Journal of Gastrointestinal Cancer (2019) 50:978–982
https://doi.org/10.1007/s12029-018-0159-3

CASE REPORT

Hepatocellular Carcinoma with Orbital Metastasis: a Unique Multidisciplinary Case Report

Matthew Michael Sochat[1] · Jinhua Piao[2] · Nishant Poddar[1]

Published online: 13 August 2018

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignancy and the second most common cause of cancer-related mortality worldwide. Higher prevalence is seen in Asia and other developing countries [1]. Both the incidence and the mortality from this cancer are increasing in the USA [2]. Metastasis to the orbit is rare in hepatocellular carcinoma, with infrequent mention in the literature to date [3–5]. Approximately 50% of these unusual cases represent the initial diagnosis of metastatic disease.

Treatment is challenging and generally requires a multimodal treatment plan to optimize both outcomes and quality of life. Our review of the literature notes radiation and systemic therapies to be the mainstay, but there is rare mention of more invasive treatments such as surgery and radioembolization, likely because such patients often have impaired functional status and are poor surgical candidates.

Here, we report a case of orbital metastasis as the initial presentation of metastatic HCC in a 60-year-old male of Chinese descent with previously treated hepatitis C virus (HCV) infection, successfully treated with a multimodal approach including radioembolization, surgery with reconstruction, external beam radiotherapy, and systemic therapy, whose right orbit remains free of disease over 1 year after treatment initiation.

We verify that all authors had equal access to the data and played a role in the writing of this manuscript.

✉ Matthew Michael Sochat
Matthew.Sochat@health.slu.edu

[1] Division of Hematology/Oncology, St. Louis University School of Medicine, Second Floor, Cancer Center Building, 3655 Vista Avenue, St. Louis, MO 63110, USA

[2] Division of Pathology, St. Louis University School of Medicine, 1402 South Grand Boulevard, St. Louis, MO 63104, USA

Case Presentation

A 60-year-old Chinese male with a history of genotype 6 HCV infection, successfully treated to a sustained virologic response (SVR) with interferon and ribavirin in 2006, presented to the emergency department in July of 2016 with complaints of an enlarging right eye orbital mass, proptosis, and diplopia. He had noted a growing mass in his right orbit for the past 6 months and complained of both pain during mastication and dull right-sided headaches. Mild weight loss of 2–3 lbs was noted. On exam, a firm, fixed mass was identified in the right temporal area. His right eye had prominent proptosis and mild conjunctival erythema. Neurological examination revealed intact visual fields in the right eye with deficits in right eye abduction, elevation, and depression.

He was referred to ophthalmology, where biopsy of the mass was done, revealing polygonal tumor cells with eosinophilic granular cytoplasm and rounded nuclei, some with prominent nucleoli, along with bile pigment (Fig. 1a, b). Immunohistochemistry showed strong, diffusely positive Hep-par with a granular pattern (Fig. 1c). CAM5.2 was also strongly positive. Cytoplasmic staining revealed Glycapin-3 positivity. The tumor was negative for Vimentin, S-100 (Fig. 1d), Mart/Mel A, HMB45, RCC, CK7, PSA, BerEp4, Ca-P, HepBsAg, HepBcAg, and MOC-31. Magnetic resonance imaging (MRI) of the brain and orbit to better visualize the lesion revealed a destructive enhancing mass centered in the lateral wall of the right orbit measuring 5.8 cm × 3.4 cm × 4.9 cm (Fig. 2a, b). The mass extended laterally and inferiorly into the right masticator space. It also extended anteromedially into the extraconal compartment of the right orbit, exerting mass effect on the right lateral rectus muscle and right optic nerve without direct invasion of either structure. No intraconal extension was evident. Erosion through the right greater wing of the sphenoid bone with minimal right middle cranial fossa invasion was seen, without mass effect upon the right temporal pole.

