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Case Report

Hepatocellular carcinoma metastatic to the pituitary gland without an identifiable primary lesion ☆

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ABSTRACT

Hepatocellular carcinoma is one of the most common malignancies worldwide. However, brain metastases from this cancer are incredibly rare. While the hepatocellular carcinoma mortality rate in the United States has been increasing, hepatocellular carcinoma is rare among patients without underlying liver disease. Here we present a patient with a history of left optic nerve meningioma treated with stereotactic radiosurgery who presented with acute vision loss. Magnetic resonance imaging revealed an enhancing mass lesion in the region of the sella turcica. Neurosurgical histopathology revealed a metastatic lesion consistent with hepatocellular carcinoma. Systemic workup failed to identify a primary liver lesion.

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide [1,2]. Related risk factors include but are not limited to chronic liver disease, hepatitis B or C infection, cirrhosis, alcohol abuse, nonalcoholic steatohepatitis, and aflatoxin exposure [1–3]. In 2020, liver cancer was the third leading cause of malignancy related death worldwide [4]. The most common sites of extrahepatic HCC metastases are to the lung, bone, and lymph nodes with less common sites including the adrenal gland, peritoneum, skin,

Abbreviations: HCC, Hepatocellular carcinoma; MRI, Magnetic resonance imaging; TNTS, Trans-nasal trans-sphenoidal; CT, Computed tomography; FSRT, Fractionated stereotactic radiotherapy; HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; AFP, Alpha 1-fetoprotein; AFP-L3, lens culinaris agglutinin-reactive fraction of alpha fetoprotein; DCP, des-gamma-carboxy prothrombin; ARG1, Arginase-1.

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and muscle [5]. Brain metastases from HCC are incredibly rare, with a reported incidence of 0.33% and median overall survival of 1.2-2.4 months [6,7].

We report a case of HCC presenting with visual disturbances caused by a single sellar metastasis of hepatocellular carcinoma from an unknown primary in the setting of a patient with a history of left optic nerve meningioma treated with stereotactic radiosurgery.

Case presentation

A 72-year-old male presented to the emergency department with 10 days of worsening right sided homonymous hemianopsia. History is significant for left optic nerve lesion presumed to be meningioma diagnosed 5 years prior. He underwent fractionated stereotactic radiotherapy with a dose of 2500 cGy in 5 fractions to the left optic nerve sheath lesion. Follow-up MRI brain with and without contrast reported a decrease in abnormal enhancement.

On presentation to the emergency department, physical exam was insignificant except for right homonymous hemianopsia. MRI brain with and without contrast shown in Fig. 1 reported an enhancing lobulated sellar mass associated with abnormal enhancement extending into the right optic nerve with compression of optic chiasm. An MRI brain performed 5 months prior was available for comparison with no such mass is seen in the previous MRI except some asymmetry on the left side of the pituitary gland. Due to the rapid growth of the mass, differential diagnosis included pituitary macroadenoma, atypical meningioma, or malignancy.

He was admitted to the hospital and evaluated by neurosurgery, ophthalmology, and endocrinology. Endocrinology labs noted increased follicle stimulating hormone (15.2 mU/mL, reference range 0.0-12.4 mU/mL) and decreased free thyroxine (0.90 ng/dL, reference range 0.93-1.70 ng/dL). Serum labs performed for suspicion of a secretory pituitary adenoma resulted normal, including prolactin (11.2 ng/mL, reference range 4.0-15.2 ng/mL), IGF-1 (96 ng/mL, reference range 52-222 ng/mL), and ACTH (22.5 pg/mL, reference range 7.2-63.3 pg/mL). Both endocrinology and ophthalmology recommended outpatient workup. Given the stability of the patient, he was discharged home with close outpatient follow-up for surgical planning within the next week.

The patient returned to the emergency department 4 days later with acute worsening vision in the right eye. MRI pituitary/sella including brain with and without contrast reported no significant interval change in size of the sellar mass.

He was admitted and started on dexamethasone and underwent transnasal transsphenoidal resection of the sellar lesion.

