

Case Report

Mandibular Metastasis as the First Manifestation of Hepatocellular Carcinoma: A Case Report

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Keywords

Metastatic malignancies · Hepatocellular carcinoma · Immunohistochemical markers · Diagnostic challenge

Abstract

Metastatic malignancies of the oral cavity are rare lesions, accounting for only 1–4% of all oral malignancies, and can occur in the jaw bones, the oral soft tissues, or even both. Although hepatocellular carcinoma is the most common primary hepatic tumor, no more than 1% of the cases show oral involvement. When metastatic tumor involves the oral cavity, the most frequent site is the posterior angle of the mandible. Histologically, hence, immunohistochemical markers are used for diagnosis. Glypican-3 and HepPar1 are the markers that can be used to confirm the microscopic diagnosis of HCC. Very rarely, hepatocellular carcinoma (HCC) metastasizes to the oral cavity, and such cases have a poor prognosis due to delay in diagnosis. We present a 74-year-old male with a metastasis of HCC in the left mandibular body as the first manifestation. Histologic examination confirmed metastatic hepatocellular carcinoma in the oral mucosa with immunohistochemical (IHC) markers. A review of pertinent literature was performed. Given the rarity of the disease, treatment principles are based mainly on retrospective series and case reports. We report an exceptionally unusual presentation with few cases (<70) reported in the literature, thus representing a diagnostic challenge.

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Introduction

Hepatocellular carcinoma (HCC) is a primary tumor of the liver (comprising 75–85% of cases) and is the third leading cause of cancer death worldwide in 2020, with approximately 906,000 new cases and 830,000 deaths (8.3%) [1]. Of the primary tumor types that do metastasize to the facial area (oral and maxillofacial region), those of the thyroid, lung, and kidney are the most frequent, and HCC is <1% [2–4].

HCC frequently metastasizes to the lungs (34–70%), followed by the abdominal lymph nodes (16–45%), bones (6%), and brain. However, metastasis to the maxillofacial area is rare; when it occurs, HCC usually affects the mandible instead of the maxilla or temporal region [5–8].

HCC metastatic to the oral cavity and jaws is uncommon, with <70 cases being reported in the literature since its first description by Dick et al. [8] in 1957. This article presents an extremely rare case of metastatic HCC that involved the mandible and was properly diagnosed using immunohistochemical markers.

Case Report

A 74-year-old male with a previous medical history of alcohol abuse was referred for an evaluation. He had a swelling on the left side of his face that rapidly increased in size and hypoaesthesia in the distribution territory of the mental nerve. In addition, he also developed a growth on the gum, which was also rapidly increasing in size, causing a gradual reduction in the opening of the mouth and the loss of teeth. Since the swellings and growths were sudden in onset, irregular in shape, rapidly increasing in size, and destroying the surrounding structures, a provisional diagnosis of malignant growth was made.

Dental panoramic radiographs were obtained first as an initial examination. Suspicious bone lesion of the mandible wall was observed in the radiograph. Orthopantomography showed generalized severe bone loss; undermining at the level of the left mandibular body and isodense image with defined limits and irregular edges; conditioning a localized permeative pattern in the lower molar area left that extends from the crestal area of the residual ridge to the roof of the dental canal, generating erosion of the same; and tomographic signs suggestive of bone tumor lesion (Fig. 1).

A few days later, fine-needle aspiration biopsy (FNAB) with an approach from the facial lesion was performed for further diagnosis. This procedure showed atypical clusters of cells, which turned out to be hepatocytes owing to their sinusoid-like thin blood vessels with abundant cytoplasm, characteristic findings of liver cells (Fig. 2).

Immunohistochemistry revealed positive staining for human hepatocyte paraffin (HepPar1) antibody, glypican-3, arginase, alpha-fetoprotein, and cytokeratin-C. These findings were consistent with metastatic HCC (Fig. 2). CD34 was positive but it is not a marker for HCC.

The patient was transferred to oncology department for further evaluation and treatment. His laboratory studies without alteration in liver function tests or hepatitis virus (A, B, and C) were ruled out.

Cranial, neck, thorax, and abdomen computed tomography with contrast revealed a hepatic lesion with arterial enhancement and late venous lavage, as well as bone metastatic lesions at the level of the 2nd right rib, 1st left rib, and sixth and twelfth thoracic vertebrae (Fig. 3). Considerable growth of the oral lesion was observed in the weeks after biopsy. He started lenvatinib; however, he completed a month of treatment, because he presented with systemic arterial hypertension, asthenia, anorexia, diarrhea, and weight loss. The patient died within 10 months.

