

Solitary skull metastasis as the first symptom of hepatocellular carcinoma: case report and literature review

Xieli Guo^{1,2}

Jiangliu Yin³

Yugang Jiang¹

¹Department of Neurosurgery, Second Xiangya Hospital of Central South University, Changsha, Hunan, People's Republic of China;

²Department of Neurosurgery, Jinjiang Hospital of Quanzhou Medical College, Jinjiang, Fujian, People's Republic of China; ³Department of Neurosurgery, Changsha Central Hospital, Changsha, Hunan, People's Republic of China

Abstract: Skull metastasis from hepatocellular carcinoma (HCC) is reported rarely. In addition, solitary skull metastasis as the first symptom of HCC is reported even less. Here, we reported a case of solitary skull metastasis as the first symptom of HCC and reviewed the literature on skull metastasis. A 49-year-old male patient was admitted to Jinjiang Hospital of Quanzhou Medical College with a painless parietal-occipital scalp mass, and he denied any history of hepatic disease. A cranial computed tomography demonstrated a hypervascular enhancement with osteolytic change in the right parietal-occipital region, cranial magnetic resonance imaging indicated a highly enhanced and osteolytic skull tumor, and abdominal computed tomography showed a huge tumor in the liver. The other examinations showed no other metastases. Laboratory data showed no liver dysfunction while hepatitis B surface antigen was positive, and alpha fetal protein level was high. A craniectomy was performed and the mass was totally removed. The histological diagnosis was skull metastasis from HCC. The patient was subsequently treated by transcatheter arterial chemoembolization. In a review of published literature, the incidence of skull metastasis from HCC in the period between 1990 and 2011 has significantly increased. The misdiagnosis rate of skull metastases as the first symptom from HCC was high. Therefore, it is necessary to give each patient with a scalp mass that has invaded the skull a liver ultrasound or computed tomography scan. On the other hand, we found that metastases that occurred in the calvaria site were more frequent than those that occurred in the skull base and facial skeleton. This may be worthy of further investigation in the future.

Keywords: hepatocellular carcinoma, skull metastasis, bone metastasis, positron emission tomography

Case report

A 49-year-old male visited Jinjiang Hospital of Quanzhou Medical College with the complaint of a painless mass in the right parietal-occipital region of the skull. The mass was found incidentally 1 month earlier by the patient himself and it had grown rapidly. He denied any head traumas or any significant medical problems, including prior history of hepatic disease or chronic alcoholism. Bony window of cranial nonenhanced computed tomography (CT) scan showed a 5×5 cm² soft tissue mass with irregular destruction (Figure 1A), and contrast-enhanced CT scan showed a hypervascular enhancement with osteolytic pathological change in the parietal-occipital region of the skull (Figure 1B). On admission, neurological and physical examinations revealed no neurological deficits, hepatomegaly, or obvious abnormalities except a painless non-movable mass about 5×5 cm² in size over the right parietal-occipital region. Laboratory data showed no liver dysfunction while HBsAg (hepatitis B surface antigen) was

Correspondence: Yugang Jiang
Department of Neurosurgery, Second Xiangya Hospital of Central South University, 139 renmin Middle Road, Changsha, Hunan, 410011, People's Republic of China
Tel/fax +86 159 6079 5588
Email: yugangjiang123@126.com

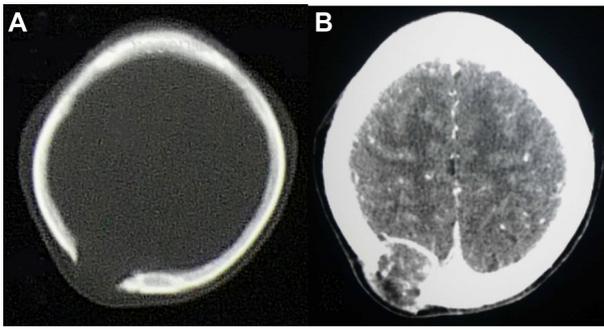


Figure 1 CT of cranial bones.
Notes: (A) Bony window of cranial CT scan showed a 5 × 5 cm² soft tissue mass within the irregularly destructive area of the right parietal-occipital region of the skull. (B) Contrast-enhanced CT scan showed a hypervascular enhancement with osteolytic pathological change in the parietal-occipital region of the skull.
Abbreviation: CT, computed tomography.

positive, and AFP (alpha fetal protein) level was high (Table 1). On cranial magnetic resonance imaging, the tumor was a homogeneous well-defined mass with involvement of the inner and outer skull table. It revealed isosignal intensity on T2-weighted (Figure 2A) and T1-weighted imaging (Figure 2B), with significant enhancement by gadolinium (Figure 2C). Abdominal B ultrasound showed a large mass in the right lobe of the liver (Figure 3); therefore,

