CASE REPORT

Two rare forms of hepatocellular carcinoma metastases

Nicole M Gentile,¹ Kyle M McKenzie,¹ Ryan T Hurt²

¹Department of Medicine, Mayo Clinic, Rochester, Minnesota, USA
²Department of General Internal Medicine, Mayo Clinic, Rochester, Minnesota, USA

Correspondence to
 Dr Ryan T Hurt,
 hurt.ryan@mayo.edu

SUMMARY

An 80-year-old man with known metastatic hepatocellular carcinoma, not on current treatment, was presented with bleeding gingival and penile masses. Bleeding from both sites was able to be controlled with local treatment and subsequent discontinuation of his clopidogrel. The gingival mass was biopsied and was found consistent with metastatic hepatocellular carcinoma. Owing to the concern of recurrent bleeding, the penile mass was not biopsied. Given the significant progression of his disease, the patient was discharged to hospice care.

BACKGROUND

This case report is important because we demonstrate a unique presentation of hepatocellular carcinoma (HCC) with metastases to the gingiva and likely the penis. A review of the literature demonstrates the rarity of this presentation. We want to emphasise that in patients with a new gingival or penile lesion that intermittently bleeds, one should consider HCC in the differential.

CASE PRESENTATION

An 80-year-old man, with known metastatic HCC diagnosed 2 years prior to presentation and ischaemic stroke 5 years prior, presented with a bleeding penile mass and an enlarging mandibular mass. At the time of admission, he was not receiving any treatment for his HCC and was still on clopidogrel for the treatment of his prior stroke.

His oncological history began in January 2010 when he presented with an acute onset of abdominal pain. CT of the abdomen and pelvis demonstrated a 6×6.3 cm left hepatic mass with haemorrhage at the subcapsular level extending into the retroperitoneal space. Emergent hepatic angiogram and embolisation were performed. Subsequent liver biopsy revealed moderately differentiated HCC. He underwent a partial hepatectomy which confirmed a 15.5×7.4×4.2 cm mass with a central area of necrosis demonstrating moderately differentiated HCC. He was followed regularly by medical oncology and serial imaging with CT of the abdomen and the pelvis. Six months later, CT demonstrated a hypervascular 1.9 cm lesion which had grown from 5 mm 3 months prior in the eighth liver segment; this was the first recurrence of his HCC. He underwent radiofrequency ablation of this lesion. In addition, in July 2010, metastasis to the lungs was found. CT of the chest demonstrated more than 20 new nodules in each lung with bilateral mediastinal nodal widening, and an

enhancement was seen. In attempts to slow down the disease progression, he was started on sorafenib at 200 mg two times a day for 1 month and was increased to 400 mg two times a day after that. He continued the treatment for an additional 5 months without side effects. However, despite this, he presented with disease progression on CT with an increase in the number of pulmonary lesions noted, as well as in the development of new hepatic lesions. After 6 months of treatment, sorafenib was discontinued secondary to disease progression, this being about 5 weeks prior to hospital admission.

One month prior to admission, he described occasional episodes of mandibular bleeding associated with the insertion of his lower partial denture and with eating. He complained of lower mandibular pain associated with chewing. One month prior to admission, he lost a tooth leading to the discovery of an enlarging gingival growth on the anterior lower mandible. This gingival mass was biopsied by a local ear, nose and throat physician 1 week prior to admission. At approximately the same time he lost the tooth, he noted a small mass on his penis which bled intermittently, initially controlled by applying pressure. Both the mandibular and penile masses continued to enlarge and bleed intermittently prior to admission.

On the day of admission, he presented with poorly controlled bleeding from the penile lesion that resolved with the application of pressure dressings. Clopidogrel was subsequently discontinued. An examination revealed a 2.5 cm mass on the right lower gum line. A genital examination revealed a 1 cm fungating mass emanating from the coronal margin of the penis.

INVESTIGATIONS

Panorex was performed and showed a 1.2 cm lytic lesion in the right anterior mandibular cortex just adjacent to the midline (figure 1). During this hospitalisation, the patient had an acute episode of dyspnoea. To investigate his dyspnoea, CT angiography of the chest was performed for the evaluation of pulmonary embolism. The CT was negative for pulmonary embolism, but did show extensive progression of his pulmonary metastasis (figure 2).

