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Case Report

Isolated calvarial lesion as the initial presentation of metastatic hepatocellular carcinoma: A case report and review of the literature

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) contributes significantly to global cancer-related mortality, often because patients present at advanced stages of the disease. HCC commonly metastasizes to the lung, abdominal lymph nodes, and bone. However, even among bony metastases, calvarial lesions are exceptionally rare, especially in the initial presentation.

Case Description: We describe a unique case of a 65-year-old African American woman who presented with a rapidly growing skull lesion as her first clinical sign of metastatic HCC. Imaging revealed an extensive soft-tissue mass involving the left calvaria and partially obstructing the superior sagittal sinus. We suspected that the lesion was a meningioma and offered surgery. Histological examination and further systemic workup later confirmed HCC. She was started on adjuvant therapy but unfortunately deteriorated from complications secondary to disease progression. We also reviewed the literature on cases of isolated calvarial metastases as the initial presentation of HCC. A total of 36 case reports were reviewed which included 38 patients. There were 32 males (84.2%), and the mean age was 58.97 ± 9.09 years old. The most common location of presentation was the parietal or occipital region (13, 34.2%), and 18 patients (47.4%) underwent neurosurgical treatment of the lesion. Among the 26 cases that had a follow-up, 84.6% (n = 22) did not survive treatment, and the mean survival time was 6.15 ± 5.94 months.

Conclusion: Isolated calvarial lesions are rarely the initial presenting sign of metastatic HCC. Often, these lesions may be misdiagnosed as benign tumors, such as meningiomas or hemangiopericytomas, given their appearance on imaging. However, early identification of HCC skull lesions is crucial to initiating treatment, including resection, radiation, and immunotherapy, which may help improve symptoms and extend survival. Our case report adds to the limited literature on this exceedingly rare entity.

Keywords: Calvarial metastasis, Hepatocellular carcinoma, Literature review, Metastatic brain tumor

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common form of cancer globally but ranks second in cancer-related mortality.[12,31] The disease is prevalent in regions where hepatitis B

virus (HBV) infection is endemic, particularly in Asian and African nations. Dietary exposure to carcinogenic aflatoxins produced by *Aspergillus* fungi has also significantly elevated the risk of HCC in these countries.[31,58,63] In Western Europe and North America, increasing rates of HBV and hepatitis C virus (HCV), alcoholism, obesity, metabolic syndrome, and diabetes have contributed to a rising incidence of HCC.[3,58]

Early diagnosis of HCC, defined as stage 0 or A by the Barcelona Clinic Liver Cancer (BCLC) staging system, is associated with improved survival. Patients have up to three nodules in their liver with preserved liver function.[41] Patients with early-stage HCC who receive a transplant, resection, or local ablation have an expected 5-year survival rate of over 70%.[50] American and European society guidelines recommend screening high-risk patients, including patients with cirrhosis and chronic HBV infections, with biannual ultrasounds and alpha-fetoprotein (AFP) testing for detection of HCC.[13] However, despite these recommendations, only 40% of patients with HCC are diagnosed early.[49] In advanced BCLC stages C and D, patients have portal invasion and/or extrahepatic metastases and diminishing liver function. Expected survival is between 2 months and 2 years.[12]

HCC most commonly spreads to regional lymph nodes and the lungs, while bone metastases remain relatively uncommon.[35,56] Metastases to the skull, especially isolated instances such as the one presented here, are exceptionally rare, with only a limited number of documented cases.[46,56] In this report, we describe a unique case of an isolated skull lesion as the presenting sign of HCC in a 65-year-old woman. While rare, osseous metastases should remain on the differential for calvarial lesions. Patients with HCC calvarial lesions should be referred early for radiotherapy, chemotherapy, and surgical resection to relieve pain and reduce the risks of neurological sequelae with the goal of improving quality of life or even extending survival.[6,14] The purpose of this paper is to provide a case of a calvarial lesion as the initial presentation of HCC and provide a review of case reports and studies.