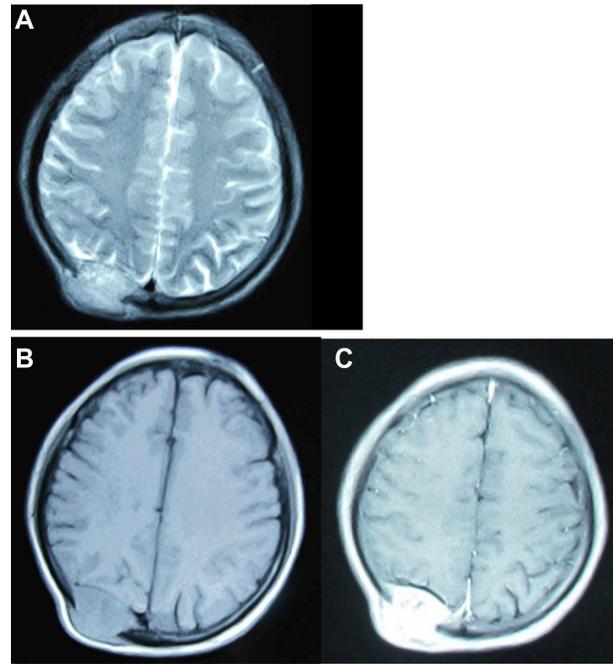


Figure 2 MRI of cranial bones.
Notes: (A) T2-weighted MRI and (B) T1-weighted MRI demonstrated a homogeneous, well-defined, and isosignal intensity carcinoma in the right parietal-occipital region. (C) Gadolinium enhanced T1-weighted MRI images showed a strong enhancement of the carcinoma.
Abbreviation: MRI, magnetic resonance imaging.

Table 1 Laboratory data on admission

Hematology	Blood chemistry	Serological tests	Coagulation tests
WBC 6.46 × 10 ⁹ /L	T-Bil 15.30 μmol/L	AFP 12511.0 ng/mL	PT 10.30 s
RBC 4.00 × 10 ⁹ /L	D-Bil 4.83 μmol/L	CEA 1.7 ng/mL	APTT 24.40 s
Hb 118.00 g/L	TP 59.60 g/L	CA 19-9 15.6 μ/mL	TT 15.70 s
Ht 29.5%	Alb 37.00 g/L	CYFRA 21-I 5.21 ng/mL	PT% 154.80%
Plate 110 × 10 ⁹ /L	Glb 22.60 g/L	HBsAg (+)	D-dimer 435.00 μg/L
	AST 37 μg/L	HCVAb (-)	
	ALT 33 μg/L		
	GGT 138 μg/L		
	ALP 153 μg/L		
	CHE 32 μg/L		
	LDH 166 μg/L		
	T-chol 3.56 mmol/L		

Abbreviations: Hb, hemoglobin; Ht, hematocrit; Plate, platelets; RBC, red blood cells; WBC, white blood cells; T-Bil, total bilirubin; D-Bil, direct bilirubin; TP, total protein; Alb, albumin; Glb, globulin; AST, aspartate transaminase; ALT, alanine transaminase; GGT, gamma glutamyl transpeptidase; ALP, alkaline phosphatase; CHE, cholinesterase; LDH, lactate dehydrogenase; T-chol, total cholesterol; AFP, alpha fetal protein; CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9; CYFRA 21-I, Cytokerantin-19-fragment CYFRA 21-I; HBsAg, hepatitis B surface antigen; HCVAb, hepatitis C virus antibody; PT, prothrombin time; APPT, activated partial thromboplastin time; TT, thrombin time; s, seconds.

a contrast-enhanced CT of the abdomen and a nonenhanced CT of the breast were taken. Contrast-enhanced CT of the abdomen showed a huge enhanced carcinoma in the right lobe of the liver (Figure 4A–C). Nonenhanced CT of the breast showed no lung metastases (Figure 5). A single-photon emission computed tomography of total skeletal bones showed no metastases (Figure 6). Our diagnosis was

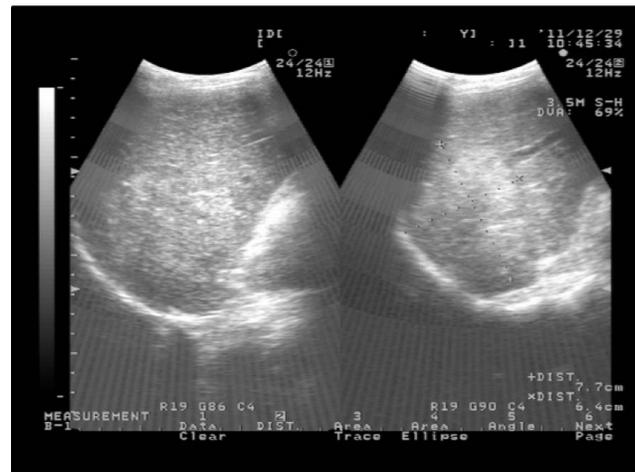


Figure 3 Abdominal B ultrasound showed a large mass in the right lobe of the liver.



Figure 4 Contrast-enhanced computed tomography of abdomen showed a huge enhanced carcinoma in the liver.
Notes: (A) Plain. (B) Arterial phase. (C) Portal phase.



Figure 5 Computed tomography (CT) of breast showed no lung metastases.

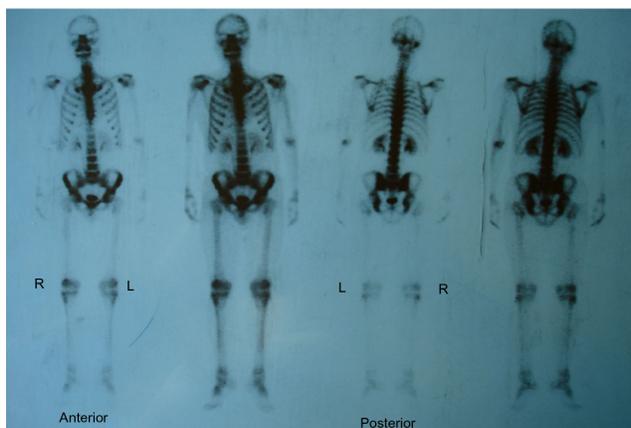


Figure 6 Single-photon emission computed tomography of total skeletal bones showed no other metastases.

hepatocellular carcinoma (HCC) with skull metastasis and chronic hepatitis B.

The carcinoma was radically resected with surrounding normal bone via right parietal-occipital craniectomy under general anesthesia. During the operation, a large and well-demarcated reddish-brown mass was found to have penetrated both tables of the skull through the diploic space. The carcinoma looked like cauliflower, and the underlying dura was intact and did not show any evidence of gross carcinoma invasion. The dural surface attached to the carcinoma was curetted and the rough surface of the dura was cauterized by bipolar forceps. The carcinoma was totally removed. Histopathological examination of the carcinoma revealed pleomorphic tumor cells with eosinophilic cytoplasm, and prominent nucleoli and mitosis arranged in trabecular and solid pattern. The pathological findings confirmed the diagnosis of metastatic HCC (Figure 7A and B). Postoperative recovery was satisfactory. To treat the primary carcinoma, transcatheter arterial chemoembolization with pirarubicin (40 mg), carboplatin (200 mg), floxuridine (250 mg), Lipiodol, and Gelatin sponge particles was performed after selecting a feeding artery of the tumor on aortography. The patient was discharged 1 month later. The patient survived after half a year of follow up and did not show any evidence of recurrence in the skull. However, because of the recurrence of hepatocellular carcinomas, the patient died from liver failure in the 18 months since he received transcatheter arterial chemoembolization.

Discussion

Hepatocellular carcinoma is the fifth most common cancer in the world and is especially prevalent in Africa and East Asia.¹ The incidence of HCC in developing countries is

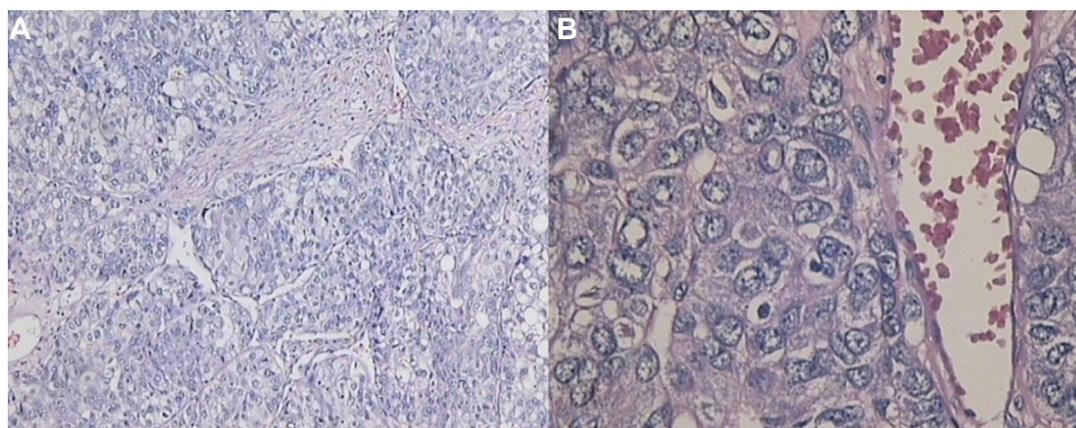


Figure 7 The histopathological characteristics of carcinoma and the immunohistochemical finding.

Notes: (A) Histopathological characteristics of carcinoma. The carcinoma showed thick trabecular growth pattern with intercellular canaliculi resembling liver cell plates and sinusoids. The carcinoma cells maintain a polygonal shape and have abundant granular eosinophilic cytoplasm, round vesicular nuclei, and prominent nucleoli (HE $\times 200$). (B) The immunohistochemical finding. The carcinoma cells show glypican-3 (+), AFP (-), villin (++), CK7 (-), CK20 (-), vimentin (-), CD10 (-), and Ki67 (+) of about 30%. **Abbreviations:** HE, hematoxylin-eosin staining; AFP, alpha fetal protein; CK, creatine kinase; CD, cluster of differentiation or leukocyte differentiation antigen; Ki67, nuclear-associated antigen Ki67.

third most common of the various types of cancer.² Intrahepatic metastasis is the most common metastasis of HCC. Extrahepatic metastases of HCC usually occurs in the regional lymph nodes (16%–40%) and lungs (34%–70%), but less commonly in the skeleton (1.6%–16%).^{3–6} In skeleton metastasis, HCC usually metastasizes preferentially to the vertebral column, pelvis, femora, and ribs, but rarely to the skull. The incidence of skull metastases from HCC is 0.4%–1.6%,^{3–5,7,8} and 9% of patients with calvarial metastases have other skeletal deposits.⁹

After a thorough search of the literature, we found 48 articles in total describing patients who were identified with calvaria, skull base, or facial skeleton metastasis from HCC, which formed the basis of this review. In our review of published literature, a total of 59 patients with skull metastasis from HCC were found.^{1,3,7,8,10–53} The incidence of skull metastasis from HCC in the period between 1990 and 2011 was significantly increased compared to incidence in the period between 1966 and 1989 (45:14, respectively)

Table 2 Summary of reported cases in the literature with skull metastases from HCC (n=59)*

Period	Calvarial metastases	Skull base metastases	Facial skeleton metastases	Total
1966–1989	6	4	4	14
1990–2011	25	12	8	45
Total	31	16	12	59

Note: *Fourteen cases in the literature with solitary skull metastases from HCC were reported.

Abbreviation: HCC, hepatocellular carcinoma.

because of the prolonged survival rate of HCC patients due to the recent progress in both the diagnosis and treatment of the primary lesion after 1990. Metastases occurring in the calvarial site were more frequent than those occurring in the skull base and facial skeleton (31:16:12, respectively) (Table 2). This may be because of the fact that calvarial metastases are more easily found and HCC cells have more affinity to calvaria. In our review, 24 cases with the skull metastases as the first symptom from HCC (24/59, 41%) and 14 cases with the solitary skull metastases from HCC (14/59, 24%) were identified (Table 3). In all 24 cases of the skull metastasis as the first symptom from HCC, almost 71% of these cases were misdiagnosed (17/24). The reason for the high rate of misdiagnosis is that the incidence of skull metastasis of HCC is low and doctors lack a full understanding of this disease. We must pay more attention to such cases in order to reduce the misdiagnosis rate, diagnose as early as possible, and give the patients best treatment to improve their prognosis and quality of

Table 3 Summary of reported cases in the literature with skull metastases as the first symptom from HCC (n=33)

Period	Misdiagnosis*			Total
	Calvarial metastases	Skull base metastases	Facial skeleton metastases	
1966–1989	4 (4)	0 (0)	1 (1)	5 (5)
1990–2011	10 (8)	7 (4)	2 (0)	19 (12)
Total	12	7 (4)	3 (1)	24 (17)

Note: *The data in parentheses is the number of patients who were misdiagnosed.

Abbreviation: HCC, hepatocellular carcinoma.

life. Molecular imaging by positron emission tomography is, therefore, set to probe the molecular abnormalities that are the basis of disease and provide different additional biochemical or molecular information about primary brain tumors.^{54,55} In all, it is necessary to give each patient with a scalp mass that has invaded the skull molecular neuroimaging, such as positron emission tomography, to reduce the misdiagnosis rate and to rule out the possibility of skull metastasis from HCC.

Disclosure

The authors report no conflicts of interest in this work.

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