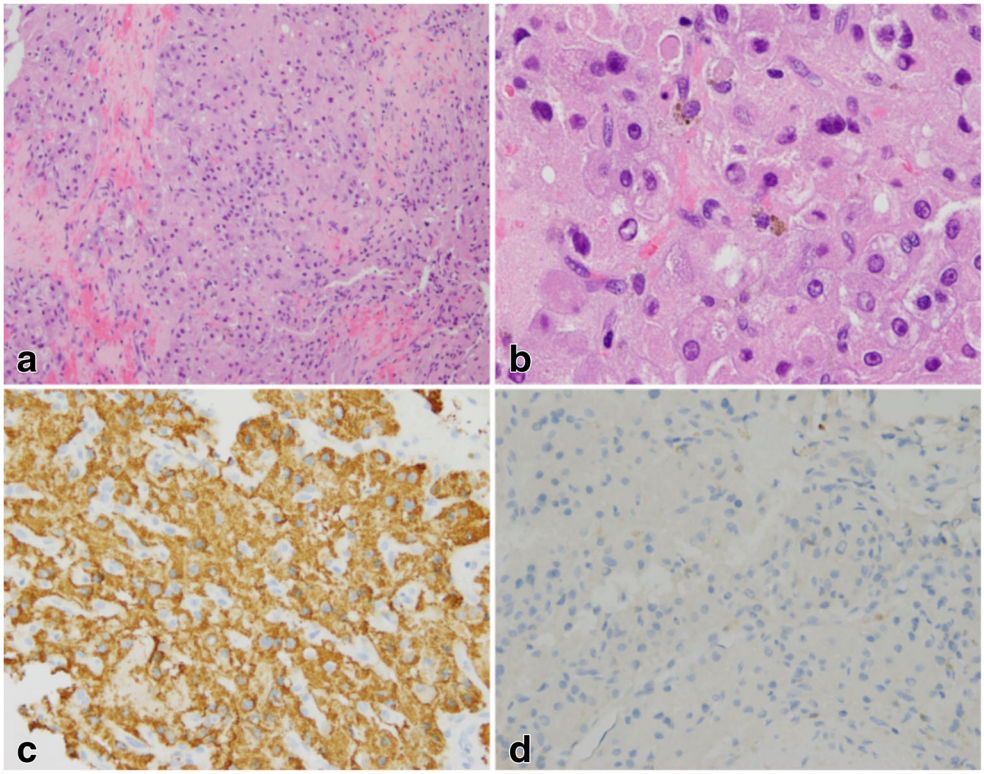

Fig. 1 Histopathology of right orbital mass. **a** Hematoxylin and eosin (H&E) stained section of hepatocellular carcinoma metastatic to the right orbital wall (× 100); **b** representative section of the tumor with bile pigment (arrow) (× 400); **c** tumor cells demonstrate strong and diffuse immunoreactivity for Hepar 1 (× 400); **d** negative immunoreactivity for S-100 in tumor cells (× 400)

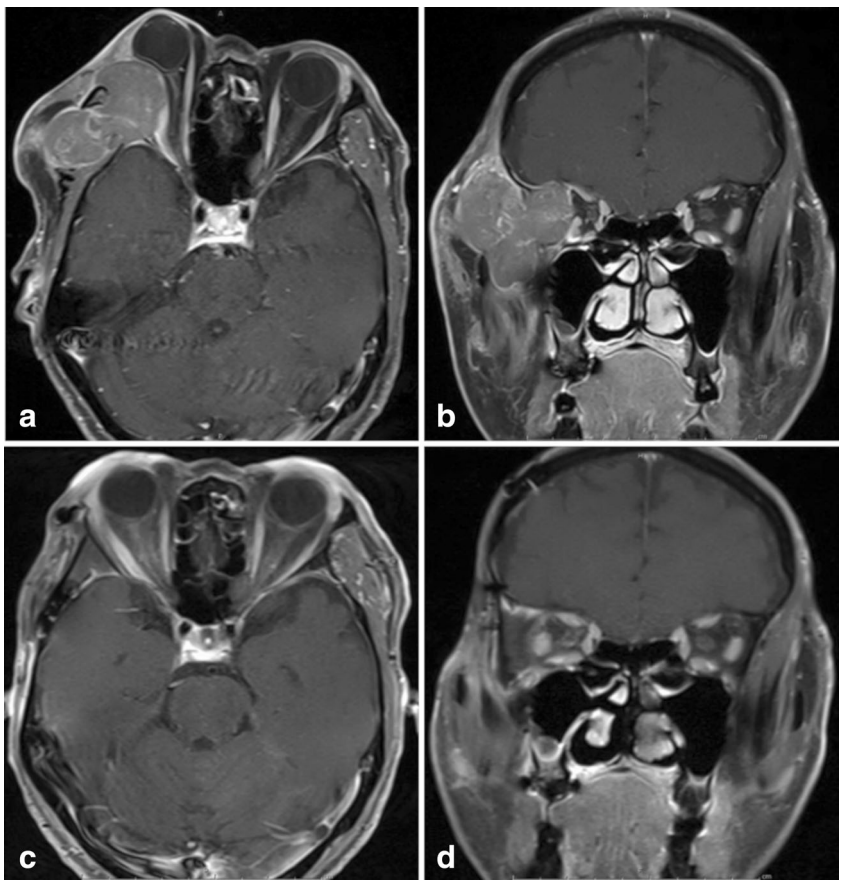

Fig. 2 Magnetic resonance imaging (MRI) of right orbital wall mass, pre- and post-intervention. **a**, **b** axial and coronal T1-weighted MRI images of the right orbital mass lesion shown via biopsy to be metastatic hepatocellular carcinoma (HCC). Note mass effect upon right eye structures, including the optic nerve and globe, without invasion into these structures. **c**, **d** Equivalent T1 axial and coronal views show the right orbit after successful metastasis radioembolization followed by resection with skull reconstruction

The patient underwent staging CT scan of the chest and triple phase liver scan. He was found to have an arterially enhancing mass in hepatic segments 6 and 7, measuring 6.9 × 6.9 × 5.1 cm with washout and delayed capsular formation radiographically consistent with HCC. He had liver nodularity on imaging and left hepatic lobe enlargement consistent with cirrhosis. There were no ascites or varices. An incidental finding of polycystic kidneys were noted in imaging. The patient was diagnosed with HCC with oligometastatic disease to the right orbit. Laboratory findings revealed an elevated alpha-fetoprotein (AFP) level of 25,609 ng/ml (reference range 0.0–8.3 ng/ml). Aspartate transaminase, alanine transaminase, total bilirubin, and prothrombin time were normal. Serum creatinine was mildly elevated at 1.4 g/dL. Albumin was decreased at 2.9 g/dL, thought to be from to poor oral intake due to pain with mastication. Quantitative HCV RNA reverse transcriptase-polymerase chain reaction was performed on a serum sample and no viral RNA was detected. Hepatitis B virus (HBV) testing by quantitative polymerase chain reaction was also negative.

The patient underwent angiography and embolization of the right external carotid artery to decrease the tumor size prior to surgery. He subsequently underwent stereotactic cranial orbital zygomatic resection and resection of metastatic disease involving the orbit, infratemporal fossa, and middle cranial fossa. As tumor resection required complete removal of the right sphenoid bone, he required intraoperative skull reconstruction with a custom-fitted orbitozygomatic Medpor sheet.

He was later treated with adjuvant radiation therapy with 37.5 Gray in 15 fractions to the right temple region. The primary site of disease in hepatic segments 6 and 7 was treated with embolization of the right hepatic artery with Yttrium-90 (Y-90) microspheres. Following recovery, he was started on sorafenib for his metastatic hepatocellular carcinoma, with occasional treatment holidays due to hand-foot syndrome. With comprehensive treatment, the patient noted resolution of his eye pain, diplopia, and pain with mastication. His oral intake improved and his albumin levels normalized.

Subsequent staging scans 6 months after treatment initiation noted residual liver disease, the interval development of filling defects in the hepatic artery secondary to direct HCC invasion, progressing necrotic abdominal adenopathy likely representing metastasis, and the rise of several metastatic lytic lesions, including T11 and the left occipital condyle of the skull. Some of these lesions progressed while on sorafenib therapy. He was therefore switched from sorafenib to regorafenib, and palliative radiation to T11 and the left occipital condyle was administered due to bone pain. He did not tolerate regorafenib and was therefore switched to nivolumab monotherapy. On this therapy, he successfully achieved and maintained stable disease.

