
SHORT COMMUNICATION

Mucosal and Subcutaneous Metastasis from Hepatocellular Carcinoma: A Case Report

Su Pin Choo, *BMedSci, BMBS, MRCP, FAMS (Med Oncology)*, Nagavalli Somasundaram, *MBBS, MRCP, MMed*

Division of Medical Oncology, National Cancer Centre Singapore, Singapore

ABSTRACT

Hepatocellular Carcinoma (HCC) is rising in incidence worldwide, especially in areas endemic for chronic viral hepatitis. Distant metastases are common especially in lungs and bones. Subcutaneous or mucosal metastases, however, are rare. We report a case of both mucosal and subcutaneous metastases in the same patient.

Keywords: Hepatocellular carcinoma, Mucosal, Cutaneous, Metastases

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer in men and the ninth in women¹ worldwide and has an increased incidence in areas endemic for chronic viral hepatitis. The majority of HCCs present at an advanced stage and common sites of extra-hepatic metastases include the lungs, intra-abdominal lymph nodes and bones. We report a case of gingival and subcutaneous metastasis from HCC.

CASE REPORT

The patient involved was a 48-year-old Chinese male who lived in Batam, Indonesia. He was a known hepatitis B carrier but did not have any evidence of liver cirrhosis. He was first diagnosed with HCC in 2010 in a private centre, when he presented with abdominal pain and was found to have an 8-cm tumour in the right lobe of the liver with an elevated alpha-fetoprotein (AFP) level of >9000 µg/L. He underwent transarterial chemo-embolisation followed by right hepatectomy in 2010. Histology confirmed the presence of a 9-cm moderately differentiated HCC with an adjacent 2.5-cm tumour. The presence of lymphovascular invasion was also noted. The surgical margins were free of tumour involvement. In February 2012, he was found to have a new left lung nodule on surveillance imaging; this was proven to be metastatic HCC, on biopsy.

He was started on thalidomide and capecitabine as he could not afford sorafenib due to personal financial constraints². After two months, the AFP level decreased and there was complete response of the lung metastasis. However, new subcutaneous nodules were discovered over his right shoulder and in the gingiva. These lesions were excised and proven to be HCC metastases. In view of disease progression, thalidomide and capecitabine were discontinued. He was not on any systemic treatment until February 2013, when he developed multiple lung nodules and lymphadenopathy. It was at this stage that he first presented to us and was offered a clinical trial drug in view of good functional status and organ function. He was noted to have a subcentimetre nodule under the chin prior to initiation of the clinical trial. He continued on the trial till September 2013, when he was found to have progression of disease in the liver and skin.

Hepatocellular carcinoma is the second most common cause of death from cancer worldwide¹. It often occurs in the background of cirrhosis, commonly caused by hepatitis B or C infection, or alcohol consumption. Therefore, HCC is more common in Asian countries where hepatitis B and C infections are endemic. Hepatocellular carcinoma is the fourth most common cause of cancer in

Singaporean men and the third cause of cancer-related deaths in men³. Extra-hepatic metastases in HCC occur in the advanced stages in about 30–50% of patients. The most common sites of extrahepatic metastasis are the lungs, followed by abdominal lymph nodes and bones⁴.

Head and neck or subcutaneous metastases from HCC are uncommon. Oral cavity or gingival metastases account for about 1% of malignant oral neoplasms⁵. Cutaneous or subcutaneous metastases that are not related to biopsy needle tracks are rare. To date, there are over 60 case reports in the literature of the presence of isolated metastasis involving tongue, gingiva, parotid gland, mandible and zygoma⁶. Young *et al.* reported a case of metastatic HCC presenting as a parotid swelling which was eventually proven to be metastatic HCC⁷. A retrospective analysis of autopsy reports of 31 patients with HCC revealed one case of skin and one of oral cavity metastasis⁴; these were the first manifestation of HCC in the individual patients. Isolated cases of cutaneous metastasis have also been reported, less commonly than oral cavity metastasis. Cutaneous metastases are often mistaken for pyogenic granuloma or haemangioma^{4,7–9}. However, in these case reports, multiple uncommon sites have not been reported.

Hepatocellular carcinoma predominantly spreads via a haematogenous route. As such in most of the reported cases, including this case, patients often present with lung metastases prior to developing metastases in other unusual areas. Other modes of dissemination include portal venous and lymphatic spread. In patients without lung metastases, it is hypothesised that HCC spreads via the valveless vertebral venous plexus (Batson's plexus) allowing tumours in the lower part of the body to bypass the lungs to access the oral mucosa^{6,11}; this postulation needs further investigation. As for non-iatrogenic cutaneous metastases, there does not seem to be a clear predisposing factor that contributes to the increased incidence.

Racial predilection seems to exist in development of metastases to skin and oral cavity. Almost 60% of such cases are reported in Asians¹², although this may be a reflection of the increased incidence of HCC in the Asian population. Regarding oral cavity metastases, males appear to have an increased incidence, with a male: female ratio of 9:1¹². With advancements in the treatment of HCC and patients

having prolonged survival, more such cases may come to light.