Final surgical pathology revealed metastatic hepatocellular carcinoma. The pathology report reported sections showing large fragments of tissue composed of a mix of normal-appearing anterior pituitary as well as multiple broad nests and sheets of metastatic carcinoma with elevated mitotic activity. The cells had rounded to oval nuclei, some with prominent nucleoli, as well as abundant pink to amphophilic cytoplasm. Some cells had multiple small cytoplasmic vacuoles. Some focal trabecular architecture was also appreciated. Reticulin stain confirmed the loss of normal acinar architecture in the areas of metastasis. Some PAS positivity was noted within the neoplasm. The cells were diffusely immunopositive for CAM5.2, ARG1, and HSA. A significant subpopulation of tumor cell nuclei was immunopositive for SATB2 and SALL4. Ki67 confirmed a fairly brisk proliferation index (at least 50%). Stains targeting chromogranin, synaptophysin, TTF-1, ACTH, LH, prolactin, TSH, GH, FSH, P53, RCC, CD30, P40, P63, NKX3.1, GATA3, PAX8, PSA, CK20, and CK7 were all negative.

Postoperative MRI reported large residual mass in the suprasellar cistern extending to and elevating the optic chiasm. Staging scans including computed tomography (CT) abdomen and pelvis with contrast, CT thorax with contrast, and MRI abdomen with and without contrast were all insignificant with no reported primary cancer, no morphologic changes of the liver to suggest cirrhosis or metastatic lesions concerning for malignancy. Bone scan reported no evidence of osteoblastic metastatic bone disease. Tumor markers were obtained. Alpha 1-fetoprotein (AFP) was elevated to 9370 ng/mL (normal <9 ng/mL), CA 19-9 was elevated to 59 U/mL (normal <35 U/mL), and CEA was normal.

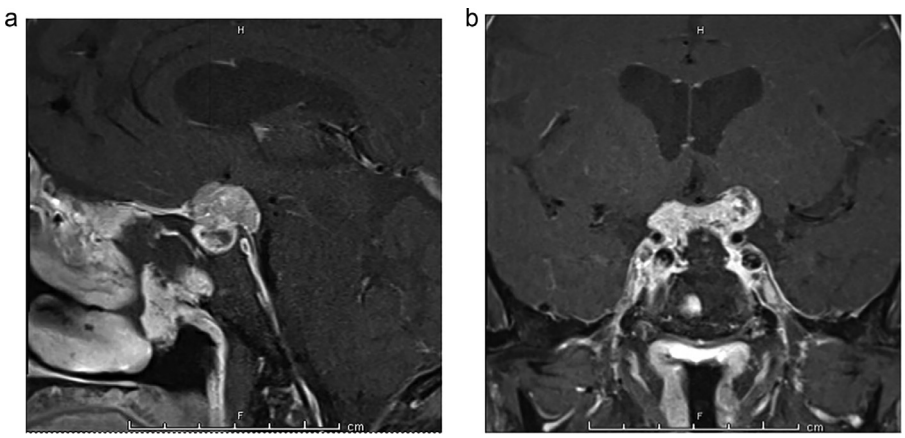

Fig. 1 – MR imaging of the brain with intravenous contrast in the sagittal (A) coronal and (B) planes. T1 weighted images demonstrated an enhancing lobulated sellar mass lesion associated with abnormal enhancement extending into the right optic nerve with compression of optic chiasm.