METHODS

PubMed and Embase databases were searched in April 2024 for case studies, reports or case series of skull metastases as the initial diagnoses for HCC. Articles were selected from 1980 to the present in the English language. All references were merged using a citation manager, and a title and abstract review was performed. Articles searched for papers that presented case reports or series with granular patient data. Systematic reviews, meta-analyses, and articles that did not provide sufficient granular data for cases were excluded from the study. Non-human studies were excluded from the study. Studies that included known diagnoses or recurrence of treated HCC were also excluded from the study. Following the title and abstract review, the following data were abstracted from full text review: age, gender, presenting symptoms, relevant laboratory values such as viral hepatitis titers, AFP, size and location of the metastasis, intervention, and overall survival. Care was taken to remove duplicated cases reported across studies by cross referencing patient demographics, patient history, and laboratory values.

CASE DESCRIPTION

Clinical presentation

A 65-year-old African American woman with a body mass index of 28.21 kg/m^2, 25-year smoking history, and chronic obstructive pulmonary disease presented with an enlarging solitary, firm, and protruding scalp mass that was tender to touch. She had no prior cancer diagnosis, hepatitis exposure, or history of cirrhosis preoperatively. Other than a headache, she did not have any neurological symptoms or focal deficits.

She had a computed tomography (CT) scan of the head, which showed a solitary mass at the vertex of the left calvaria. The mass extended both intracranially and extracranially, measured 8.5 cm × 8.5 cm × 5.5 cm, and crossed the midline, encroaching on the superior sagittal sinus [Figure 1]. A magnetic resonance imaging (MRI) of the brain showed an isointense lesion on T1 with heterogeneous enhancement after contrast administration and a mixed isointense and hyperintense mass on T2 [Figure 2]. The mass extended across the midline and inferiorly, resulting in partial compression of the underlying left frontoparietal parenchyma with no associated vasogenic edema. Given the increasing size of the lesion and the need for tissue diagnosis, we planned for surgical resection. We obtained a CT venogram to evaluate the patency of the superior sagittal sinus preoperatively. It demonstrated a partially occluded sinus at the site of the lesion but patency anteriorly and posteriorly. We also created a custom polyether ether ketone (PEEK) implant to fill the expected skull defect from the resection of the lesion.

Operative details

On the day of surgery, it was apparent that the lesion was even larger than it was at the clinic visit. We made a bicoronal incision to have adequate exposure to the lesion and left the temporalis muscle fascia intact at the inferior aspect of the incision bilaterally. Immediately, we encountered the lesion eroding through the bone into the subgaleal space. As we began the resection, we noted it to be extremely friable and hypervascular. Thus, we had to remove the lesion in a piecemeal fashion. While removing the extracranial portion of the lesion, the patient had lost enough blood, requiring vasopressor support despite blood transfusion. Therefore, we decided to close and stage the remainder of the resection. We allowed the patient to recover from surgery and brought the patient back to

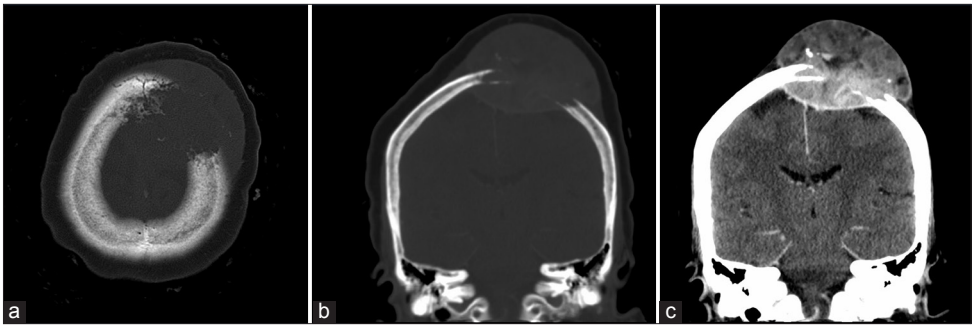

Figure 1: Preoperative computed tomography demonstrating a left parasagittal erosive calvarial lesion; (a) bone window axial image, (b) bone window coronal image, and (c) soft-tissue post-contrast coronal image.