Pathology of the mandibular biopsy demonstrated oral squamous mucosa with a submucosal proliferation of malignant epithelioid cells arranged in a trabecular architecture (figure 3; H&E, ×200). Immunohistochemically, the tumour cells are positive for Hepar-1 (figure 4A) and glypican-3 (figure 4B), supporting the diagnosis of metastatic HCC.

To cite: Gentile NM, McKenzie KM, Hurt RT. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-008886

Figure 1 Panorex: lytic lesion right anterior mandibular cortex (black arrow).

DIFFERENTIAL DIAGNOSIS

The likely diagnosis is metastatic HCC. Less likely in the differential diagnosis could include other malignancies such as squamous cell carcinoma of the penis. Other non-cancerous conditions include condylomata, syphilis, chancroid and Bowen's disease. One condition, queyrat erythroplasia presents with penile bleeding similar to our patient.

TREATMENT

Not applicable as the patient decided to pursue palliative comfort.

OUTCOME AND FOLLOW-UP

Biopsy results from the oral lesion showed a malignant neoplasm, most consistent with metastatic HCC. No biopsy was taken from the penile mass as there was concern for bleeding. Furthermore, the patient wished to pursue palliative measures. He was discharged to hospice care. The patient died within 2 months of hospital discharge.

DISCUSSION

HCC is the fifth most common cancer in the world in men and seventh most common cancer in women with epidemiology impacted depending on country of origin.^{1 2} Incidence varies from greater than 20 per 100 000 individuals in areas such as sub-Saharan Africa to less than 5 per 100 000 individuals in North America.¹ Some postulate that the incidence is associated

Figure 2 CT of the chest, pulmonary embolism protocol: negative for pulmonary embolism but shows multiple pulmonary metastases.

Figure 3 Mandibular biopsy: oral squamous mucosa with a submucosal proliferation of malignant epithelioid cells arranged in a trabecular architecture (H&E, ×200).

with hepatitis B and C infections; however, there is concern as areas of low incidence will see an increase in HCC as the incidence of hepatitis C infection increases.^{1 3} The mean age of diagnosis also varies by location.¹ For instance, in areas such as China where more individuals are affected with hepatitis, the mean age of diagnosis is 55–59 years compared with areas where hepatitis infection is less common; therefore, the mean

Figure 4 Immunohistochemically, the tumour cells are positive for Hepar-1 (A) and glypican-3 (B), supporting the diagnosis of metastatic hepatocellular carcinoma.

age of those affected may be greater than 75 years.¹ In addition to infection with hepatitis B or C, other aetiologies include alcoholic cirrhosis, haemochromatosis, autoimmune liver diseases, such as primary biliary cirrhosis, and aflatoxin exposure.² These likely contribute to HCC via processes including inflammation and damage at the hepatocellular level that may lead to cirrhosis, premalignant changes and ultimately to HCC.²⁻⁴

It is known that HCC may metastasise to the lungs, abdominal lymph nodes and skeletal system including the vertebrae, ribs, sternum, pelvis and adrenal glands.⁵⁻⁷ However, metastasis of HCC to the mandible and penis are rare phenomena with limited case reports described in the literature.⁸⁻¹¹

Treatment for HCC depends on staging and extent of tumour burden in the liver. Some methods of staging involve the Child-Turcotte-Pugh system, which can influence potential surgical resection, in addition to the Tumour Node Metastasis staging system which ranges from stage I to IV.²⁻⁴ Depending on staging, hepatic resection may be curative; however, there is an association with high recurrence.¹² Recurrence is influenced by tumour size (eg, greater than 5 cm in diameter), lack of a tumour capsule and vascular involvement.⁴ Chemotherapy has been used in combination or as sole therapy.⁴ For those who are not surgical candidates, various approaches may be used including percutaneous ethanol injection, transcatheter arterial chemoembolisation and radiofrequency ablation.⁴ Ultimately, there is a high death rate with HCC.¹

Focusing on those with HCC orofacial metastasis, a large case series (n=98) demonstrated 68 individuals, the mean age of men was 63.3 years, with metastatic lesions to the mandible, and time to death range of 1.5 weeks to 3 years.³

Unfortunately, in some patients, HCC is discovered only after the patient presents with the discovery of a mandibular growth.³⁻⁵ Because of haematopoietic tissue, the mandible and gingiva are potential metastatic sites.⁵ Hypotheses for this method of metastasis propose that the tumour cells reach the mandible by route of communication between the hepatic artery and portal vein as well as venous plexus system of the abdomen and pelvis communication with the vertebral plexus system ultimately leading to haematogenous dissemination.⁷

