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Extensive Solitary 7 × 9 × 11 cm Extracranial and Intracranial Metastasis from Hepatocellular Carcinoma with Orbital Infiltration

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Abstract

We report the case of a 78-year-old male patient with a solitary 7 cm × 9 cm × 11 cm extracranial and intracranial metastasis from hepatocellular carcinoma. Because of the swelling of his right temporal region, a benign soft-tissue tumor was initially considered as a cause. A resection attempt was performed, resulting in severe bleeding from tumor tissue. A biopsy provided diagnostic evidence of HCC. Eighteen months later the patient presented with a symptomatic secondary generalized seizure and the tumor threatened to ulcerate through the skin. A diagnostic assessment revealed that the tumor extended to the skull base and had infiltrated the orbita, dura, and calvaria.

Keywords: Hepatocellular carcinoma; Intracranial metastasis; Extracranial metastasis; Orbital infiltration

Introduction

The incidence of hepatocellular carcinoma (HCC) is increasing in Germany (5 cases per 100,000 persons) as a result of the growing number of patients with cirrhosis of the liver. Male gender, obesity and diabetes mellitus are important risk factors. People aged between 50 and 60 years are most commonly affected. The main cause of HCC (80% to 90%) is liver cirrhosis of any etiology (Table 1). Non-cirrhotic causes of HCC are non-alcoholic steatohepatitis, aflatoxin B1, androgen abuse and chronic hepatitis B infection.

Only 10% of HCCs metastasize via the hematogenous way and thus spread to extrahepatic sites 23. The most common sites of HCC metastasis are the regional lymph nodes, the lungs, bone, and the adrenal glands 11. The most frequent extrahepatic site of hematogenously spread metastases is the lung (40%).

The signs and symptoms of HCC are usually nonspecific and are only exhibited in more advanced stages of disease. They may include pain in the upper abdomen, fatigue, loss of weight and appetite, and jaundice.

Etiology of liver cirrhosis		Percentage
Toxic origin	Alcohol	50% to 60%
	Non-alcoholic fatty liver disease	<5%
	Occupational exposure (e.g. tetrachloromethane)	<1%
Infectious origin	Hepatitis C	>20%
	Hepatitis B	<10%
	Parasites (Leishmania, Plasmodium, Schistosoma)	<1%
Medications	Amiodarone, methotrexate (and other chemotherapeutic agents)	<5% to 10%
Autoimmune diseases	Autoimmune hepatitis	1% to 5%
	Primary biliary cholangitis, primary sclerosing cholangitis	1% to 3%
Metabolic disorders	Haemochromatosis	1% to 3%
	Wilson's disease	1%
	Alpha-1 antitrypsin deficiency	<1%
	Porphyria	<1%
Vascular origin	Budd-Chiari syndrome	<1%
	Cardiac cirrhosis	1% to 2%
	Osler's disease	<1%
Cryptogenic origin	Unknown cause after a comprehensive diagnostic evaluation	10%

Table 1: Possible causes of liver cirrhosis.

Primary tumor	Percentage
Bronchial carcinoma	40% to 60%
Breast cancer	10% to 40%
Malignant melanoma	10% to 55%
Tumors of the urogenital tract	5%
Tumors of the gastrointestinal tract	5%

Table 2: Frequency distribution of intracranial metastases.

Curative treatment modalities are an option only in the absence of vascular infiltration and in the absence of metastasis at the time of diagnosis. Such cases can be surgically managed by partial hepatectomy or liver transplantation.

The median survival of patients receiving palliative care for HCC with metastases or vascular invasion is 6-12 months from the time of diagnosis.

Intracranial metastases arise mainly from non-small-cell and small-cell bronchial carcinoma and cancers of the breast, kidneys, and colon. Hemorrhagic intracranial metastases classically originate from malignant melanomas, choriocarcinomas, renal cell carcinomas, and testicular cancer (Table 2).

Clinically, patients with brain metastases usually exhibit focal neurological deficits, personality changes or loss of vigilance as a result of an increase in intracranial pressure.

