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Single Case

Intraparenchymal Hemorrhage due to Brain Metastasis of Hepatocellular Carcinoma

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Keywords
Hepatocellular carcinoma · Brain metastasis · Intraparenchymal hemorrhage

Abstract
Although extrahepatic metastases from hepatocellular carcinoma (HCC) are present in only 5–15% of cases, they are certainly factors associated with poor prognosis. The main sites include lung, lymph nodes, bones, and adrenal glands, in descending order. Metastasis in the central nervous system is extremely rare, and the incidences vary from 0.6 to 1.7%. We report a case of a 54-year-old man previously diagnosed with alcohol-induced cirrhosis of the liver and HCC. The patient was admitted presenting progressive left hemiparesis and headache which started 2 days earlier, with no history of cranioencephalic trauma. After admission, cranial computed tomography revealed an intraparenchymal hemorrhage area with surrounding edema in the right frontal lobe. An angioresonance requested showed a large extra-axial mass lesion located in the right frontal region with well-defined contours and predominantly hypointense signal on T2 sequence. At first, the radiological findings suggested meningioma as the first diagnostic hypothesis. However, the patient underwent surgery. The tumor was completely removed, and the morphological and immunohistochemical findings

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were consistent with metastatic hepatocarcinoma associated with meningioma. In postoperative care, the patient did not recover from the left hemiparesis and manifested Broca's aphasia. He had a survival time of 24 weeks, presenting acute liver failure as his cause of death. There is a lack of evidence supporting a specific management of patients with brain metastasis from HCC. Furthermore, there are no studies that evaluate different modalities of therapeutics in brain metastasis of HCC due to the rarity of this condition. Therefore, management must be individualized depending on probable prognostic factors in these patients.

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide. It is responsible annually for 250,000 to 1 million deaths globally [1–4]. It is the fifth most frequent cancer in men and the seventh in women [5]. The incidence varies widely, not only among continents, but also among different locations within the same country. This is due to the fact that environmental risk factors and hepatitis virus exposures vary within different geographic regions. High-incidence regions are generally those endemic for hepatitis B virus (HBV), such as sub-Saharan Africa and Southeast Asia [6]. In contrast, North and South America, Australia, and most of Europe are areas of a low incidence of HCC, with about 3 cases per 100,000 per year.

However, in the past few decades, the HCC incidence changed not only in the high-incidence regions, where it has been decreasing, but also in the low-incidence areas, where it has been increasing [8, 9]. It is proposed that the increasing incidence of HCC in countries such as the United States, Canada, United Kingdom, and Australia is associated mainly with the peak of the incidence of cirrhosis due to chronic hepatitis C and with the increasing prevalence of nonalcoholic fatty liver disease [8–11]. It is probable that the decreasing incidence of HCC in high-incidence areas is due to HBV vaccination and treatment and the increase of the availability of screening programs in patients with chronic liver disease.

Brazil has a low incidence of HCC – 3.5 new cases annually for men and 3.7 for women per 100,000. Currently, there is little evidence regarding the epidemiology of HCC in Brazil. Nevertheless, the data available suggest that the different distribution of HCC prevalence is due to the heterogeneous prevalence of HBV in Brazil [12].

We report the case of a patient with alcohol-induced cirrhosis and HCC, in which progression developed an intraparenchymal hemorrhage due to brain metastasis from the HCC.

Case Report

A 54-year-old male with cirrhosis due to chronic alcoholic liver disease presented to our hospital with progressive left hemiparesis and headache which started 2 days earlier, with no history of head trauma. A previous diagnosis of HCC was made in August 2015 with a triple-phase CT abdominal scan, which showed a solid mass in the liver, hypodense, measuring 5.2 × 4.7 cm in the axial plane in the left lobe, with slightly heterogeneous enhancement

by means of contrast in the arterial phase, and slightly hypodense in the excretory phase (Fig. 1). The plan was to perform a transarterial chemoembolization, but the patient was lost to follow-up after the diagnosis. The patient was using propranolol, furosemide and lansoprazole. Also, he was being treated for systemic hypertension with enalapril and amlodipine, for type 2 diabetes mellitus with metformin and for dyslipidemia with simvastatin.

On physical examination, the patient was alert, oriented, and cooperative. Pupils were equal, round, reactive to light and accommodation. Glasgow Coma Scale was 15. He presented loss of strength in his left upper and lower members, but worse distally graded as II/IV. There were no sensory deficits. The Babinski reflex was positive in the left member. Other physical observations were unremarkable. Laboratory values were: glucose 160 mg/dL, sodium 139 mmol/L, potassium 3.9 mmol/L, international normalized ratio 1.2, activated partial thromboplastin time 24.5 s, hemoglobin 13.6 g/dL, leukocyte count 6,680/mm^3, platelet count 103,000/mm^3, total bilirubin 1.7 mg/dL, serum albumin 3.5 g/dL, creatinine 0.6 mg/dL; Child-Pugh score A, and MELD-Na score 11.2.

A cranial CT scan demonstrated an intraparenchymal hemorrhage area in the high convexity of the right frontal lobe, associated with surrounding edema, with about 4.7 cm of determining mass effect, with slight deviation of the midline. There was no evidence of head injury (Fig. 2).