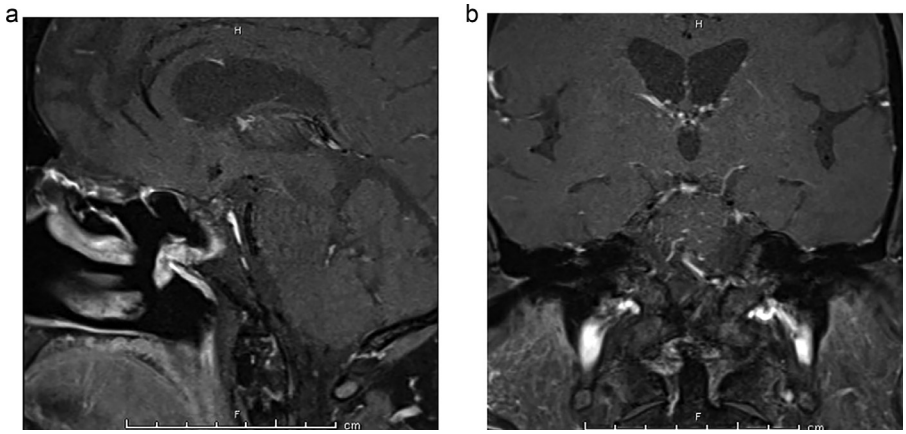

Figure 2 – MR imaging of the brain with intravenous contrast in the sagittal (A) coronal and (B) planes on T1 weighted images demonstrated interval resection of the mass with prominent curvilinear enhancement at the posterior aspect of the clivus, in the bilateral parasellar area, and at the planum sphenoid consistent with a small amount of residual mass.

The patient underwent postoperative fractionated stereotactic radiotherapy to the residual tumor (2750 cGy in 5 fractions) followed by atezolizumab and bevacizumab planned for 12 cycles. On initiation of radiation therapy the patient was completely blind in both eyes. After completing radiation the patient regained usable vision with residual right hemianopsia.

Imaging at 4 months follow-up is shown in Fig. 2. MRI sagittal T1-weighted images demonstrated prominent curvilinear enhancement at the posterior aspect of the clivus and in the bilateral parasellar area, and at the planum sphenoid, decreased in size compared to immediate postoperative scans, consistent with a small amount of residual mass. AFP at 6 months follow-up was 113 ng/mL.

Discussion and conclusions

HCC is rare among patients without liver disease. Hepatitis B virus infection is the most common cause of HCC worldwide whereas hepatitis C virus (HCV) infection is the main cause of HCC in Western countries and Japan, and the incidence of HCC due to nonalcoholic fatty liver disease is increasing [8]. Another important risk factor for HCC is alcohol consumption, with heavy drinking defined as 3 or more drinks per day resulting in a 16% increase of liver cancer in a meta-analysis of 19 prospective studies [9]. The United States has seen an increase HCC in mortality rate by 43% between 2000 and 2016, from 7.2 to 10.3 deaths per 100,000 people [10]. Due to the often concomitant cirrhosis, management of HCC requires a multidisciplinary team with treatment options including liver transplantation, surgical resection, percutaneous ablation, radiation, and transarterial and systemic therapies [2].

Screening for hepatocellular carcinoma is performed on patients defined to be at increased risk, not the general population. It is recommended to screen all patients with cirrhosis and subgroups of patients with chronic hepatitis B virus infections [11,12]. Ultrasound imaging is widely used as imaging modality of choice to identify intrahepatic lesions, but limitations exist for capturing nodules less than 2 centimeters in size which can be compounded by central obesity, hepatic steatosis, or operator experience [11,13]. In fact, ultrasound imaging alone has been found to have a low sensitivity to detect early-stage HCC in patients with cirrhosis, and additional screening tools such as AFP measurement are recommended [14]. CT and MRI can be used as abdominal imaging to identify intrahepatic lesions with reported 90% sensitivity for tumors larger than 2 centimeters, however there is a need for large cohort studies to support the use of cross-sectional imaging in HCC screening [13,15].

AFP is a biomarker that has long been associated with HCC, namely in early HCC detection. The use of AFP as a serum biomarker is controversial, with most support for using AFP as an adjunct to liver ultrasonography to improve surveillance sensitivity compared to ultrasonography alone [16]. A cutoff of 20 ng/mL is commonly used, however it is important to note that APF may be elevated in patients with active hepatitis but no evidence of HCC [13]. A value of 400 ng/mL is definitive for HCC diagnosis. Other available serum-based biomarkers include lens culinaris agglutinin-reactive fraction of (AFP-L3) and des-gamma-carboxy prothrombin. The GALAD score combines gender, AFP-L3, AFP, and des-gamma-carboxy prothrombin for superior detection of HCC compared to any biomarker or ultrasound imaging alone [13]. Our patient's AFP was elevated to 9370 ng/mL, well above the 400 ng/mL threshold indicative of a HCC diagnosis.