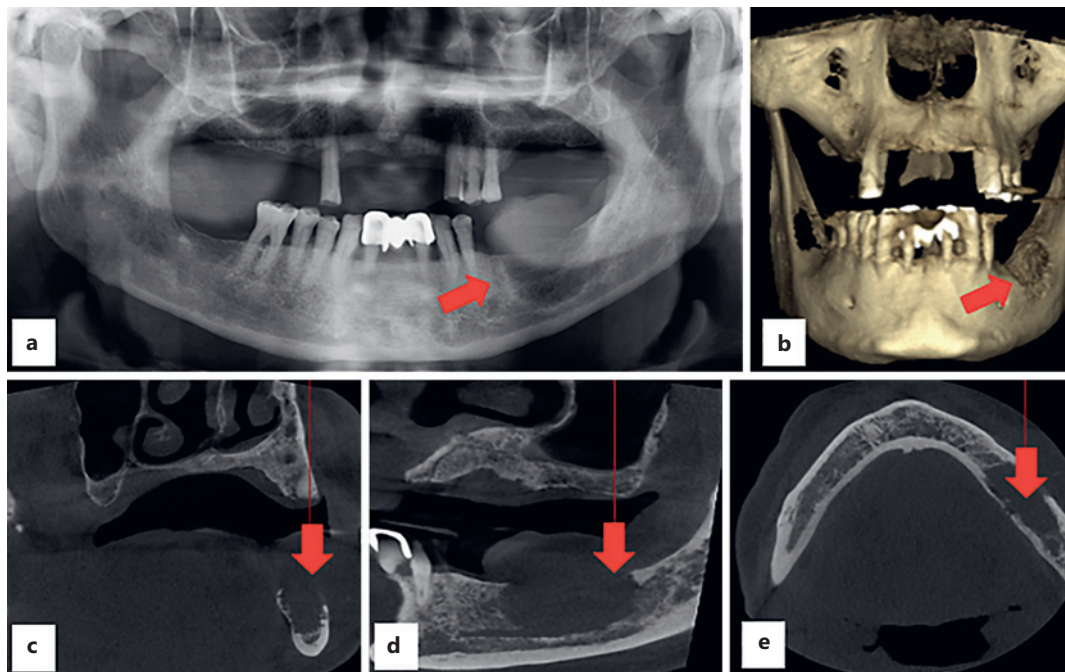


Fig. 1. Orthopantomography showed generalized severe bone loss (**a, b**); undermining at the level of the left mandibular body and isodense image with defined limits and irregular edges; and conditioning a localized permeative pattern in the lower molar area left that extends from the crestal area of the residual ridge to the roof of the dental canal, generating erosion of the same (**c–e**).

Discussion

Hepatocellular carcinoma (HCC) is the most common hepatic malignancy, and about one-third of HCC metastasize to extrahepatic sites like the lungs, regional lymph nodes, and bone (vertebrae, ribs, and long bones). Metastatic HCC has a male predilection (especially in patients over the age of 60 years) that resembles the characteristics of primary HCC [1, 2].

Of the primary tumor types that do metastasize to the facial area (oral and maxillofacial region), the most common sites are the breast (21.8%), followed by the lung (12.6%), adrenal (8.7%), kidney (7.9%), bone (7.4%), colorectum (6.6%), prostate (5.6%), and HCC <1%. The primary site differed between genders: for women, it was the breast (42%), followed by the adrenal (8.5%), colorectum (8%), female genital organs (7.5%), and thyroid (6%); for men, it was the lung (22.3%), followed by the prostate (12%), kidney (10.3%), bone (9.2%), and adrenal (9.2%).

Histologic types most frequent are adenocarcinomas of the breast (19%), colorectum (6%), and prostate (5.6%); adrenal neuroblastoma (8.7%); renal cell carcinoma (5.8%); and squamous cell carcinoma of the lung (8.9%) [2–11].

Although its distant metastasis to the orofacial region is uncommon, the mandible or the gingiva of the mandible is the most frequent target; most mandibular lesions are located in the posterior mandible (48%), maxillary gingiva (14%), mandible body (11%), mandible (8%), and mandibular gingiva (6%) [5–12]. In the oral cavity, metastases are most common in the mandible (80–85%), followed by the maxilla, but both are involved in 5% of cases. In this case report, the affectionation is located in the mandible, which coincides with the aforementioned percentages.

In different publications, it has been reported that HCC metastatic to the oral cavity has more predilection to men than women (46:4 male-to-female ratio); 90% of the patients were

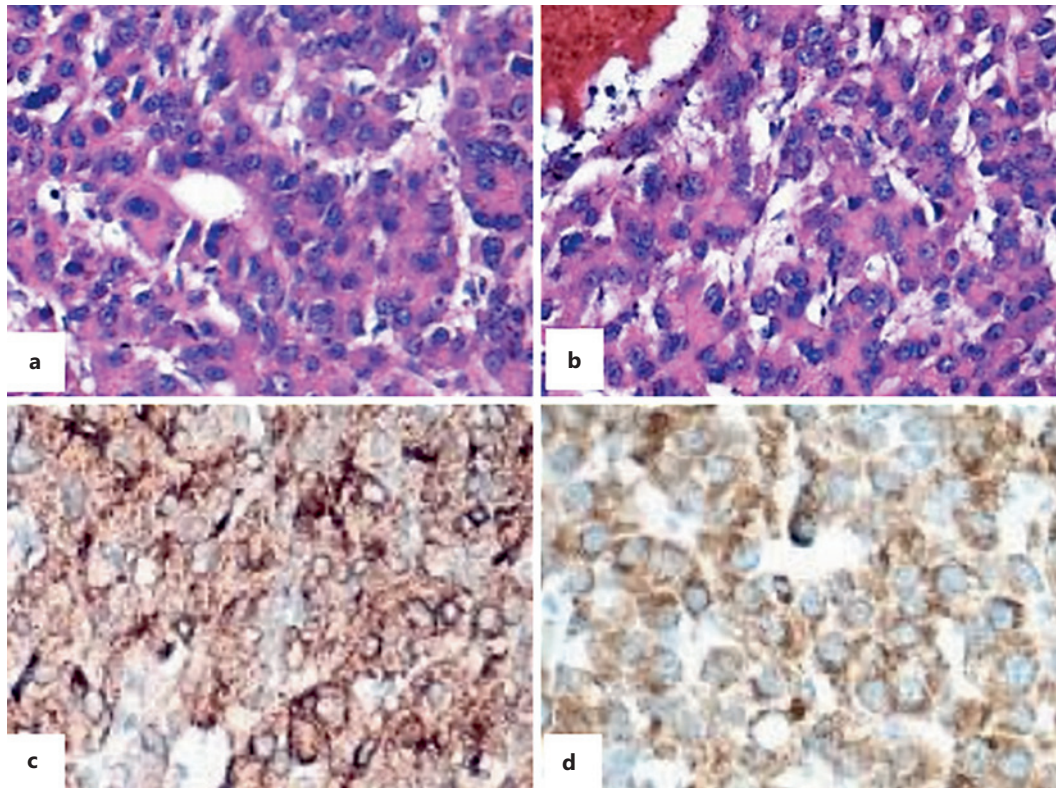


Fig. 2. The microscopic study showed atypical clusters of cells, which turned out to be hepatocytes owing to their sinusoid-like thin blood vessels with abundant cytoplasm, characteristic findings of liver cells (**a, b**). Immunohistochemistry revealed positive staining for human hepatocyte paraffin (HepPar1) antibody and glypican-3 diffuse positive (**c, d**).

older than 50 years of age; most cases involved the mandible and the maxilla, and minor cases in the tonsil and the zygomatic bone [2, 5, 12–14].

Clinical Features

The clinical manifestations of the disease – swelling and hypoesthesia in the distribution territory of the mental nerve – collected in our patient coincide with those reported in other cases. The presence of toothache is more unusual [12, 15].

Hepatocellular carcinoma clinically appears as a tumor mass in the oral cavity that may mimic an odontogenic tumor when it occurs as a swelling and oral squamous cell carcinoma when associated with surface ulceration [2, 16]. The most frequently affected mandibular intraosseous locations are the posterior region, the angle, and the ramus, a pattern attributed to the presence of hematopoietic tissue in these areas. The lesion size and degree of bone destruction suggest that this metastatic deposit may have been centered in the gingiva [2, 5, 17].