One common presentation or complication that has been highlighted in reports of metastatic HCC in the oral cavity is bleeding^{13,14}. Metastatic HCC has a higher tendency to bleed, due to underlying coagulopathy and vascularity of the tumour itself. Bleeding in mucosal areas may potentially be difficult to control¹⁰. While systemic therapy should be the mainstay of care in metastatic disease, these local lesions can be palliated with either surgical resection or radiotherapy. Radiation treatment was found to have satisfactory results with low toxicity profile in patients with subcutaneous metastasis¹⁵. Huang *et al.* reported 83.3% partial response rate with radiotherapy to subcutaneous metastases from HCC¹⁶. Since expected survival with metastatic HCC is measured in months, a low-risk and effective procedure is required for good palliation of such mucosal or subcutaneous lesions. Whether HCC patients with subcutaneous and mucosal metastases have a different biology and outcome as compared to patients with other visceral metastases is not known. Metastatic HCC should be a consideration in patients with a history of HCC or risk factors for the disease and present with unexplained subcutaneous or mucosal lesions.

REFERENCES

1. Ferlay J, Soerjomataram I, Ervik M, Forman D, Bray F, Dikshit R, et al. GLOBOCAN 2012: estimated cancer incidence, mortality and prevalence worldwide in 2012 [Internet]. Lyon: International Agency for Research on Cancer; 2013 Dec 12 [updated 2014 Jan 9; cited 2014 Jul 15]. Available from: <http://globocan.iarc.fr>.
2. Ang SF, Tan SH, Toh HC, Poon DY, Ong SY, Foo KF, et al. Activity of thalidomide and capecitabine in patients with advanced hepatocellular carcinoma. *Am J Clin Oncol* 2012;35(3):222–7 doi: 10.1097/COC.0b013e31820dbf56.
3. National Registry of Diseases Office. Singapore cancer registry [Internet]. Singapore: Ministry of Health, National Registry of Diseases Office; 2008 [updated 2014 Jun 30; cited 2014 Jul 15]. Available from: <https://www.nrdo.gov.sg/page.aspx?id=76>.
4. Terada T, Masuo H. Unusual extrahepatic metastatic sites from hepatocellular carcinoma. *Int J Clin Exp Pathol* 2013;6(5):816–20.
5. Kuo I-J, Chen P-R, Hsu Y-H. Gingival metastasis of primary hepatocellular carcinoma — case report. *Tzu Chi Med J* 2006;18(2):145–7.
6. Pires FR, Sagarra R, Correa ME, 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 doi: 10.1016/j.tripleo.2003.09.018.
7. Yu YD, Kim DS, Jung SW, Lee JH, Chae YS, Suh SO. Metastatic hepatocellular carcinoma to the parotid gland: case report and review of the literature. *Int J Surg Case Rep* 2013;4(1):76–80 doi: 10.1016/j.ijscr.2012.08.018.

8. Rueben S, Owen D, Lee P, Weiss A. Hepatocellular carcinoma with cutaneous metastases. *Can J Gastroenterol* 2009;23(1):23–5.
9. de Agustin P, Conde E, Alberti N, Perez-Barrios A, Lopez-Rios F. Cutaneous metastasis of occult hepatocellular carcinoma: a case report. *Acta Cytol* 2007;51(2):214–6 doi: 10.1159/000325720.
10. Al-Mashat FM. Hepatocellular carcinoma with cutaneous metastasis. *Saudi Med J* 2004;25(3):370–2.
11. Appenzeller J, Weitzner S, Long GW. Hepatocellular carcinoma metastatic to the mandible: report of case and review of literature. *J Oral Surg* 1971;29(9):668–71.
12. Batson OV. The function of the vertebral veins and their role in the spread of metastases. 1940. *Clin Orthop Relat Res* 1995;(312):4–9.
13. Ramon Ramirez J, Seoane J, Montero J, Esparza Gomez GC, Cerero R. Isolated gingival metastasis from hepatocellular carcinoma mimicking a pyogenic granuloma. *J Clin Periodontol* 2003;30(10):926–9 doi: 10.1034/j.1600-051X.2003.00391.x.
14. Junquera L, Rodríguez-Recio C, Torre A, Sanchez-Mayoral J, Fresno MF. Hepatocellular carcinoma metastatic to the mandible: a case involving severe haemorrhage *Med Oral* 2004;9(4):345–9.
15. Walter CM, Kirby EJ, Vasconez HC, Rinker BD. Hepatocellular carcinoma metastatic to the scalp. *J Craniofac Surg* 2011;22(2):720–1 doi: 10.1097/SCS.0b013e3182077843.
16. Huang YJ, Tung WC, Hsu HC, Wang CY, Huang EY, Fang FM. Radiation therapy to non-iatrogenic subcutaneous metastasis in hepatocellular carcinoma: results of case series. *Br J Radiol* 2008;81(962):143–50 doi: 10.1259/bjr/81811976.