A diagnosis of HCC can be established using cytology or histology, or by noninvasive imaging with CT or MRI. Both the AASLD and EASL guidelines detail that HCC can be diagnosed based on imaging alone if a new mass of at least 1 centimeter demonstrates arterial hyper-enhancement and venous washout in a cirrhotic liver using either multiphasic contrast CT or MRI [16]. MRI and CT imaging should be used as a diagnostic tool based on the contrast enhancement in the arterial phase followed by the disappearance of contrast in the venous phase, with biopsy reserved for nondescript lesions [13]. Staging scans are comprised of CT chest, abdomen, and pelvis plus bone scans following a new HCC diagnosis.

The histopathology of HCC is variable with differing stages of hepatocyte dedifferentiation. Advanced HCC can show neovascularization, vascular infiltration, absence of portal tracts within the tumor, and classic histologic patterns. These patterns include: trabecular/sinusoidal, pseudoglandular, solid, and undifferentiated [17]. A number of immunohistochemical markers are diagnostically useful. Arginase-1 (ARG1) is a sensitive and specific marker of hepatocytes that was positive in the patient's specimen [18]. CAM5.2 is another stain indicative of HCC that was positive in the patient's specimen. Other positive immunohistochemical stains in HCC include HepPar1, glypican 3, AFP, polyconal CEA, and albumin ISH [19]. The patient's specimen demonstrated gross histological characteristic of carcinoma including but not limited to elevated mitotic activity, prominent nucleoli, and reticulin staining confirming the loss of normal acinar architecture. Immunohistochemical staining was consistent with HCC, including positive ARG1 and CAM5.2.

Literature review reveals a paucity of cases of HCC presenting initially with brain metastases [20–23]. Of all cases, the most common initial manifestation was intracranial hemorrhage due to intracranial metastasis. Notably, to the best of our knowledge there are only 4 other cases of metastatic HCC with an unknown primary site of HCC [23–27]. A retrospective analysis from Korea determined the incidence of brain metastases from HCC to be 0.9% [28]. Likewise, a retrospective analysis from China determined the incidence of brain metastases from HCC to be 0.47% [29]. In the US, the largest retrospective review to date on brain metastases from HCC resulted in 0.39% of all brain metastases were from HCC [30].

While rare, the incidence of brain metastases is increasing internationally with treatment advances and improvements in overall survival [30–32].

In this study, the patient presented with focal neurologic deficits without evidence of the typical clinical presenting symptoms associated with HCC. Given the clinical presentation and imaging results, the differential diagnosis included pituitary adenoma, meningioma, or malignant metastasis. Pituitary adenomas are neuroendocrine tumors that can be secretory or nonsecretory, and depending on the location they may cause mass effect presenting as visual field defects. When a pituitary adenoma is at least 10 mm in size it is classified as a pituitary macroadenoma and may secrete excess hormones including prolactin, growth hormone, adrenocorticotropic hormone, or thyrotropin [33]. Pituitary adenomas are quite common, with reported prevalence as high as 10% of the population [33]. Serum studies in this patient were negative for secretory pituitary adenoma, with prolactin, ACTH, and IGF-1 within normal limits. Histologic descriptions of pituitary neuroendocrine tumor architecture varies, with most tumors cells being epithelioid and with uniform nuclear morphology [34]. Corticotrophs may strongly stain positive for CAM5.2, as demonstrated in this patient, however this patient lacked the characteristic elevation in ACTH. Also, on the differential included meningioma, a benign and common primary brain tumor. Histologic descriptions vary by World Health Organization subtype and grade, with Grade 3 anaplastic variant having malignant cytomorphology that can resemble a carcinoma, melanoma, or high-grade sarcoma. However, these tumors also exhibit typical meningioma features including psammoma bodies or meningothelial whorls and nuclear pseudoinclusions to establish a diagnosis of meningioma [35]. This patient's lesion was characterized by malignant features, including: multiple broad nests and sheets of metastatic carcinoma, abundant pink to amphophilic cytoplasm, elevated mitotic activity, and loss of normal acinar architecture on reticulin staining. The most common origin for brain metastases are lung cancer, breast cancer, melanoma, colorectal cancer, and renal cell carcinoma [36]. In the case of an unknown primary tumor upon discovery of malignant histopathology, immunohistochemical profiles can aid in discovery of the primary site. The patient's cells were diffusely immunopositive for CAM5.2, ARG1, and HSA. Additional stains proved to rule out tumors of neuroendocrine origin, including chromogranin and synaptophysin. Due to the rapid rate of tumor growth, suspicion was raised for metastatic disease. Expert histopathological analysis confirmed HCC, supported by serum AFP well above the diagnostic cutoff value, however extensive workup with comprehensive abdominal imaging and whole body staging scans was unable to determine the primary disease site. To the best of our knowledge, this is the first study to report hepatocellular carcinoma presenting with intracranial metastasis with an unknown liver primary site and no associated clinical symptoms.