Treatment can consist of the surgical removal or stereotactic percutaneous single-dose irradiation (with a gamma-knife or linear accelerator) with or without whole-brain radiation therapy (WBRT) [1-

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12]. The mean survival of patients with brain metastases depends on prognostic factors, which are listed in Table 3. Using these criteria, the risk profile of patients can be determined on the basis of the Graded Prognostic Assessment (GPA) (Table 4). Meta-analysis data suggest that the mean survival of patients with intracranial metastases that are operable and can be irradiated (30-40 Gy) after surgery is 19.4 months regardless of the primary tumor.

We report the case of a 78-year-old male patient with a huge solitary extracranial and intracranial metastasis from hepatocellular carcinoma with infiltration of the skull base, orbita and calvaria. We describe special aspects of the clinical signs and symptoms and diagnosis of a HCC metastasis at this rare location and discuss the diagnostic and therapeutic management as well as the clinical presentation of the patient.

Case Presentation

In February 2016, a 78-year-old male patient with a history of a secondary generalized seizure was referred to us by our neurology department. Visual inspection revealed asymmetry of the head as a result of a temporal swelling on the right side (Figures 1A-1C).

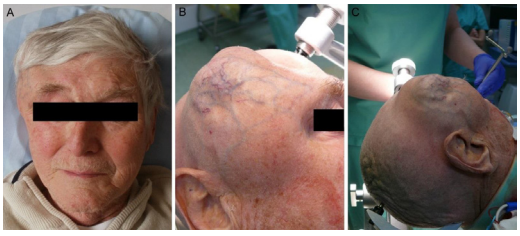
The skin overlying the swelling was found to be visibly tense. Subcutaneous vascular markings were increased. When asked, the patient reported that the swelling had increased in size over the past eighteen months and had not caused him any discomfort. A benign soft-tissue tumor was suspected initially. In January 2015, a

Prognostic factors	Scoring criteria		
	0	0.5	1
Age (years)	>60	50–59	<50
Karnofsky Performance Score	<70	70–80	>80
Number of brain metastases	>3	2–3	1
Extracranial metastases	Present	–	Absent

Table 3: Prognostic factors for patients with brain metastases and Graded Prognostic Assessment (GPA) scoring criteria. The sum of the scores for each prognostic factor is the GPA score for an individual patient.

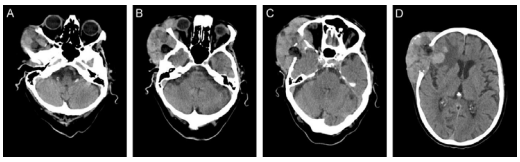
GPA class	Score	Median survival
I	3.5–4	11 months
II	3	6.9 months
III	1.5–2.5	3.8 months
IV	0–1	2.6 months

Table 4: GPA classes (defined by GPA scores) and correlating median survival times.



Clinical appearance of the right-sided frontotemporal space-occupying lesion (A–C). A: Preoperative photograph of the patient demonstrating asymmetry of the head caused by the frontotemporal space occupying lesion on the right side. B–C: Intraoperative photographs, which were taken after shaving of the scalp, reveal an inhomogeneous surface architecture and pathological vascular markings.

Figure 1: Clinical appearance.



Non-contrast-enhanced axial CCT images from inferior to superior (A–D) demonstrating a right-sided inhomogeneous mass in the temporal fossa (A), a peribulbar intraorbital and extraorbital tumor (B), destruction of the squamous part of the temporal bone and the greater wing of the sphenoid bone on the right side allowing the metastasis to spread to intraorbital sites (C), frontotemporoparietal osteolysis with intracranial infiltration, right-sided frontal intracerebral bleeding in the process of being absorbed, and perifocal edema (D).