Surveillance MRI scans of the right orbit were performed every 3 months. Scans performed approximately 18 months after definitive chemoembolization and surgery showed a sustained remission of the orbital oligometastasis (Fig. 2c, d).

Discussion

HCC is an aggressive and difficult-to-treat malignancy that causes significant morbidity and mortality. The detection of metastatic disease may be the initial presentation. Orbital wall metastases are rare and the optimal course of management not well-established given the anatomical complexity of the site, the aggressive nature of the malignancy, and the commonly impaired performance status of inflicted patients. This case highlights the efficacy of a multimodal approach by combined specialties to treat one such patient, including ophthalmology, neurosurgery, medical oncology, radiation oncology, and hepatology. With this unique approach, our patient's debilitating visual symptoms brought about by his orbital metastasis resolved completely and his quality of life improved dramatically.

The vast majority of HCC patients have underling liver disease with cirrhosis, as was the case with our patient [6]. In the USA, HCV is a common cause of cirrhosis, although increasing data show that metabolic disorders such as nonalcoholic fatty liver disease (NAFLD) are also increasing in prevalence and constitute the underlying etiology behind a growing number of HCC cases [7]. Per the American Association for Study of Liver Disease (AASLD), surveillance for HCC has been shown to confer a survival benefit by allowing for the detection of earlier disease that can be completely cured. However, the interval of testing, the modality to use, and which specific populations benefit the most remains controversial [8]. Studies on HBV-infected patients have shown a significant benefit from screening, even when there is no cirrhosis, but it is unclear if these can be applied to populations with order etiologies, including HCV [8, 9]. Most patients deemed high risk are currently screened with abdominal ultrasound, with or without a serum AFP level, every 6 months [10].

Also controversial is whether or not the achievement of a sustained virologic response (SVR) in HCV decreases the risk of HCC development. Treatment of active HCV infection has been shown to confer a benefit in patients who develop HCC [10]. However, in patients cured of their HCV without HCC, there is evidence that an increased risk of HCC relative to the general population. HCC surveillance may be recommended in such patients even after successful hepatitis C treatment [11, 12]. It remains to be seen if the recent surge in HCV cure rates with the newer targeted antiviral agents will allow for more data to be collected and analyzed on this matter.

Metastases from HCC are common and confer a poorer outcome, as cure is unlikely to be achieved. Common sites of metastases include the lungs and bone. Bone metastases confer a particularly poor prognosis, with a 1-year survival rate of approximately 50% [13]. Metastases specifically to the orbital bones are rare, but in those studied, the reported outcome is similarly poor, with median survival times of 10.2 months (±2.3 months) from the time of diagnosis [4]. Some patients received radiation therapy alone in case reports and to our knowledge, this is the first case report where the patient is treated with embolization of the right external carotid artery followed by surgical resection and radiation therapy with complete response to therapy in the orbit region [5].

In our patient, in addition to locoregional control of his primary tumor and comprehensive surgical and radiation treatment of his right orbital metastasis, systemic therapy with sorafenib was initiated. This agent, a broad inhibitor of tyrosine kinases including Raf, EGFR, and PDGFR, demonstrates efficacy against HCC cells [14]. In the SHARP trial, sorafenib conferred a 4-month overall survival (OS) and 3-month progression-free survival (PFS) advantage compared to those treated with placebo [15]. It can be safely combined with other therapies (e.g., radioembolization with Y-90 as was the case with our patient). Side effects may necessitate treatment breaks, however, and progression of the HCC on sorafenib is not uncommon. Such patients benefit from a switch of therapy. The broad tyrosine kinase inhibitor regorafenib is a viable option, as was done in our patient after progression was detected [16]. More recently, the programmed death ligand-1 (PD-1) inhibitor nivolumab was shown to be effective per the CheckMate 040 study, and in our patient was instrumental in achieving stable disease after regorafenib was no longer tolerated [17].

Conclusions

HCC bone metastases are uncommon, and orbital involvement is rare yet debilitating. This case represents a novel multidisciplinary approach to one such patient presenting with symptomatic orbital oligometastatic HCC, involving right external carotid artery embolization followed by surgical resection and adjuvant radiotherapy with a complete, durable response. Our patient experienced improved quality of life and survival from definitive interventional metastatic lesion management. Systemic therapy with sorafenib combined with Y-90, followed by regorafenib and nivolumab, highlight the efficacy of the expanding systemic therapy armamentarium available for HCC. More studies are needed to determine if patients with oligometastatic presentations can have improved survival and quality of life from prompt and comprehensive multidisciplinary evaluations.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Informed Consent Informed consent was obtained from all individual participants included in the study, when applicable.

References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C. Globcan 2008 v2. 0. Cancer incidence and mortality worldwide: IARC Cancer Base No. 10. Lyon, France. International Agency for Research on Cancer. 2010, Accessed: May 5th, 2018: http://globocan.iarc.fr.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016;66:7–30. https://doi.org/10.3322/caac.21332.
3. Gupta R, Honavar SG, Vemuganti GK. Orbital metastasis from hepatocellular carcinoma. Surv Ophthalmol. 2005;50:485–9. https://doi.org/10.1016/j.survophthal.2005.06.014.
4. Eldesouky MA, Elbakary MA, Shalaby OE, Shareef MM. Orbital metastasis from hepatocellular carcinoma: report of 6 cases. Ophthalmic Plast Reconstr Surg. 2014;30:78–82. https://doi.org/10.1097/IOP.0b013e31829f3a57.
5. Quick AM, Bloomston M, Kim EY, Hall NC, Mayr NA. Complete response to radiation therapy of orbital metastasis from hepatocellular carcinoma. World J Gastroenterol: WJG. 2009;15:6000–3. https://doi.org/10.3748/wjg.15.6000.
6. Petrick JL, Braunlin M, Laversanne M, Valery PC, Bray F, McGlynn KA. International trends in liver cancer incidence, overall and by histologic subtype, 1978–2007. Int J Cancer. 2016;139:1534–45. https://doi.org/10.1002/ijc.30211.
7. Makarova-Rusher OV, Altekruse SF, McNeel TS, Ulahannan S, Duffy AG, Graubard BI, et al. Population attributable fractions of risk factors for hepatocellular carcinoma in the United States. Cancer. 2016;122:1757–65. https://doi.org/10.1002/cncr.29971.
8. Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology. 2018;67:358–80. https://doi.org/10.1002/hep.29086.
9. Zhang B-H, Yang B-H, Tang Z-Y. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol. 2004;130:417–22. https://doi.org/10.1007/s00432-004-0552-0.
10. Song P, Cai Y, Tang H, Li C, Huang J. The clinical management of hepatocellular carcinoma worldwide: a concise review and comparison of current guidelines from 2001 to 2017. Bioscience Trends. 2017;11:389–98. https://doi.org/10.5582/bst.2017.01202.
11. Aleman S, Rahbin N, Weiland O, Davidsdottir L, Hedenstierna M, Rose N, et al. A risk for hepatocellular carcinoma persists long-term after sustained virologic response in patients with hepatitis C-associated liver cirrhosis. Clin Infect Dis. 2013;57:230–6. https://doi.org/10.1093/cid/cit234.
12. Ogawa E, Furusyo N, Kajiwara E, Takahashi K, Nomura H, Maruyama T, et al. Efficacy of pegylated interferon alpha-2b and ribavirin treatment on the risk of hepatocellular carcinoma in patients with chronic hepatitis C: a prospective, multicenter study. J Hepatol. 2013;58:495–501. https://doi.org/10.1016/j.jhep.2012.10.017.
13. Kim S, Chun M, Wang H, Cho S, Oh YT, Kang SH, et al. Bone metastasis from primary hepatocellular carcinoma: characteristics of soft tissue formation. Cancer Res Treat. 2007;39:104–8. https://doi.org/10.4143/crt.2007.39.3.104.

14. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359:378–90. https://doi.org/10.1056/NEJMoa0708857.
15. Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2009;10:25–34. https://doi.org/10.1016/S1470-2045(08)70285-7.
16. Bruix J, Qin S, Merle P, Granito A, Huang YH, Bodoky G, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;389:56–66. https://doi.org/10.1016/S0140-6736(16)32453-9.
17. El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet. 2017;389:2492–502. https://doi.org/10.1016/S0140-6736(17)31046-2.