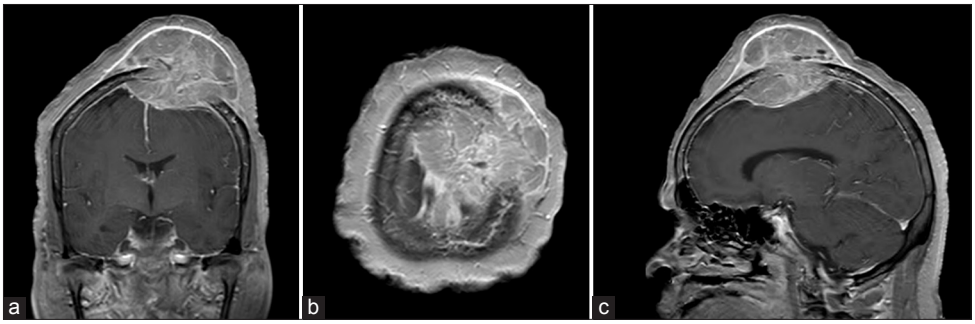

Figure 2: Preoperative magnetic resonance imaging T1-weighted post-contrasted scans (a) coronal, (b) axial, and (c) sagittal cuts showing an avidly enhancing left frontoparietal bony lesion with a dural base over the superior sagittal sinus.

the operating room 5 days later. During the second stage of the procedure, we drilled burr holes on either side of the superior sagittal sinus anteriorly to the lesion and posterior to the lesion. We then elevated a craniotomy flap encompassing the calvarial lesion. After removing the bone flap, we found the remaining tumor adherent to the midline dura and carefully dissected it from the underlying dura. Since the bone flap was infiltrated with tumor, we replaced the skull defect with the PEEK implant and a large titanium mesh. A postoperative MRI confirmed gross total resection of the mass [Figure 3].

Postoperative course

After surgery, the patient was admitted to the neurological intensive care unit. She recovered well and was discharged on postoperative day 11.

While awaiting her biopsy results, we obtained a CT scan of the chest, abdomen, and pelvis to identify a possible primary malignancy. The CT scan revealed a mass in the left hepatic lobe. Further evaluation of the mass with a liver ultrasound showed that it was a benign cyst, but there were nodular components within the cyst suggestive of hepatic dysfunction or cirrhosis. Her AFP level was notably elevated to 5369.3 ng/mL, and a hepatitis panel was positive for hepatitis A, B, and C.

Histology of the surgical tissue sections showed a neoplasm with high mitotic activity and areas of necrosis. The tumor exhibited a trabecular architectural pattern with intervening dilated vascular channels. The tumor cells were polygonal in shape, characterized by irregular nuclei with vesicular chromatin, prominent nucleoli, and clear cytoplasm. Immunohistochemical staining indicated positive expression for Cam5.2, Arginase, HepPar-1, and Albumin in situ hybridization, with focal positivity for somatostatin receptor Type 2 (SSTR2), all markers which have been identified in primary HCC.[28,29] Other markers, namely, epithelial membrane antigen (EMA), progesterone receptor (PR), paired box gene 8 (PAX8), cluster of differentiation 10 (CD10), renal cell carcinoma (RCC), S100, and Melanoma Cocktail staining, yielded negative results, ruling out other metastatic and primary tumor etiologies [Figure 4].

At the time of discharge, she was diagnosed as having BCLC stage A HCC. She was started on durvalumab and tremelimumab immunotherapy[1] and had begun palliative radiation therapy. Before completing these adjuvant therapies, however, she was readmitted for hemorrhagic shock due to acute hematochezia (postoperative day 77). She developed multiorgan failure and required intubation

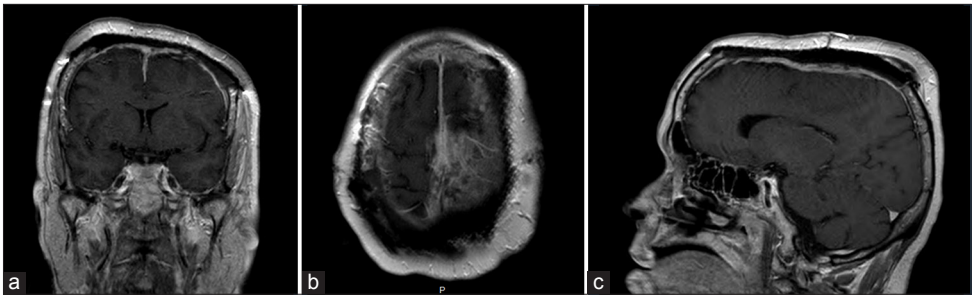

Figure 3: Postoperative magnetic resonance imaging T1-weighted post-contrasted scans (a) coronal, (b) axial, and (C) sagittal cuts demonstrating a gross total resection of the calvarial lesion.

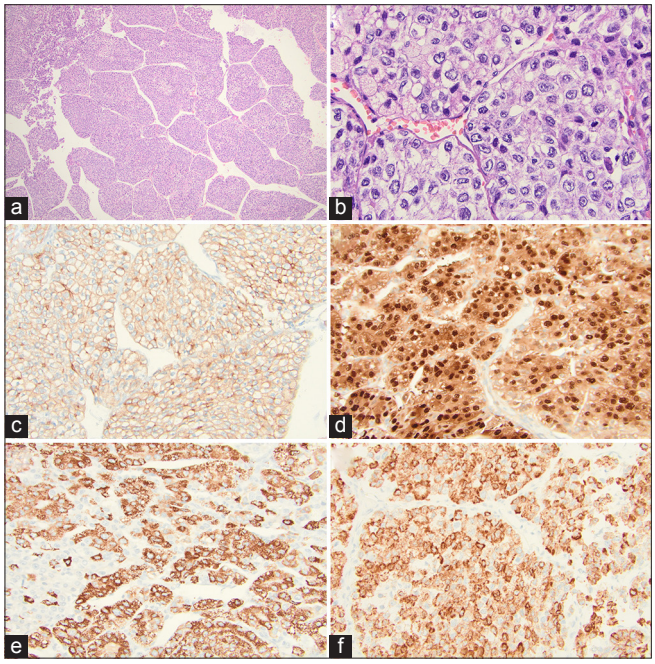

Figure 4: Histological examination of the surgical tissue specimen. (a) The tumor has a trabecular architecture with intervening dilated vascular channels. (b) The tumor cells are polygonal and have irregular nuclei with vesicular chromatin, conspicuous nucleoli, and clear cytoplasm. (c-f) The tumor stains positive for Cam5.2, Arginase, HepPar-1, and Albumin ISH.

and dialysis. The family ultimately decided to transition the patient to comfort care.

LITERATURE REVIEW

A total of 123 articles were screened of which 36 case reports were reviewed, of which 38 patients were included in the study. Figure 5 is a PRISMA diagram of the included studies. Among the 38 cases, the mean age was 58.97 ± 9.09 (median 59, interquartile range [IQR] 53.5–65) years old. There were 32 males (84.2%). 17 (44.7%) cases presented with growing skull lesions, and 15 (39.5%) presented with associated cranial deficits. Among the 38 cases, 17 (44.7%) had cirrhosis on presentation. The most common location of presentation was the parietal or occipital region (13, 34.2%), and 18 of the cases underwent neurosurgical treatment of the lesion (47.4%). Among the 26 cases containing a patient follow-up, 15.4% (n = 4) reported patient survival after treatment. Of the 84.6% (n = 22) that did not survive treatment, there was an average survival of 6.15 ± 5.94 months (median 4, IQR 0.97–10.3).

The remaining details are shown in Table 1.

DISCUSSION

The clinical presentation of HCC varies greatly depending on the grade of the tumor, the patient's hepatic function at the time of diagnosis, and the underlying cause. In patients with cirrhosis, overt symptoms are often evident, including manifestations of chronic liver disease such as ascites, jaundice, encephalopathy, and variceal bleeding.[3] The clinical presentation also varies geographically. In southern Africa and Asia, where HBV and HCV infections are prevalent, patients with HCC often exhibit signs of hepatic decompensation, such as jaundice, ascites, or encephalopathy.[31] Conversely, in countries with lower rates of HBV and HCV, such as the United States and Western European nations, many cases of HCC are detected through laboratory screening. In fact, approximately 40% of patients in these regions are asymptomatic at the time of diagnosis.[42]

HCC screening practices vary by country and are based on the prevalence of risk factors such as chronic HBV, HCV, and cirrhosis.[13] Countries with high rates of chronic HBV infection, such as China or South Korea, have national or regional screening programs for HCC. Countries such as Japan, with high rates of chronic HCV infection and cirrhosis, also implement routine screening for HCC.[48] Periodic abdominal ultrasounds or CT and serum AFP measurements are recommended in patients with HBV or HCV at risk for developing HCC.[19] While there is no routine screening in the United States, the American Association for the Study of Liver Diseases (AASLD) does provide guidelines for HCC surveillance in certain high-risk groups, particularly

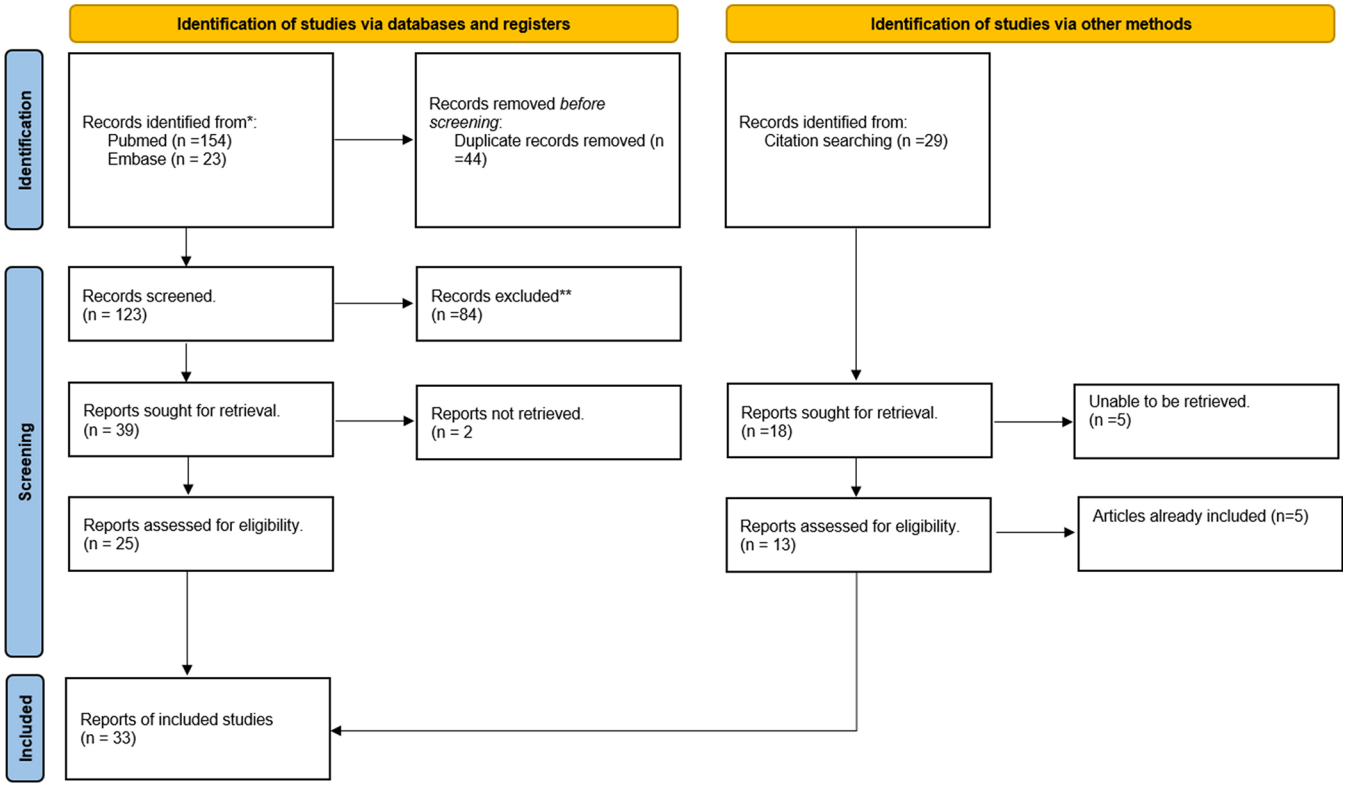

Figure 5: Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram of included studies.

individuals with cirrhosis. HCC risk sharply increases after cirrhosis develops, and the AASLD recommends ultrasonography, with or without AFP testing, every 6 months among these patients.[4,30] Despite these screening programs, patients may still present at an advanced stage.[15,20] Therefore, it is important to recognize that patients without a diagnosis of HCC may present with metastatic tumors, such as an isolated skull lesion, as the initial presentation.

Skeletal metastasis from HCC is an indication of advanced disease. It is a relatively rare occurrence, but certain osseous sites are more frequently affected, including the vertebrae, sternum, ribs, and long bones.[7,23] However, skull metastases are extremely uncommon, with only a few documented case reports in the literature.[6,24,25,32,46] In one of the largest series of HCC patients,[14] only 1.2% (8 out of 673 patients) had skull metastases. In another case series of nine patients of HCC with skull metastasis,[33] three presented with skull metastases as their initial manifestation of HCC. All the observed calvarial lesions were osteolytic. Common symptoms reported among these patients included the presence of a painful mass, headaches, and neurologic deficits.[33] Hsieh *et al.*[21] reported that 59% of patients with HCC-skull metastases experienced pain at the site of the skull lesion, with 15% reporting headaches and 3% experiencing seizures.

For patients with metastatic HCC calvarial lesions, therapeutic options remain palliative due to the advanced stage of the disease.[51] Out of the nine patients with calvarial metastases in the Murakami *et al.* series, five underwent radiation therapy, two received embolization, and only one underwent surgical resection.[33] The location of the lesion may guide management. Kim *et al.*[24] in a series of 39 patients found radiation therapy to improve cranial neuropathies for skull base lesions. However, this study included a heterogeneous sample of patients who received radiation alone, radiation plus surgical resection, and radiation plus systemic therapy, without comparisons among groups, making it difficult to comment on the effectiveness of each treatment modality. Due to their rarity, HCC-skull metastases are not often reported in the literature, and there is no consensus recommendation on the role of embolization, radiation, or resection in management.[14,21]

For our patient, she initially sought medical attention due to a growing skull lesion and headaches, without any neurological deficits. On imaging, the lesion was avidly enhancing and appeared to have a dural base with osseous erosion. Given no cancer history and the imaging appearance, including lack of cerebral edema, we suspected that the lesion was a meningioma. We considered hemangiopericytoma, given the hypervascularity observed during surgery. A preoperative staging CT scan of the chest, abdomen, and pelvis could have revealed other metastatic lesions, which would have narrowed the differential to a metastatic skull lesion. The

Table 1: Review of case reports and series of calvarial metastases as initial HCC presentation.