Figure 2: Non-contrast-enhanced cranial CT.

resection attempt was therefore performed on an outpatient basis at another institution. The procedure was discontinued when arterial bleeding from the tumor bed occurred. Emergency wound revision was performed, and a tumor biopsy specimen was obtained. After surgery, cranial imaging was undertaken for the first time, which could demonstrate the presence of frontotemporal osteolysis. At that time point, the tumor extended to the greater wing of the sphenoid bone on the right side. Highly hypervascularized, yellow tissue of a loose lobular architecture was detected during surgery. Computed tomography of the chest and the abdomen demonstrated tiny pulmonary nodules in both the right upper and lower lobes and revealed multiple inhomogeneous lesions of the liver. Diagnosis of HCC was then confirmed by liver parenchyma biopsy. Based on available findings, the tumor was staged as T3b N0 pM1 G2 according to the TNM system. A histological examination of the cranial biopsy specimen confirmed that the right temporal space-occupying lesion was an extracranial and intracranial metastasis from HCC.

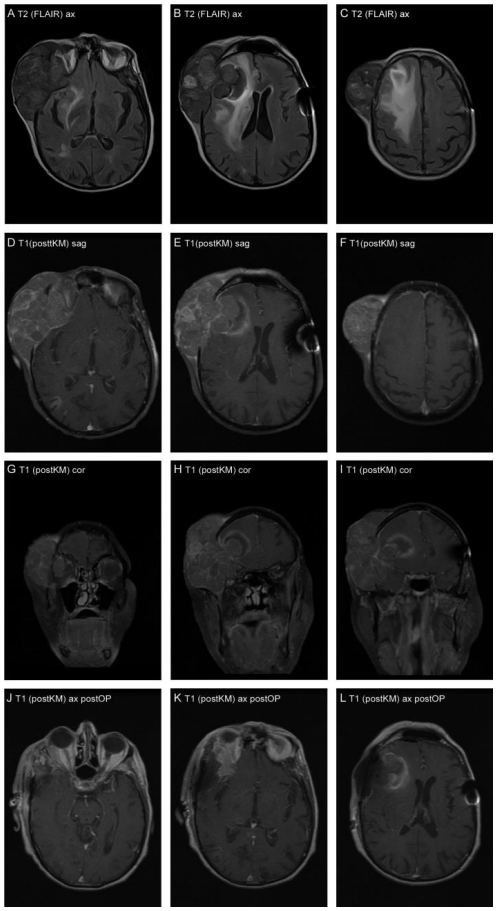
Based on these findings, the patient underwent irradiation of the right temporal region at a dose of 30 Gy in ten fractions and subsequently received palliative chemotherapy with sorafenib, a multikinase inhibitor, at a dose of 400 mg BID, which was soon discontinued because of severe leukoencephalopathy. In November 2015, the patient underwent total hip replacement and adjuvant irradiation, because of bone metastases in the region of the right hip joint.

In February 2016 the patient experienced a secondary generalized seizure. CCT demonstrated a progressive tumorous space-occupying lesion, which had penetrated the skull base and had infiltrated the orbita with extracranial and intracranial involvement and with cranial osteolysis and lysis of the temporal muscle (Figures 2A-2D). There was no liver cirrhosis or ascites and several years of exposure to asbestos in the patient's past medical history. The initial neurological assessment was largely unremarkable. Laboratory tests showed mildly elevated levels of transaminases and a mild increase in C-reactive protein. Preoperative MRI scans of the skull demonstrated an inhomogeneous frontotemporal space-occupying lesion on the right side with a maximum size of 7 cm × 9 cm × 11 cm.

In addition, cranial MRI revealed perifocal edema and compression of the right lateral ventricle with a midline shift to the left of approximately 8 mm (Figures 3A-3L). After diagnostic imaging a joint decision was made to proceed with surgical debulking of the tumor. The planned surgical procedure was performed using neuronavigation and microsurgical techniques (Figures 4A and 4B). In the region of the optical nerve and the retrobulbar area, tumor tissue was left in place with a view to prevent visual loss.

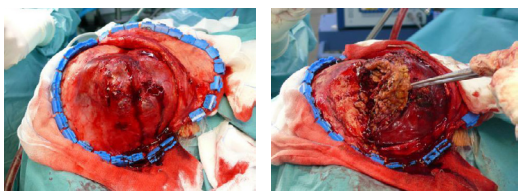
Postoperative, he presented with left-sided hemiparesis,

predominantly in the leg, which gradually subsided during treatment with dexamethasone. Two weeks later, the patient was independently mobile with a rollator. Postoperative MR imaging demonstrated a satisfactory resection (Figures 3J-3L). Histopathological and immunohistochemical analysis of the biopsy material showed that all tumor cells expressed hepatocyte paraffin 1 (Hep par1), arginase und cytokeratin-8 (CK8), which are markers for HCC. Moreover, 30% of the cells were positive for glypican 3 and periodic acid–Schiff (PAS). Osteolytic bone fragments were detected in tumor tissue. These findings confirmed the diagnosis of an extracranial and intracranial soft-tissue and bone metastasis from a HCC which had been established a year before (Figure 5).



Non-contrast-enhanced (A–C) and contrast-enhanced (D–L) MR images of the skull. A–C: T2-weighted FLAIR images demonstrating marked perifocal edema in the frontal lobe and compression of the right lateral ventricle with a midline shift. D–I: Axial (D–F) and coronal (G–I) contrast-enhanced T1-weighted images demonstrating a 7 cm by 9 cm by 11 cm inhomogeneous frontotemporal space-occupying lesion on the right side. J–L: Postoperative axial contrast-enhanced T1-weighted images demonstrating residual tumor tissue at intraorbital and periorbital sites.

Figure 3: Cranial magnetic resonance imaging.



Intraoperative images after exposure of the tumor using a modified Dandy flap (A–B). A: The image shows an inhomogeneous subperiostal and subfascial tumor capsule. The temporal muscle cannot bedifferentiated from the tumor mass. B: Tumor debulking revealing yellow, tubular tissue that is partially necrotic.

Figure 4: Intraoperative images of the tumor.

Figure 5: Postoperative view following resection of the HCC metastasis. The anatomical symmetry of the skull was largely restored.

Repeat palliative radiation therapy of the right temporal region was performed at a total dose of 30 Gy in order to prevent rapid progressive growth of the metastasis. As expected, the underlying disease continued to progress despite extensive debulking. Approximately three months after surgical tumor resection, the patient, who had moved to a hospice, died from pneumonia in the presence of lung metastases.

Discussion

This case of a solitary extracranial and intracranial metastasis from a hepatocellular carcinoma involves a number of diagnostic, clinical and therapeutic aspects that should be further discussed.

From a diagnostic perspective, the question arises as to why no diagnostic imaging of the skull had been performed prior to planning outpatient tumor resection. An exploratory ultrasound scan would have been sufficient to demonstrate the extent, hypervascularity and heterogeneity of the space-occupying lesion that was suspected to be a tumor so that a malignancy would have been considered in differential diagnosis.

Treatment included neurosurgical wound revision, during which a biopsy specimen was obtained for confirmation of the diagnosis, and adjuvant radiotherapy. The question must be asked why tumor debulking had not been performed at this stage of treatment to delay neurological symptoms and visual impairment in a patient who still enjoyed a good quality of life. The long period without any symptoms and the high surgical risk were the most important aspects against this approach.

When tumor debulking was performed at our institution, the extent of resection was found to be satisfactory from a surgical perspective. We must nevertheless admit that surgery did not markedly prolong the life of the patient, who ultimately died from pulmonary infection. The treatment approach that was used in the case presented here and consisted of palliative care and active surveillance can thus be considered as adequate since all important decisions following the diagnosis of HCC had been taken with utmost caution and in accordance with the patient's wishes after careful consideration of the advantages and disadvantages of different treatment options.

Clinically, the case described here is particularly interesting because

HCC is usually solitary and mostly occurs in patients with pre-existing cirrhosis of the liver. In this case, HCC was not linked to liver cirrhosis and presented intrahepatically as multiple inhomogeneous liver lesions. Risk factors for the development of HCC were the patient's advanced age, male gender, diabetes mellitus and obesity.

