and gender

The disease occurred amongst patients aged between 32 and 82 years, with a median age group of 60 years. Males were more commonly affected with male to female ratio of 7.75 (Table 1).

Pre-existing liver disease

Amongst the cases reviewed by literature search, 21 cases showed history of liver disease, of which viral hepatitis accounted for the maximum cases, chronic hepatitis B infection followed by chronic hepatitis C infection. Alcohol related cirrhosis was found to be present in 3 cases while 3 other cases were reported to have nondescript chronic liver disorders predisposing to the malignancy. The remaining cases published did not mention to have had any diagnosed preexisting liver disease (Table 1).

Oral cavity metastasis as the first manifestation

16 cases presented primarily as an oral cavity lesion with no signs and symptoms of the primary tumor. As per the distributions of these lesions described in Table 1, most cases presented as gingival lesion particularly involving the mucosa lining the mandible with associated destruction of the underlying bone in many cases. All patients were symptomatic and the symptoms commonly included rapid growth, bleeding and dislocation of tooth.

Metastasis to sites other than oral cavity

The most frequent metastatic site was lungs (Table 1). The other sites which the HCC metastasize to include lymph nodes, brain and

adrenal glands in the descending order of frequency [7]. As per the Table 1, 14 cases presented with oral cavity metastasis in the absence of metastatic deposits elsewhere.

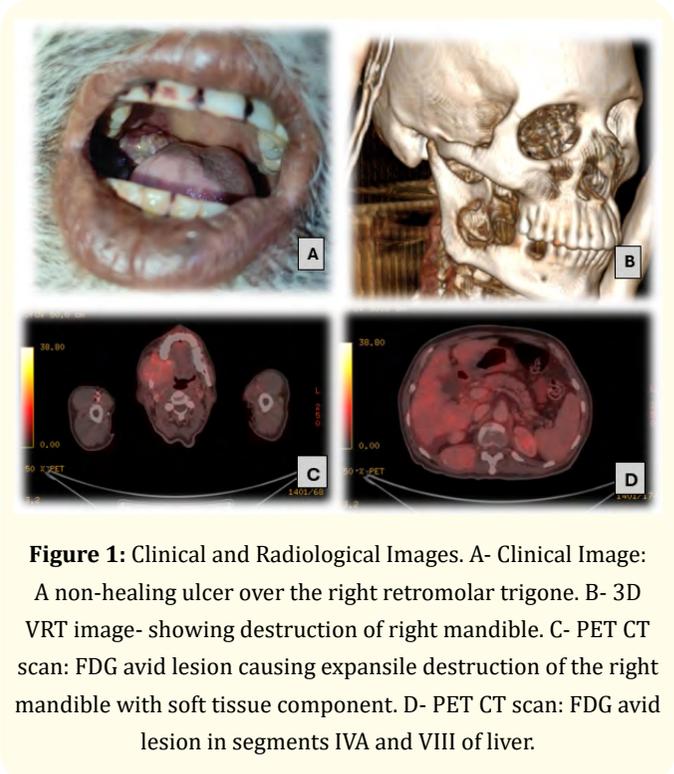


Figure 1: Clinical and Radiological Images. A- Clinical Image: A non-healing ulcer over the right retromolar trigone. B- 3D VRT image- showing destruction of right mandible. C- PET CT scan: FDG avid lesion causing expansile destruction of the right mandible with soft tissue component. D- PET CT scan: FDG avid lesion in segments IVA and VIII of liver.

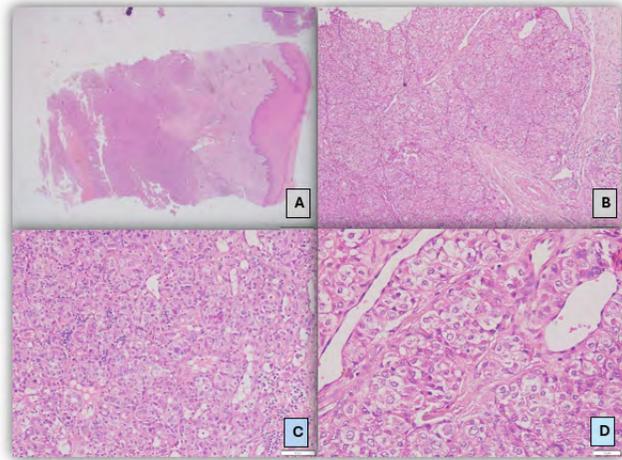


Figure 2: Microphotograph of Hematoxylin and Eosin stained sections of the lesion: A- Low power view showing biopsy lined by stratified squamous epithelium with an invasive tumor in the subepithelium, B and C- (10x fd and 20x fd) Neoplastic cells arranged in macrotrabeculae and small aggregates separated by thin capillary channels. Scattered foci showing lymphoplasmacytic inflammatory infiltrate noted. D- Neoplastic cells are polygonal with round to oval pleomorphic nuclei, vesicular chromatin, prominent nucleoli and eosinophilic to clear cytoplasm.