Author-Year	Patient	Symptoms	Viral hepatitis	Liver path	AFP (ng/mL)	Site of Met	Size of mass (cm)	Intervention	Time to death (mo)
Zakaria *et al.*, 2023[62]	53 M	CN deficit	former HBV+			Petrous temporal bone		Chemotherapy	4
Yang *et al.*, 2011[58]	61 M	CN deficit	HBV+, HCV+	Cirrhosis	5,200	Temporal Bone	5	Radiation	7
Nemetz, 2013[36]	54 M	CN deficit	Chronic HCV			Temporal bone	2.7	Radiation+ Chemotherapy	4
Yoshida, 1993[60]	78 F	Growing mass, headache			1500	Frontal Bone	2.5	Surgery	8
Shim *et al.*, 2008[46]	71 M	Growing mass	HCV+		2.5	Occipital bone	3×4	Surgery	
Guo *et al.*, 2014[17]	49 M	Growing mass	HBV+		12511.0	Parieto-occipital bone	5×5	Surgery	18
Shiraishi *et al.*, 1992[47]	45 M	CN deficit	former HBV	Liver dysfunction	13,958	Clivus		Chemotherapy	1
Trivedi, 2009[55]	40 M	CN deficit	Hbsag+		3.4	Sphenoid bone and clivus		Radiation	4
Pirbhai, 2013[39]	66 M	Growing mass		Cirrhosis	1210	Sphenoid wing		Radiation+ Chemotherapy	
Subasinghe *et al.*, 2015[51]	56 M	Growing mass			>3920	Occipital bone	10	Surgery	
Nakagawa *et al.*, 1992[34]	52 M	Headache	HCV+	Cirrhosis	13,541	Occipital bone	2	Surgery	2
Chan *et al.*, 2004[6]	75 F	Growing mass			wnl	Frontal Bone	2.5×3	Surgery	
Shah, 2015[44]	65 M	CN deficit				Clivus	3.1×3.2×4.4	Surgery	
Han *et al.*, 2017[18]	66 M	Headache	former HBV+	Cirrhosis	46.8	Occipital bone	6×5	Surgery	
Delgado Maroto *et al.*, 2019[9]	59 F	General malaise	HCV+	Cirrhosis	2476	Frontoparietal bone		Surgery	0.133
Ogosawara, 1988[37]	62 M	Growing mass				Occipital bone		Surgery	
Shibukawa, 1995[45]	77 F	Growing mass				Temporal bone		Surgery	8
Polat, 2017[40]	66 M	Growing mass				Parietal/Vertex		Surgery	
Sadik *et al.*, 2019[43]	54 M	Growing mass	Chronic HBC	Cirrhosis		Parietal/Vertex	3×4	Surgery	0.86
Susheela, 2015[53]	40 M	Growing mass	HBsAg+		6889	Frontal bone		Chemotherapy	12
Garcia Madrona, 2018[16]	52 M	Headache	HCV+	Cirrhosis		Occipital bone		Radiation+ Chemotherapy	0.5
Sun *et al.*, 2021[52]	49 M	Headache	HBV+			Occipital bone	9.5×5.3×8.6	Surgery	

(*Contd...*)

Table 1: (*Continued*).

Author-Year	Patient	Symptoms	Viral hepatitis	Liver path	AFP (ng/mL)	Site of Met	Size of mass (cm)	Intervention	Time to death (mo)
Yasunaga *et al.*, 1982[59]	53 M	Growing mass				Parieto-occipital bone	10×10	Surgery	
Kleinjung and Held, 2001[26]	59 M	CN deficit			2458	Sphenoid bone	7×5 × 4	Radiation	2
Chye *et al.*, 2015[8]	69 F	Growing mass, general malaise	HCV+		3815.1	Temporal bone		Surgery+Radiation	
Den Hollander *et al.*, 2013[10]	46 M	Growing mass, headache	HCV+		>200,000	Temporal bone	4×6		0.1
Torres *et al.*, 2002[54]	66 F	Growing mass		Cirrhosis	329	Occipital bone	5×4 × 1		1.5
Yu and Tierney, 2015[61]	65 M	CN deficit			"Low"	Clivus			
Lakshminarayan, 2013[27]	62 M	Headache, CN deficit		Cirrhosis	"Elevated"	Clivus			
Cathel, 2019[5]	65 M	Headache, CN deficit				Clivus			
Phadke, 1981[38]	55 M	General malaise		Cirrhosis		Parietal bone			0.25
Al-Ghanoudi, 2015[2]	63 M	Headache, CN deficit	HCV+	Cirrhosis	10.2	Sphenoid bone			
Faraji Rad *et al.*, 2010[11]	54 M	Headache, CN deficit		Transaminitis	39	Sphenoid bone and clivus			
Murakami *et al.*, 1995[33]	57 M	Headache, dysphagia		Chronic liver disease		Temporal bone		Radiation	21
Murakami *et al.*, 1995[33]	59 M	Headache, diplopia		Chronic liver disease		Temporal bone		Radiation	11
Murakami *et al.*, 1995[33]	59 M	Growing mass		Chronic liver disease		Sphenoid bone		Transcatheter arterial embolization	12
Jegou *et al.*, 2004[22]	55 M	Growing mass		Cirrhosis		Frontal Bone	6	Radiation+ Chemotherapy	8
Wakisaka *et al.*, 1990[57]	58 M	Diplopia, ptosis, exophthalmos				Frontal bone		Surgery	10