Only 10% of HCCs metastasize via the hematogenous route. As in the case presented here, the most common site of metastasis is the lung. Our patient presented with pulmonary metastases and an extracranial and intracranial metastasis from HCC.

Intracranial metastases account for approximately 40% of brain tumors and are predominantly found at parietal (40%) or frontal (30%) sites. Only 10% of intracranial metastases are located in the temporal region, as in this case. Intracranial metastases usually originate from primary tumors other than HCC. Meta-analysis data suggest that the mean survival of patients with intracranial metastases after surgery and postoperative irradiation is 19.4 months, regardless of the primary tumor [13-20]. The median survival of patients with HCC and metastasis is 6-12 months. In the case presented here, the patient survived for 17 months after diagnosis. He had a good quality of life and was able to lead an autonomous life although he was assigned to GPA risk class III.

In the international literature, there are only nine completely documented case reports and four small case studies with 45 patients 4, 15 patients 26, 14 patients 25 and 33 patients 27 with intracranial HCC metastases (Table 5). The majority of cases were published in the Asian literature. In the European literature, there is only one insufficiently documented report of an Italian patient with Hepatitis C who presented with cerebral metastases from HCC 7. Unlike our patient, all of the aforementioned patients developed severe neurological symptoms. To our knowledge, an HCC metastasis that measures 7 cm × 9 cm × 11 cm has not yet been described in medical literature. Prior to and apart from the secondary generalized seizure, our patient did not exhibit any neurological deficits in spite of the considerable size of the tumor. In addition, the extracranial and intracranial sites of metastasis and the infiltration of the orbita, meninges and calvaria are features that have not been described anywhere else in the literature and make this case unique. The considerable extent of extracranial disease, which has not yet been reported in the literature, is particularly noteworthy. Findings are inconclusive as to whether metastatic growth originated from calvarial bone and meningeal tissue. Even the osteolytic bone fragments that were detected in the histological analysis did not allow the pattern of growth to be reconstructed precisely.

Year	Place of institution	Site of metastasis	Patient age	Gender	Survival time
2010	Seoul (Korea)	Right parieto-occipital	51	Male	8 days
2015	Kaohsiung (Taiwan)	Left temporal	69	Female	Unknown
2015	Osaka (Japan)	Left parietal	46	Male	4 months
2014	Guangxi (China)	Left frontal	43	Male	Unknown
2014	Chiba (Japan)	Right parieto-occipital	76	Male	5 months
2013	Chiba (Japan)	Right frontal	32	Male	5 months
1990	Mie (Japan)	Right parietal	70	Male	4 months
2010	Cheonan (Korea)	Right parietal	53	Male	Unknown
2008	São Paulo (Brazil)	Right frontotemporal	57	Male	15 months

Table 5: Overview of the case reports that have so far been published on intracranial HCC metastases (nine cases from Asian countries and one case from South America).

Clinically, progressive extracranial involvement became manifest when the tumor threatened to ulcerate through the skin in the right temporal region and progressive intracranial involvement manifested itself as a loss of vision.

The available literature shows that the metastasis described here is a very rare manifestation of hepatocellular carcinoma and should be considered in the differential diagnosis of cranial space-occupying lesions with a view to ensuring that the patient receives appropriate palliative care [21-27].

Conclusion

We report the case of a patient with a right temporal swelling that appeared to be benign but was found to be a solitary 7 cm × 9 cm × 11 cm extracranial and intracranial metastasis from a HCC. This case is unique because of the unusual location and because of the large discrepancy between the size of the intracranial metastasis and the relatively mild neurological signs and symptoms. Epidemiological data relating to the European population suggest that primary tumors other than HCC tend to be considered in the differential diagnosis of a metastasis like the one described here.

A simple ultrasound scan would have demonstrated the presence of a temporal tumor mass and osteolysis of the calvaria and would have prevented the complication of severe arterial bleeding and would have shown the malignant nature of the lesion. We present this case of a patient with a rare and unique condition in order to illustrate the possible consequences that an insufficient diagnostic assessment may have and to advise caution in future cases that are similar to the one described here.

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