Radiographic Features

On radiographs, HCC metastatic to the jaw – or to the gingiva with intraosseous extension – typically has a destructive, radiolucent appearance with ill-defined borders lacking sclerotic

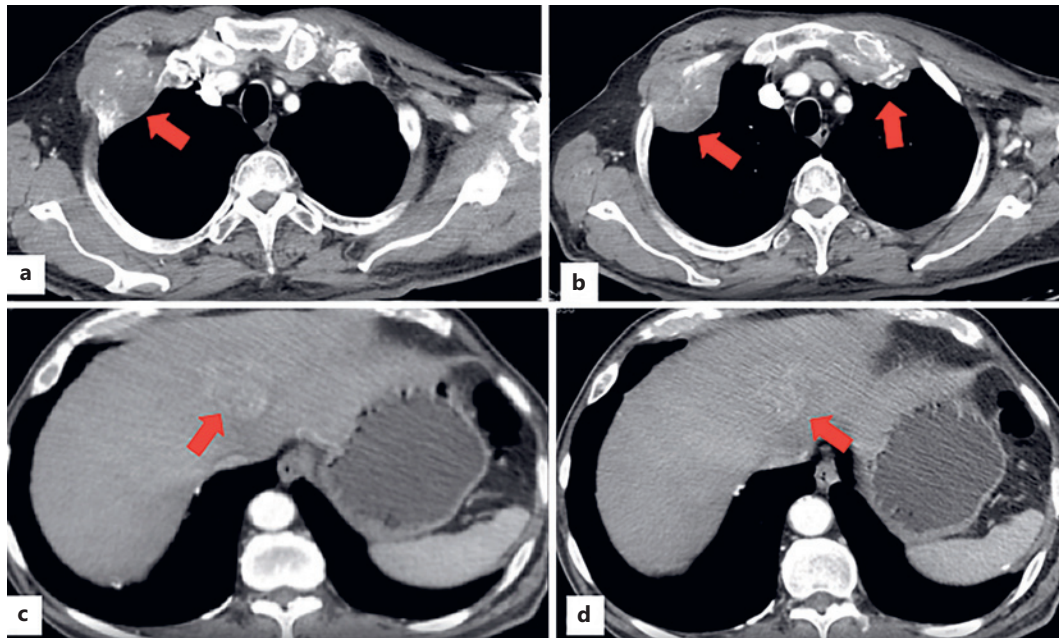


Fig. 3. Thorax and abdomen computed tomography with contrast revealed bone metastatic lesions at the level of the 2nd right rib, 1st left rib, and sixth and twelfth thoracic vertebrae (**a, b**) and a hepatic lesion with arterial enhancement and late venous washout (**c, d**).

limits, having an appearance like that expected in a malignant lesion [18]. Such diagnostic imaging findings serve to support the clinical diagnosis of a malignant lesion, aiding in distinguishing this condition from more common reactive lesions such as pyogenic granulomas [19]. The jaw lesions may be the initial manifestation of the metastatic disease in the majority of cases, thereby mimicking an odontogenic lesion, leading to a faulty diagnosis and subsequent delay in management [20].

Histopathological Factors

The establishment of the diagnosis of metastatic HCC in the oral region may be difficult, particularly when the primary tumor has not yet been identified. Severe postoperative hemorrhage during or after incisional biopsy has been reported due to the vascularity of this lesion, so it is recommended that only FNAB should be attempted as a surgical diagnostic procedure when HCC is strongly suspected [21].

Findings regarding hematoxylin and eosin-stained sections may suggest a hepatic origin, but immunohistochemical analysis is often required to aid in distinguishing metastatic HCC from other oral metastatic tumors. Histologically, the lesion may comprise strands or duct-like patterns composed of cells resembling hepatocytes in a highly vascular stroma. It can mimic adenocarcinoma with a pseudo-glandular pattern or may be poorly differentiated, causing difficulty in detecting the cells of origin [22].

Hence, immunohistochemical (IHC) markers are used for diagnosis. Glypican-3 and HepPar1 are the markers that can be used to confirm the microscopic diagnosis of HCC [13, 19, 22–24]. In the present case, a malignant lesion in the mandible bone was confirmed as a rare case of metastatic HCC from a primary hepatic lesion based on the differential diagnosis made using computed tomography (CT) and FNAB along with immunohistochemistry. CD34 is

positive for vessels in HCC but negative for sinusoids in a non-neoplastic liver. CD34 is, however, a marker of endothelial cells in vessels other than the hepatic sinusoid. In this case, CD34 was positive but is not a marker for HCC.