CN: Cranial nerve, HBV: Hepatitis B virus, HCV: Hepatitis C virus, AFP: Alpha fetal protein, HCC: Hepatocellular carcinoma

patient would have still required, at a minimum, a biopsy for histologic confirmation before initiating treatment. Ultimately, the patient's positive hepatitis antigens and a high AFP, as well as the tissue histopathologic features and immunohistochemical staining positive for Cam5.2, Arginase, HepPar-1, and Albumin *in situ* hybridization, with focal positivity for SSTR2 confirmed the diagnosis of metastatic HCC. Interestingly, the characteristic sinusoid microvascular growth pattern commonly associated with HCC can occasionally be misinterpreted as the solid pattern observed in anaplastic or malignant meningiomas.[52]

HCC skull metastases, unfortunately, reflect a poor prognosis. The patient in our study presented as a BCLC stage A, but over three months, rapidly progressed in disease severity. On her second admission, she developed multiorgan failure, ultimately succumbing to the disease. Our literature review focused on cases with cranial metastasis as the initial presentation of HCC from 1980 to the present, encompassing 38 articles and 40 patients. Unlike previous studies that varied in scope–containing nonspecific intracranial/intraparenchymal metastasis,[62] or skull metastasis in the setting of known HCC,[17] or metastasis only to the skull base[11] – our review reviews only intracranial, calvarial metastases as an initial presentation of HCC.

Among the selected patients, there was an age range of 40–78 with an 84.2% male predominance. Similarly, Sadik *et al*.,[43] report an age range of 38-81 with a predominately male sample (94%). Han *et al*.,[18] in their review of 10 patients, demonstrated a smaller range from 38 to 69 years old and also a predominantly male sample as well (70%). This review finds that 44.7% of patients presented with a growing subcutaneous mass, and 39.5% had cranial neuropathies. In comparison, Sadik *et al*., find 59% of initially presented with scalp lesions. Of the patients who present with skull base lesions, 59% had cranial neuropathies.[43] The findings within the paper reiterate the findings presented in these other reviews.

Survival was reported for 22 patients, which ranged from 4 days to 21 months post-diagnosis. Surgical removal was the most common intervention in our review in 47% of cases. In contrast, the Sadik *et al*.,[43] series of 17 reports shows that 94% of patients underwent surgical resection and a mortality rate of 24% (four patients), ranging from 5 days to 13 months post-diagnosis. However, the limited sample size of Sadik *et al*.[43] presents an issue in interpreting the efficacy of surgical intervention and comparative treatment outcomes. One consideration, and a potential area for retrospective critique, would have been to pursue a more extensive systemic workup before surgery. While the patient presented with a symptomatic, enlarging dural-based lesion exhibiting local mass effect would still have resulted in operative intervention, the additional workup may have provided earlier insight into an underlying disseminated malignancy. This could have prompted earlier involvement from oncology, even though, in many cases, definitive management still hinges on obtaining primary tissue diagnosis. Consequently, a larger patient sample with specific criteria similar to our review is essential for a better understanding of HCC skull metastases and will ultimately guide future management and treatment protocols.

CONCLUSION

Isolated intraosseous skull masses are relatively uncommon lesions, and the differential is broad. Metastatic lesions are among the considerations; however, skull lesions are usually not the first presentation of malignancy. In HCC, the number of documented cases of calvarial lesions is low, and the appearance of a solitary calvarial lesion as the initial presentation of HCC is exceptionally rare. Our case report adds to the limited literature on the presentation, diagnosis, and management of HCC skull lesions.

Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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