Further, HCC metastasis to the penis is an even more rare occurrence.⁸ In one such case, a 67-year-old man with a history of chronic hepatitis B and HCC on biopsy status post right partial hepatectomy presented with a lesion on the left glans 10 months following surgery.⁸ Histopathology was consistent with carcinomatous tissue within the vascular spaces which led to a suspicion for the spread of HCC.⁸ Given the rarity of metastasis to the penis, hypotheses for metastasis include direct extension, retrograde venous or lymphatic flow and arterial embolisation.⁸ Treatment options include excision, penectomy or palliative therapy.⁸ Overall, the prognosis is poor and approximately 50% of patients die within 6 months.¹³

It is important to emphasise that the biopsy of these lesions are associated with an increased risk of bleeding.³ There are reports of significant bleeding and severe acute haemorrhage with the initial biopsy despite normal coagulation studies in patients with orofacial metastasis.³ One such case was of a 74-year-old woman with an ulcerative buccal mass, metastatic HCC to the mandible, who on biopsy had uncontrollable blood loss.⁷ This large amount of bleeding could not be controlled

with electrocauterisation or angiographic embolisation and ultimately required palliative radiotherapy.⁷

In our patient, owing to the increased risk of bleeding, it was decided not to perform biopsy of the penile lesion, as it was not going to change his management. It is strongly felt by our oncology attending physician that the penile lesion represented the extension of the HCC. If we had opted for biopsy, a fine needle aspiration (FNA) biopsy is recommended as the first option with open biopsy reserved if FNA is non-diagnostic.³⁻⁵ Our patient who died 2 months following hospitalisation was consistent with the estimated prognosis reported in other cases of penile or oral HCC metastasis.

Learning points

- Oral and penile hepatocellular carcinoma (HCC) metastases confer a poor prognosis.
- In a patient with a history of HCC and a new penile lesion, one must consider HCC in the differential.
- In a patient with a new bleeding gingival or mandibular lesion that had a history of HCC, one must consider metastatic HCC in differential diagnosis.
- When biopsying, the HCC lesion clinicians should be cautious of uncontrolled bleeding.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology* 2012;142:1264-73 e1.
- 2 Cahill BA, Braccia D. Current treatment for hepatocellular carcinoma. *Clin J Oncol Nurs* 2004;8:393-9.
- 3 Yu S, Estess A, Harris W, et al. A rare occurrence of hepatocellular carcinoma metastasis to the mandible: report of a case and review of the literature. *J Oral Maxillofac Surg* 2012;70:1219-23.
- 4 McCaughan GW, Koorey DJ, Strasser SI. Hepatocellular carcinoma: current approaches to diagnosis and management. *Intern Med J* 2002;32:394-400.
- 5 Lasiter JC, Liess BD, Zitsch RP III, et al. An expansile mandibular mass as the initial manifestation of hepatocellular carcinoma. *Ear Nose Throat J* 2011;90:E19.
- 6 Poojary D, Baliga M, Shenoy N, et al. Adrenal insufficiency with gingival mass—an unusual presentation of hepatocellular carcinoma. *J Oral Maxillofac Surg* 2011;69:e291-3.
- 7 Huang SF, Wu RC, Chang JT, et al. Intractable bleeding from solitary mandibular metastasis of hepatocellular carcinoma. *World J Gastroenterol* 2007;13:4526-8.
- 8 Razi SS, Gottenger EE, Garcia RL, et al. An unusual case of a metastatic lesion to the penis. *J Urol* 2000;163:908-9.
- 9 Li R, Walvekar RR, Nalesnik MA, et al. Unresectable hepatocellular carcinoma with a solitary metastasis to the mandible. *Am Surg* 2008;74:346-9.
- 10 Teshigawara K, Kakizaki S, Sohara N, et al. Solitary mandibular metastasis as an initial manifestation of hepatocellular carcinoma. *Acta Med Okayama* 2006;60:243-7.
- 11 Pires FR, Sagarra R, Correa ME, et al. Oral metastasis of a hepatocellular carcinoma. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2004;97:359-68.
- 12 Kishi Y, Hasegawa K, Sugawara Y, et al. Hepatocellular carcinoma: current management and future development-improved outcomes with surgical resection. *Int J Hepatol* 2011;2011:728103.
- 13 Burgers JK, Badalament RA, Drago JR. Penile cancer. Clinical presentation, diagnosis, and staging. *Urol Clin North Am* 1992;19:247-56.

Copyright 2013 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow