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Case Report

Solitary metastasis to the skull as the first sign of hepatocellular carcinoma in a patient in long-term remission

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) is a common malignant tumor with a 5-year survival rate of 10%, presenting with extrahepatic metastases in 15–17% of patients. HCC-bone metastases represent approximately one-quarter of all HCC metastases, most frequently in the spine, pelvis, ribs, or femur. HCC-skull metastases, however, make up 0.4–1.6% of all HCC- bone metastases. Furthermore, solitary HCC-skull metastasis without known active primary HCC is an unusual presentation warranting further review and consideration.

Case Description: Here, the authors report a unique case of a solitary HCC-skull metastasis in a patient without known active cancer but in long-term remission for HCC. The patient is a 69-year-old male with past HCC who presented with a nontender skull mass. A computed tomography scan showed a heterogeneously enhancing mass centered in the high left parietal bone with intracranial extension. There was a noted mass effect on the left posterior frontoparietal region without worrisome midline shift. Pathology ultimately revealed the mass to be metastatic HCC. To aid in the understanding and clinical management of this rare presentation, we reviewed the literature regarding clinical presentation, radiological features, pathology, and outcome.

Conclusion: Ultimately, early detection of the primary source of cancer is pivotal to successful treatment and prognosis, and skull lesions such as these must include HCC in the differential diagnosis.

Keywords: Hepatocellular carcinoma, Liver metastasis, Neurosurgery, Skull metastasis

INTRODUCTION

Hepatocellular carcinoma (HCC) is the third most common malignant tumor and has a 5-year survival rate of 10%.[1] Extrahepatic metastases in 15–17% of patients with HCC.[5] Bone tissue comprises 1.6–16% of these extrahepatic HCC metastases, most commonly affecting the vertebral column, pelvis, ribs, or femurs.[8] The skull, however, makes up an exceedingly rare proportion of HCC-bone metastases—0.4–1.6%—and thus, there remains a paucity of reports featuring HCC-skull metastasis compared to other HCC metastases.[4] Furthermore, skull metastases are more frequently due to lung, breast, thyroid, and prostate cancers.[6]

Jiang *et al.* described 59 cases of HCC-skull metastasis within the literature in 2014, of which only 14 cases presented as a solitary skull lesion.[4] Since then, there have been seven additional case reports of solitary HCC-skull metastasis totaling 21 cases. Solitary HCC-skull metastasis in

the absence of a known primary cancer is even less common and has only been reported 5 times within the literature.[4,8] Interestingly, none of these cases featured patients in long-term remission for previous HCC. Here, we present a unique case of a solitary HCC-skull metastatic lesion in a patient in long-term remission of previous HCC but without known primary cancer at the time of presentation. We also provide a review of all reported solitary HCC-skull metastasis without a known primary cancer, highlighting clinical presentation, radiological features, pathology, clinical management, and outcomes.

MATERIALS AND METHODS

For the case report, the patient was identified by the senior author when presenting to the clinic. No personal identifiers are disclosed and the write-up of this manuscript is in accordance with the corresponding institution's IRB and ethical guidelines. The patient's clinical history, presentation, and management are discussed.

For the review of the literature, PubMed was used. Search terms included: "Hepatocellular carcinoma," "HCC metastasis," "HCC skull metastasis," and "skull metastasis." The resulting search results were manually filtered by authors to include articles with a title or abstract that only featured both HCC and solitary skull metastasis. Six articles were found and are highlighted.

CASE DESCRIPTION

The patient is a 69-year-old male with chronic obstructive pulmonary disease, glaucoma, cirrhosis, and past HCC who began to grow a nontender skull mass in November 2021. He did not seek care until June 2022, when he presented with focal headache at the site of the skull mass. There were no relevant findings from the general physical examination or neurological examination. The patient was neurologically intact with a soft scalp mass that was nontender with no overlying skin stigmata. The mass measured approximately 6 × 6 cm and protruded to 3 cm above the scalp surface. The scalp and hair looked completely normal except being slightly stretched over the underlying tumor. The patient did not have any associated lymphadenopathy.

The patient's oncology history is significant for HCC that was diagnosed in 2015. This was found on screening abdominal ultrasound showing a single hypoechoic lesion at the posterior right lobe of the liver measuring 2.4 × 2.1 × 2.2 cm with a 1.9 cm cyst in the inferior segment. After diagnostic biopsy, the patient underwent transarterial chemoembolization therapy to both hepatic lesions complicated by abdominal pain, constipation, nausea, and vomiting for 7 days. Since this treatment in 2015, the patient has had no recurrence of HCC or any other liver masses or cancer.

The patient declined a head magnetic resonance imaging (MRI). A computed tomography (CT) scan showed a heterogeneously enhancing mass centered in the high left parietal bone that measured approximately 5.0 × 4.5 × 4.6 cm with intracranial extension, but inconclusive on whether the mass was dural, osseous, or metastatic in origin [Figure 1]. There was mass effect on the high left posterior frontoparietal brain where there may have been a trace amount of vasogenic edema. No subfalcine or uncal herniation. The basilar cisterns appeared patent and there was no involvement of the superior sagittal sinus. The major dural

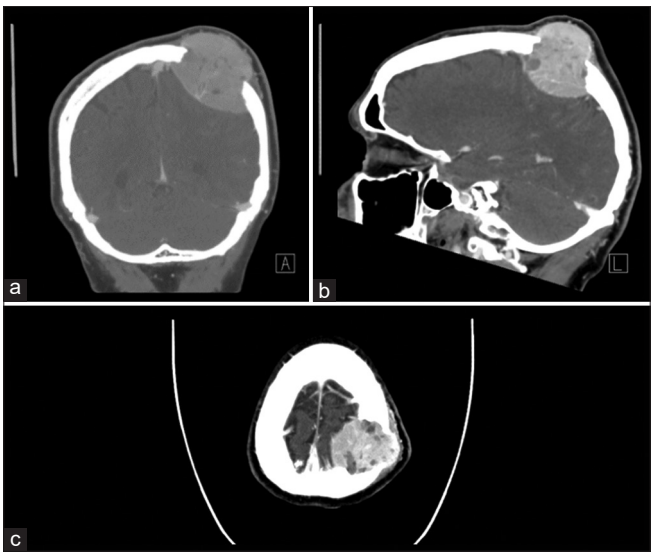

Figure 1: (a) Coronal noncontrast computed tomography (CT) radiograph. (b) Sagittal noncontrast CT radiograph. (c) Axial noncontrast CT radiograph. Scans show heterogeneously enhancing mass centered in the high left parietal bone that measured approximately 5.0 × 4.5 × 4.6 cm with intracranial extension. There is mass effect upon the high left posterior frontoparietal brain where there may have been a trace amount of vasogenic edema. No abnormal parenchymal brain enhancement is noted. No acute intracranial hemorrhage or extra-axial fluid collections were identified. No areas that are strongly suspicious for acute cortical infarction or contusion were seen.

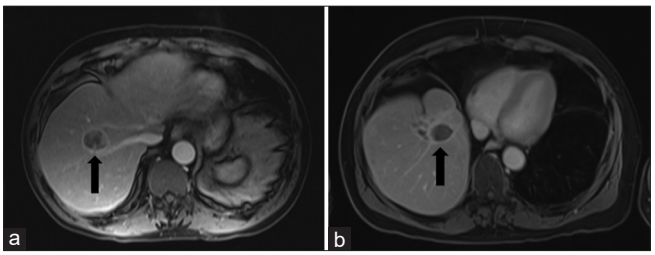

Figure 2: (a) Contrast-enhanced, fat-saturated axial T1 image before treatment. The black arrow points to a rim-enhancing lesion centered in the right hepatic lobe. (b) Contrast-enhanced, fat-saturated axial T1 image after treatment. The black arrow points to the treated lesion in the right hepatic lobe.

venous sinuses appeared patent. No abnormal parenchymal brain enhancement was noted. No masses were seen in the suprasellar cistern. The major arterial structures of the brain appeared grossly patent. No acute intracranial hemorrhage or extra-axial fluid collections were identified. No areas that are strongly suspicious for acute cortical infarction or contusion were seen.

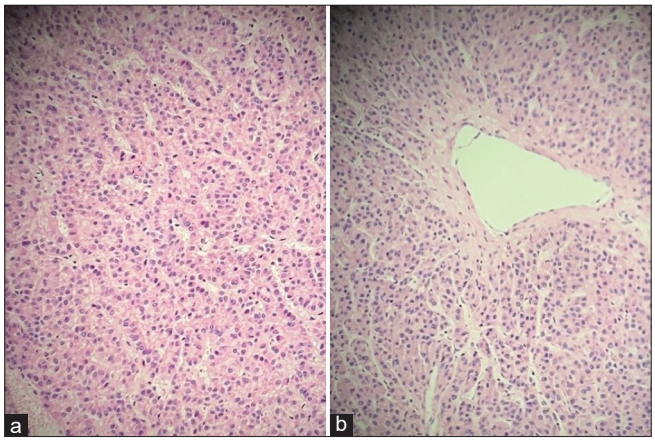

Figure 3: (a) (H&E stain, ×15) Medium power view showing epithelioid tumor cells in cords and trabeculae separated by sinusoids. The underlying tissue has been completely replaced. (b) (H&E stain, ×15) Medium power view showing thickened cords and nests (>2–3 cells thick) of tumor cells and central dilated blood vessel.

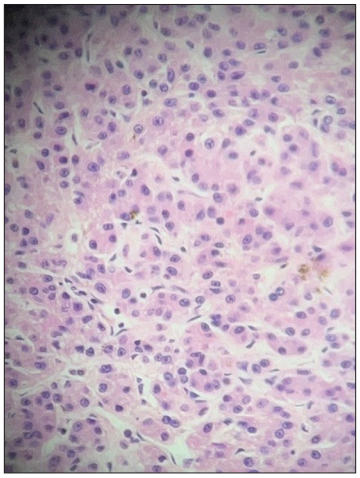

Figure 4: (H&E stain, ×25) High power view showing tumor cells with prominent nucleoli, abundant eosinophilic cytoplasm and well-defined cell borders. Please also note small spindled endothelial cells surrounding the cell nests in so-called endothelial wrapping. Occasional cytoplasmic pigmentation was also identified.

Preoperative evaluation included a CT of chest/abdomen/pelvis showing expected treated hepatic lesions and no new lesions [Figure 2]. Complete blood count, chemistry, coagulation panel, and liver function tests were within normal limits. The present skull mass was resected *en bloc* with removal of all involved skull. After retracting the uninvolved scalp, the skull was circumferentially cut 1 cm from the margin of the protruding mass and the mass and involved skull gently elevated off the dura. The dura and galea were completely intact. The tumor was quite firm and dark brown. Burr holes were placed in the skull about 1 cm from the edge of the tumor and then connected through a drill to perform a complete craniectomy with the involved intraosseous tumor. During the *en bloc* removal of the involved skull and intraosseous tumor, the tumor was noted to have a firm intact capsule over the component that had grown out of the skull and was bulging intracranially as well as the part bulging out extracranially. The tumor lifted off the dura with minimal dissection using a periosteal elevator. The dura remained completely intact and looked normal. Given the appearance of no dural invasion, a dural biopsy was not taken. One may have considered resecting the large area of adjacent dura and performing a duroplasty. That may have increased the risks of possible intradural recurrence. We did place a large titanium concave mesh to cover the skull defect after careful inspection of the resection site. A synthetic cranioplasty implant was created based on a postoperative head CT and the patient brought back to the operating room about 1 month later for implantation of it. There was minimal blood loss in both procedures.

The mass was well encapsulated and soft. Inspection after removal revealed a mass centrally necrotic with limited vascularity. Gross total resection was achieved and postoperative chemotherapy and immunotherapy were initiated with Atezolizumab and Bevacizumab. The

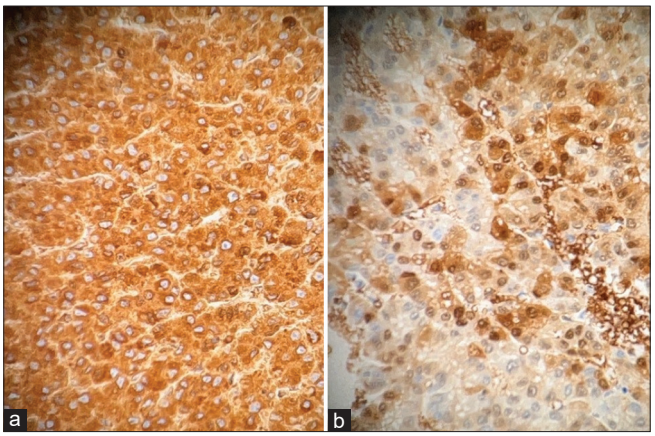

Figure 5: (a) (Hepatocyte immunostain, ×25) High power view of Hepatocyte immunostain showing strong and diffuse cytoplasmic granular staining. (b) (Arginase immunostain, ×25) High power view of Arginase immunostain showing strong focal cytoplasmic staining.

pathology analysis was consistent with the diagnosis of an intraosseous metastatic HCC-skull tumor without any neural parenchymal involvement. The tumor cells stained positive for cytokeratin AE1, AE3, hepar, and arginase-1 [Figures 3-5]. The tumor cells were negative for glypican-3, cytokeratin 7, cytokeratin 20, alfa-fetoprotein, thyroid transcription factor 1, synaptophysin, and chromogranin. The patient is still alive and has not had any recurrence of HCC in the liver, skull, or elsewhere.

REVIEW

Clinical presentation

Of the five reported cases of solitary HCC-skull metastasis without known primary cancer, the average patient age at time of diagnosis was 53.8 years (range: 40–71 years) [Table 1]. All patients were male, which reflects the overt male-skewed incidence of HCC-skull metastasis described within the literature. Prior liver disease was found in 2/5 patients (hepatitis B in one patient and long-term alcohol abuse in another patient). Four patients presented with a palpable, firm bump on the head, two of which were associated with local pain to the scalp, and two were painless. The fifth patient presented with a skull base lesion and thus, did not present with a bump on the head. Per Hsieh *et al.* 59% of patients with HCC-skull metastases reported pain at the site of skull lesion, with headaches and seizures occurring in 15% and 3% of patients, respectively.[3] The patient with the skull-base lesion presented with neurological sequalae, including right cranial nerve III, IV, and V palsy (ptosis, restricted ocular movement, and diplopia). No other patients presented with neurological symptoms. As these lesions were discovered without knowledge of primary liver carcinoma, no patients presented with symptoms consistent with hepatological or gastrointestinal pathology.

Radiological features

These reported tumors tended to be large at presentation (mean: 7.5 cm, range: 4 cm, 11 cm). Tumor location varied, but involved the occiput in 3/4 patients that had calvaria lesions (excluding the aforementioned skull-base lesion). All cases involving the calvarium were described as homogenous, well-defined lesions with gadolinium enhancement on T1-weighted MRI. On T2 sequences, the tumors appeared isointense. Only Subasinghe *et al.* and Jiang *et al.* included

Table 1: Demographic, clinical, and radiographic summary of all reported solitary HCC-skull metastasis without known primary HCC.

Author	Patient age	Patient sex	Prior liver disease	Clinical presentation	Image type	Image characteristic	Tumor largest dimension (cm)	Tumor size (cm)	Tumor location
Bernstein (2022)	#	M	HCC	Bump on head with headache	CT	Heterogeneous; enhancement; well-defined	_	_	L, parietal
Ferraz *et al.* (2016)	#	M	None	Bump on head with local pain	T1 MRI	Homogenous; gal enhancement; well-defined	#	11×10×5	R, frontal
Subasinghe *et al.* (2015)	#	M	Alcohol abuse	Painless bump on head (nonmovable)	XR CT	Unavailable	#	#	Midline occipital
Jiang *et al.* (2014)	#	M	Hepatitis B	Painless bump on head (nonmovable)	CT T1 MRI T2 MRI	Homogenous; gal enhancement; well-defined	5	5×5	R parieto-occipital
Trivedi *et al.* (2009)	#	M	None	R 3, 4, 5 cranial nerve palsy (ptosis, restricted movement, diplopia of R eyeball)	T1 MRI T2 MRI	Heterogenous	--	Unavailable	Sellar, parasellar, sphenoid, extending to clivus
Shim *et al.* (2008)	#	M	None	Nonmovable mass; intermittent mild tenderness	T1 MRI T2 MRI	Homogenous; gal enhancement; well-defined	4	3×4	Midline occipital

HCC: Hepatocellular carcinoma, MRI: Magnetic resonance imaging, CT: Computed tomography, XR: X-ray, M: Male, L: Left, R: Right

Table 2 : Surgical and pathology characteristics of all reported solitary HCC-skull metastasis without known primary HCC.

Author	Surgery	Dura in tact?	Radiotherapy in brain?	Histopathology comments	Outcome
Bernstein (2022)	*En bloc* resection	Yes	None	Cytokeratin AE1, AE3, hepar, and arginase-1	Alive at 4 months after diagnosis
Ferraz *et al.* (2016)	*En bloc* resection	No	Postoperative adjuvant radiotherapy	Villin, pCEA, CD34, CK7 and CD10, and Hepatocyte	Died 6 months after diagnosis due to liver failure
Subasinghe *et al.* (2015)	Palliative excision of scalp	Yes	None	AFP, hepar 1 staining	Unavailable
Jiang *et al.* (2014)	*En bloc* resection	Yes	None	Pleiomorphic tumor cells w/ eosinophilic cytoplasm, prominent nucleoli, mitosis	Died 18 months after diagnosis due to liver failure
Trivedi *et al.* (2009)	None	NA	3,000 cGy over 10 days to skull lesion	r AFP, cytokeratin, AE1, and epithelial membrane antigen	Died 4 months after diagnosis
Shim *et al.* (2008)	*En bloc* resection	Yes	None	Pleomorphic tumor cells with eosinophilic cytoplasm and prominent nucleoli arranged in both a trabecular and solid pattern	Alive at 9 months after diagnosis

AFP: Alfa-fetoprotein, HCC: Hepatocellular carcinoma, pCEA: Polyclonal carcinoembryonic antigen, NA: Not applicable, AE: Anticytokeratin monoclonal antibodies

CT imaging, which revealed osteolytic destruction of the skull with intracranial extension, but without penetration of the meninges or brain parenchyma.[4,8] In addition, Trivedi *et al.* and Jiang *et al.* reported a hypervascular enhancement on CT.[4,8,10] It is noted that most skull metastases are hypervascular, osteolytic, and expansile.[9] The skull-base lesion was described as a heterogenous lesion on CT. All tumors appeared as intraosseous masses and did not violate the dura or galea.

Clinical management

Proper investigation into a primary site of cancer is essential in the workup of these patients and all articles referred to this in their clinical management. Ferraz *et al.* were not specific in their workup for this.[2] Subasinghe *et al.* and Jiang *et al.* conducted abdominal CT scans,[4,8] while Trivedi and Shim mentioned "retrograde diagnostic workup was performed to detect primary cancer," but without mention to specific imaging modality.[7,10] Any skull lesion that includes metastases in the differential could be best investigated for a primary tumor through CT of the chest, abdomen, and pelvis with and without contrast.

For treatment, 3/5 studies performed *en bloc* resection with craniectomy at the site of the lesion. 1/5 performed palliative excision of the scalp, but there was no mention of rationale of palliative excision versus gross total resection.[8] 1/5 studies did not perform any surgery; conservative treatment was recommended due to the advanced stage of the disease.[10] Two studies utilized radiotherapy: one study used postoperative adjuvant radiotherapy (radiation parameters not specified)[2] and the other utilized radiotherapy, without surgery, of 3000 cGy over 10 fractions.[10] In the four cases that underwent surgery, the dura mater was found to be intact in three of the cases and not intact in one of the cases.[2]

OUTCOMES

Outcomes in these few patients remain inconsistent, yet poor. 3/5 of these patients died due to liver failure (6 months,[2] 18 months,[4] and 4 months[10]), but none to pathology involving their cranial lesions. 1/5 patients did not report an outcome and 1/5 of the patients were alive at 9 months after diagnosis.[7] Mean survival time in a case series of 41 patients with HCC-skull metastasis (solitary or multiple) was 8.9 months, with most patients dying due to liver failure or internal bleeding before extrahepatic metastases can affect mortality [Table 2].[3,6]

CONCLUSION

Purely intraosseous skull masses are uncommon. Benign and malignant lesions, including metastases, should be considered in the differential diagnosis of a skull mass. Due to their rarity, HCC-skull metastases are not often reported in the literature, and there exists a paucity of articles discussing their clinical presentation, radiological imaging, pathology, and clinical management. Furthermore, HCC-skull metastases presenting as a solitary skull lesion in patients without known concomitant cancer are exceedingly rare and have only been reported 5 times; this present case report brings that total to 6. Here, we characterized a case

and summarized the existing data on solitary HCC-skull lesions in patients without known primary cancer.

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Declaration of patient consent

Patient's consent not required as patient's identity is not disclosed or compromised.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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