Patient consent

The authors of this article obtained written informed consent by the patient.

REFERENCES

[1] Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet North Am Ed 2018;391(10127):1301–14.
[2] Vogel A, Meyer T, Sapisochin G, Salem R, Saborowski A. Hepatocellular carcinoma. Lancet North Am Ed 2022;400(10360):1345–62.
[3] Llovet JM, Kelley RK, Villanueva A, Singal A, Pikarsky E, Roayaie S, et al. Hepatocellular carcinoma. Nat Rev Dis Primers 2021;7(1):1–28.
[4] 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 A Cancer J Clin 2021;71(3):209–49.
[5] NATSUIZAKA M, OMURA T, AKAIKE T Kuwata Y, Yamazaki K, Sato T, et al. Clinical features of hepatocellular carcinoma with extrahepatic metastases. J Gastroenterol Hepatol 2005;20(11):1781–7.
[6] Wang L, Guo Y, Zhang H Li H, Wang F, Zhang J, et al. Risk factors for brain metastasis of hepatocellular carcinoma. J Healthc Eng 2022;2022:7848143.
[7] Lin X, Zhang P, Huang R Huang Y, Sun J, Zheng H, et al. Impact of homogeneous and heterogeneous risk factors on the incidence and prognosis of brain metastases in patients with hepatocellular carcinoma. Ann Palliat Med 2020;9(5):2654–67.