Treatment Options

The common staging system of HCC used to determine treatment options and prognoses classifies patients based on their tumor stage, performance status, liver function, and cancer-related symptoms. The present patient presented with advanced-stage HCC and distant metastases, the Barcelona Clinic Liver Cancer (BCLC) C, Eastern Cooperative Oncology Group (ECOG) 2, Child-Pugh B7 [2, 5, 11]. Treatment for HCC metastasis is typically palliative, and radiation therapy has been shown to be effective palliation for bony metastasis in patients with HCC [21].

In addition, targeted drugs for advanced HCC are also the standard treatment; sorafenib, lenvatinib, and apatinib are commonly used antiangiogenic agents, although the former has shown a lower response [14, 25]. Currently, the combination of atezolizumab (anti-PDL1 antibody) and bevacizumab (anti-VEGF antibody) is the first regimen that has been shown to improve overall survival compared to sorafenib in patients with metastatic hepatocellular carcinoma. However, due to the low incidence of metastasis to the mandible, there are no reports or experiences of the results with said treatment [25, 26].

Prognosis

Patients with HCC have a relatively good survival rate, with a 5-year cumulative survival rate of more than 50% when surgical treatment is performed. However, when there is bone metastasis, the survival rate decreases sharply; 1-year survival is 15–20%, and 2-year survival is around 4% [26].

Conclusion

Mandibular metastasis as the first manifestation of hepatocellular carcinoma is an exceptionally unusual presentation. We present a 74-year-old male with poor tolerance to lenvatinib and poor prognosis due to a late diagnosis and a rare metastatic presentation. Only fewer than 70 cases have been reported in the English literature. The CARE Checklist has been completed by the authors for this case report, attached in online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000529182).

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Statement of Ethics

This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines. Written informed consent was obtained from the patient's next of kin for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

The author (Ricardo Fernández-Ferreira) contributed to the conception of the case, analysis and critical revision of the content, as well as the final approval of the version to be published. Roberto Savage-Leyva, Carlos-Emmanuel-Florencio Monroy-Godínez, Germán-Raymundo Hernández-Ramírez, Jose-Manuel Torres-Zazueta, Carlos Zamorano-Vazquez, Ernesto Ceron-Ibarra, Luis-Fernando Durán-Guerrero, and Maria-del-Rocio Carranza-Sevilla contributed to the critical revision of the content, as well as the final approval of the version to be published. Rita Dorantes-Heredia carried out an exhaustive review of the histopathological characteristics of cancer and analysis of the article. We all agree to be responsible for all aspects of the job to ensure that questions related to the accuracy or completeness of any part of the job are properly investigated and resolved.

Data Availability Statement

Data supporting the findings of this study are openly available in the clinical file of the southern Medical Hospital, with registration number 861866. Additional inquiries can be directed to the corresponding author.

References

- 1 Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021 May;71(3):209–49.
- 2 Lim SY, Kim SA, Ahn SG, Kim HK, Kim SG, Hwang HK, et al. Metastatic tumours to the jaws and oral soft tissues: a retrospective analysis of 41 Korean patients. *Int J Oral Maxillofac Surg*. 2006;35(5):412–5.
- 3 Shen ML, Kang J, Wen YL, Ying WM, Yi J, Hua CG, et al. Metastatic tumors to the oral and maxillofacial region: a retrospective study of 19 cases in West China and review of the Chinese and English literature. *J Oral Maxillofac Surg*. 2009;67(4):718–37.
- 4 Lee YH, Lee JI. Metastatic carcinoma of the oral region: an analysis of 21 cases. *Med Oral Patol Oral Cir Bucal*. 2017 May 1;22(3):e359–65.
- 5 Pires FR, Sagarra R, Correa MEP, Pereira CM, Vargas PA, Lopes MA. Oral metastasis of a hepatocellular carcinoma. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2004;97(3):359–68.
- 6 Kim JS, Kim JD. Metastatic hepatocellular carcinoma on the mandible: a case report. *Korean J Oral Maxillofac Radiol*. 2005;35:215–9.
- 7 Cho J. Metastatic hepatocellular carcinoma in the maxilla and temporal bone: a rare case report. *J Korean Assoc Oral Maxillofac Surg*. 2021;47(3):224–8.
- 8 Dick A, Mead SG, Mensh M, Schatten WE. Primary hepatoma with metastasis to the mandible. *Am J Surg*. 1957; 94(6):846–50.
- 9 Fujihara H, Chikazu D, Saijo H, Suenaga H, Mori Y, Iino M, et al. Metastasis of hepatocellular carcinoma into the mandible with radiographic findings mimicking a radicular cyst: a case report. *J Endod*. 2010;36(9):1593–6.
- 10 Choi SJ, Kim YS, Kim NR, Jeong SW, Lee SH, Jeong JS, et al. A case of hepatocellular carcinoma with metastasis to gingival mucosa. *Korean J Hepatol*. 2002;8(4):495–9.