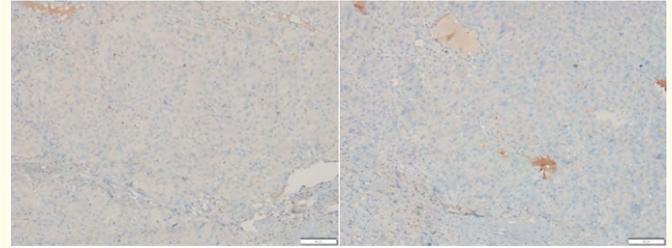
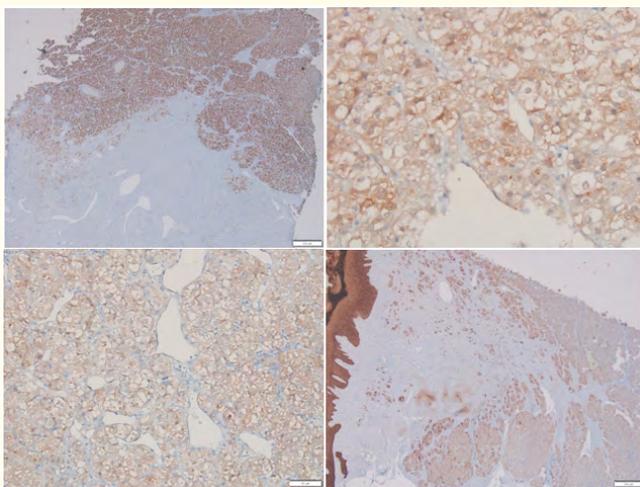


Figure 3: Immunohistochemistry staining of the sections from the lesion: A- HEPPAR1: The neoplastic cells show granular cytoplasmic positivity; B- BSEP: The neoplastic cells show membranous/canalicular positivity; C- Arginase: The neoplastic cells show cytoplasmic positivity; D- CK: The neoplastic cells show cytoplasmic positivity. E- Synaptophysin: The neoplastic cells are negative. F- Melan-A: The neoplastic cells are negative.

Discussion and Conclusion

Hepatocellular carcinoma is the most common primary liver malignancy and is usually encountered in the setting of chronic liver disease and cirrhosis. It is the sixth most common cancer and fourth leading cause of cancer related death worldwide, especially prevalent amongst the populations of East Asian countries [8]. In India, the age adjusted incidence rate of HCC for men range from 0.9 to 7.5 and for women from 0.2 to 2.2 with the highest being reported from Sikkim and Mizoram [9]. Males are commonly affected with the male: female ratio for HCC being 4:1 in India and the age of presentation varying between 40 and 70 years [9]. Clinically, patients can present with signs and symptoms related to the tumor or the underlying chronic liver disease. Multifocal HCCs are common in cirrhosis and may represent either multiple HCCs of multicentric origin or intrahepatic metastasis from a primary HCC [10]. Extrahepatic spread is common in advanced stage disease and include spread to lungs, lymph nodes, bones and adrenal glands [11].

Metastatic neoplasm of the oral cavity generally indicate a disseminated disease with a poor survival rate and is rare accounting for about 1% of all oral malignant neoplasms [4,6]. It is found that about 5% of all malignant tumors involve the oral cavity by way of metastasis [12]. The common oral sites of metastasis include the jaws with the predilection for the mandible followed by

the gingiva [13-15]. The frequently affected mandibular locations include the posterior region, the angle and the ramus. Studies have found that the liver is the most common primary site and gingiva being the most commonly affected metastatic site in such patients [4,5].

The probable pathophysiological mechanism of the metastasis of the HCC to the oral cavity still remains elusive. HCC metastasises through both hematogenous and lymphatic pathways [13,14]. The hematogenous path of oral metastasis by invasion of hepatic artery or portal venous branches is believed to be the preferred route [6,7,16]. In cases devoid of pulmonary metastasis, HCC metastasis to the oral cavity is probably via the valveless vertebral venous plexus, Batson's plexus, which bypasses the filtration through the pulmonary, inferior vena caval and portal venous circulations. Altered hemodynamics with esophageal varices as a consequence of liver cirrhosis may be yet another potential pathway of oral metastasis, especially in HCC patients with liver cirrhosis [7].

Analysis of the cases gleaned from the various existing literature provided us with new insights into the clinical and pathological characteristics of the oral metastasis in HCC. It has been found that males are more commonly affected than females probably hinting at the generally poorer oral health habits amongst the males vis a vis the females in the form of smoking and drinking [7,17]. The gingivitis which is usually associated with such poor oral habits, further favors the oral metastasis as the role of chronic inflammation has already been documented in various stages of tumorigenesis including cellular transformation, survival, proliferation, invasion, angiogenesis and metastasis [18,19].

The establishment of diagnosis of metastatic HCC in the oral cavity is difficult in patients in whom the primary tumor is yet to be recognized as in our case. Analysis of previously reported cases through literature research has revealed that such oral tumor was noted prior to the primary hepatic malignancy in about 66% of the HCC cases [7,20-22]. Further, there is the risk of misdiagnosis or even missed diagnosis and could be due to many factors. Firstly, the incidence of oral metastasis is low and the non-specific manifestation result in additional challenge in the diagnosis. Secondly, the deceptive appearance of the oral metastatic lesions. There have been documented instances where such oral metastatic lesions have been misdiagnosed as pyogenic granuloma [23,24].

Oral metastasis usually occur in the advanced stages of HCC in the majority of the cases and the interval between the diagnosis and death is usually short lived reflecting the extremely poor prognosis in such patients as many of these patients already harbour widespread metastatic disease upon further evaluation [6,7,25]. It is therefore important for the clinicians to be wary of oral cavity metastasis in patients presenting with persistent non-healing oral ulcerative lesions associated with systemic symptoms as in our case.

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