[8] Villanueva A. Hepatocellular carcinoma. N Engl J Med 2019;380(15):1450–62.
[9] Turati F, Galeone C, Rota M Pelucchi C, Negri E, Bagnardi V, et al. Alcohol and liver cancer: a systematic review and meta-analysis of prospective studies. Ann Oncol 2014;25(8):1526–35.
[10] Xu JQ. Trends in liver cancer mortality among adults aged 25 and over in the united states, 2000–2016. NCHS data brief, no 314. Hyattsville, MD: National Center for Health Statistics; 2018.
[11] Lok J, Agarwal K. Screening for hepatocellular carcinoma in chronic hepatitis B: an update. Viruses 2021;13(7):1333.
[12] Frenette CT, Isaacson AJ, Bargellini I, Saab S, Singal AG. A practical guideline for hepatocellular carcinoma screening in patients at risk. Mayo Clin Proc Innov Qual Outcomes 2019;3(3):302–10.
[13] Balogh J, Victor D, Asham EH Burroughs SG, Boktour M, Saharia A, et al. Hepatocellular carcinoma: a review. JHC 2016;3:41–53.
[14] Tzartzeva K, Obi J, Rich NE Parikh ND, Marrero JA, Yopp A, et al. Surveillance imaging and alpha fetoprotein for early detection of hepatocellular carcinoma in patients with cirrhosis: a meta-analysis. Gastroenterology 2018;154(6):1706–1718.e1.
[15] Singal AG, Lampertico P, Nahon P. Epidemiology and surveillance for hepatocellular carcinoma: new trends. J Hepatol 2020;72(2):250–61.
[16] Yang JD, Hainaut P, Gores GJ, Amadou A, Plymoth A, Roberts LR. A global view of hepatocellular carcinoma: trends, risk, prevention and management. Nat Rev Gastroenterol Hepatol 2019;16(10):589–604.
[17] Schlageter M, Terracciano LM, D'Angelo S, Sorrentino P. Histopathology of hepatocellular carcinoma. WJG 2014;20(43):15955.
[18] Yan BC, Gong C, Song J Krausz T, Tretiakova M, Hyjek E, et al. Arginase-1. Am J Surg Pathol 2010;34(8):1147–54.
[19] Chen IY, Agostini-Vulaj D. Hepatocellular carcinoma overview. PathologyOutlines.com website. https://www.pathologyoutlines.com/topic/livertumorhcc.html. Accessed November 30th, 2023.
[20] Thida C, Pokhrel A, Sun L, Wu R, Jaswani V, Wang JC. Hemorrhagic brain metastasis as an initial presentation of hepatocellular carcinoma in a patient with alcohol-related liver cirrhosis: a case report and review of literature. J Investig Med High Impact Case Rep 2022;10:232470962211177.
[21] Pan Z, Yang G, Yuan T, Pang X, Wang Y, Qu L, et al. Leptomeningeal metastasis from hepatocellular carcinoma with other unusual metastases: a case report. BMC Cancer 2014;14(1):1–5.
[22] Chang L, Chen Y, Kao M. Intracranial metastasis of hepatocellular carcinoma: review of 45 cases. Surg Neurol 2004;62(2):172–7.
[23] Lee J, Lee S. Hepatocellular carcinoma presenting as intracranial metastasis. Surg Neurol 1988;30(4):316–20.
[24] Akbar Ali Sabir, Tahira Banoo, Al Haj Mahmed, Barki Osman, Sedky Fouad, Ahmed Amir, et al. Metastatic hepatocellular carcinoma with occult primary: a case report. Saudi J Gastroenterol 1997;3(1):49–52.
[25] Hyun YS. Chest wall metastasis from unknown primary site of hepatocellular carcinoma. WJG 2006;12(13):2139.
[26] CHEN R, GAO Z, WU X, CAMPBELL JL, ZHANG P, CHEN B. Hepatocellular carcinoma presenting as thoracic spinal canal metastasis with no clinical primary foci: a report of a rare case and review of the literature. Oncol Lett 2015;10(4):2333–6.
[27] Zambrano AR, Quesada JC, Torres AM, Escobar J, Prasad M, Renjifo M, et al. Diagnostically challenging case: metastatic hepatocellular carcinoma with no liver lesion at imaging. JGO 2018;4(4):1–5.
[28] Choi HJ, Cho BC, Sohn JH Shin SJ, Kim JH, Yoo NC. Brain metastases from hepatocellular carcinoma: prognostic factors and outcome. J Neurooncol 2009;91(3):307–13.
[29] Jiang X, Ke C, Zhang G Zhang X, Sai K, Chen Z, et al. Brain metastases from hepatocellular carcinoma: clinical features and prognostic factors. BMC Cancer 2012;12(49)1-9.
[30] Falkson SR, Bhambhvani HP, Hayden Gephart M. Hepatocellular carcinoma brain metastases: a single-institution experience. World Neurosurg 2020;140:e27–32.
[31] Wang S, Wang A, Lin J Xie Y, Wu L, Huang H, et al. Brain metastases from hepatocellular carcinoma: recent advances and future avenues. Oncotarget 2017;8(15):25814–29.
[32] Xu Q, Wu P, Feng Y, Ye K, Tong Y, Zhou Y. Gamma knife surgery for brain metastasis from hepatocellular carcinoma. PLoS One 2014;9(2):e88317.
[33] Molitch ME. Diagnosis and treatment of pituitary adenomas. JAMA 2017;317(5):516.
[34] Punsoni M, Asa SL. Pituitary neuroendocrine tumor (PitNET). PathologyOutlines.com website. https://www.pathologyoutlines.com/topic/CNSpituitaryendocrine.html. Accessed November 30th, 2023.
[35] Barresi V. Anaplastic meningioma. PathologyOutlines.com website. https://www.pathologyoutlines.com/topic/cnstumoranaplasticmeningioma.html. Accessed November 30th, 2023.
[36] Achrol AS, Rennert RC, Anders C, Soffietti R, Ahluwalia M, Nayak L, et al. Brain metastases. Nat Rev Dis Primers 2019;5(5):1–27.