- 11 Grandhi MS, Kim AK, Ronnekleiv-Kelly SM, Kamel IR, Ghasebeh MA, Pawlik TM. Hepatocellular carcinoma: from diagnosis to treatment. *Surg Oncol*. 2016;25(2):74–85.
- 12 Chin A, Liang TS, Borislow AJ. Initial presentation of hepatocellular carcinoma as a mandibular mass: case report and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1998 Oct;86(4):457–60.
- 13 Tomanovic N, Krstic A, Brasanac D, Dimitrijevic M, Terzic T, Boricic I. Zygomatic bone metastasis as an initial presentation of hepatocellular carcinoma. *Arch Iran Med*. 2013;16(11):675–8.
- 14 Lei Q, Chen H, Zheng H, Deng F, Wang F, Li J, et al. Zygomatic bone metastasis from hepatocellular carcinoma and the therapeutic efficacy of apatinib: a case report and literature review. *Medicine*. 2019;98(18):e14595.
- 15 Takinami S, Yahata H, Kanoshima A, Yamasaki M, Funaoka K, Nakamura E, et al. Hepatocellular carcinoma metastatic to the mandible. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1995;79(5):649–54.
- 16 Llanes F, Sanz-Ortega J, Suarez B, Sanz-Esponera J. Hepatocellular carcinomas diagnosed following metastasis to the oral cavity. Report of 2 cases. *J Periodontol*. 1996;67(7):717–9.
- 17 Ashar A, Khateery SM, Kovacs A. Mandibular metastatic hepatocellular carcinoma: a case involving severe postbiopsy hemorrhage. *J Oral Maxillofac Surg*. 1997;55(6):547–52.
- 18 Niedzielska I, Langowska-Adamczyk H, Pajak J, Kajor M, Niedzielski Z, Goka D. Mandible metastasis of hepatocellular carcinoma. *Wiad Lekj*. 2004;57:392–4.
- 19 Ramón Ramirez J, Seoane J, Montero J, Esparza Gómez GC, Cerero R. Isolated gingival metastasis from hepatocellular carcinoma mimicking a pyogenic granuloma. *J Clin Periodontol*. 2003;30(5):926–9.
- 20 Magliocca KR, Kuklani R, Dooreck BS. Occult hepatocellular carcinoma metastatic to the mandible. *Clin Gastroenterol Hepatol*. 2009;7(4):A22, A22.e1.
- 21 Yu S, Estess A, Harris W, Dillon J. A rare occurrence of hepatocellular carcinoma metastasis to the mandible: report of a case and review of the literature. *J Oral Maxillofac Surg*. 2012;70(5):1219–23.
- 22 Daley TD, Minett CP, Driman DK, Darling MR. Oral metastatic hepatocellular carcinoma: a changing demographic in Europe and North America. Immunohistochemical advances in the microscopic diagnosis. *Oral Oncol*. 2011;47(1):62–7.
- 23 Greenstein A, Witherspoon R, Iqbal F, Coleman H. Hepatocellular carcinoma metastasis to the maxilla: a rare case. *Aust Dent J*. 2013;58(3):373–5.
- 24 Lau SK, Prakash S, Geller SA, Alsabeh R. Comparative immunohistochemical profile of hepatocellular carcinoma, cholangiocarcinoma, and metastatic adenocarcinoma. *Hum Pathol*. 2002;33(12):1175–81.
- 25 Koulouris A, Tsagkaris C, Spyrou V, Pappa E, Troullinou A, Nikolaou M. Hepatocellular carcinoma: an overview of the changing landscape of treatment options. *J Hepatocell Carcinoma*. 2021;8:387–401.
- 26 Llovet JM, Kelley RK, Villanueva A, Singal AG, Pikarsky E, Roayaie S, et al. Hepatocellular carcinoma. *Nat Rev Dis Primers*. 2021;7(1):6.