The patient underwent a cranial angioresonance for presurgical mapping, which demonstrated a large extra-axial mass lesion located in the skull of the frontal region, measuring about 4.5 × 4.2 × 3.3 cm well-defined contours of diameters, with predominantly hypointense signal on T2 sequence. The injury had some small cystic areas in between and intense enhancement by means of intravenous contrast, with vasogenic edema surrounding brain parenchyma, with small areas of bleeding (Fig. 3).

The patient underwent a decompressive craniotomy and the tumor was completely removed. There were no intercurrences during surgery. Histopathological examination revealed that morphological (Fig. 4) and immunohistochemical (Table 1) findings were consistent with metastatic hepatocarcinoma associated with meningioma.

There were no complications during surgery and postoperative care. Nevertheless, the patient did not recover from the left hemiparesis and manifested Broca's aphasia, which deteriorated progressively during the following months. After surgery, the patient received neoadjuvant radiation therapy in order to prevent cerebral metastatic relapses. There was no indication for HCC or liver therapies. From this management, the patient had a survival time of 24 weeks, presenting acute liver failure as his cause of death.

Discussion

The vast majority of HCC cases occur in patients with liver cirrhosis. At diagnosis, the clinical features are variable. Patients can be asymptomatic or only present the manifestations of decompensated liver cirrhosis [13]. Extrahepatic spread is uncommon at diagnosis, ranging from 5 to 15% of the cases [14–16]. During disease progression, these lesions have been reported to occur in approximately 13.5–42% of HCC patients [17–19]. The most common sites for metastasis are lung, intra-abdominal lymph nodes, bones, and adrenal glands. Central nervous system metastasis is extremely rare. Hence there is a lack of retrospective

studies assessing this incidence. Kim et al. [20] reported an incidence of 0.6% [21], while Friedman [22] reported an incidence varying from 0.3 to 1.7%.

In adults, the most frequent intracranial malignancies are metastasis. However, some data suggest that intracranial hemorrhage due to metastasis from distant primary cancers occurs only in between 0.9 and 11% [23].

Brain metastasis from HCC is rare. The improvement in screening and therapeutic modalities increased the survival of patients with HCC. It is expected, therefore, that the incidence of HCC with brain metastasis will increase [24]. Besides, there are no guidelines for the management of these patients, but some advanced therapeutic techniques have shown an improvement of the median survival time, such as surgical resection, local ablation, transarterial chemoembolization, and chemotherapeutic agents [24]. Nevertheless, there is a lack of studies that evaluate the survival rates of patients treated with these different therapeutic modalities.

In the natural history of the HCC, there is first a contiguous invasion of portal and hepatic veins. Usually, regional lymph nodes are affected in the sequence [25]. Afterwards, hematogenous spread tends to occur in lungs, bones, and adrenal glands [26–28]. Since the survival rates of HCC have been increasing, the central nervous system could be considered as the next metastatic site of HCC, albeit very rare. Besides, metastasis not only from HCC but also from other carcinomas commonly occurs in the middle cerebral artery territory [29]. Spontaneous intracerebral hemorrhages due to HCC metastasis are also extremely rare. There are 8 cases of spontaneous epidural hematoma [30–38] and 1 case of subdural hematoma [29] due to brain metastasis of HCC reported in the literature to this date.

Han et al. [21] retrospectively reviewed 32 cases of HCC with brain metastasis regarding clinical and radiological findings. These patients were selected from a group of 5,015 patients diagnosed with HCC, with an incidence of 0.65%. Median survival time after the diagnosis of brain metastasis was 10.4 weeks. Most cases (97%) are symptomatic. The most common findings were headache, weakness, and mental status changes. Those findings are probably associated with a high incidence of intratumoral hemorrhage. Child-Pugh score A, absence of intratumoral hemorrhage, recursive partitioning analysis class I or II and surgical resection were associated with higher survival rates.

Another relevant finding in this patient is the association between the brain metastasis from HCC and a meningioma, which is another rare situation, confirmed by the histopathological examination. Meningioma is the most frequent primary central nervous system tumor, which is responsible for about one-third of all primary brain and spinal tumors [38]. However, there are no cases reported in the literature with the association of central nervous system tumors presented in this patient.

Despite the intratumoral hemorrhage, in this case the patient's Child-Pugh score was A, which could be associated with an increase in survival. Besides, during the postoperative care, the patient did not present any complications.

Conclusion

Early recognition is certainly one of the factors related to higher survival in patients with brain metastasis from HCC, since about 90% of cases are symptomatic [15]. Besides, in

a considerable group of patients there are focal neurological deficits. Although brain metastasis from HCC is not the first hypothesis to be considered in this case, it should certainly be included as a differential diagnosis, especially with the increase in survival time in patients with HCC. There is lack of evidence not only for identifying other prognostic factors, but also for defining the appropriate treatment of these patients. Therapeutics must be individualized, considering probable prognostic factors in the decision of the management to this date.

Statement of Ethics

The patient data in the reported case are blinded so the patient cannot be identified.

Disclosure Statement

The authors have no conflict of interest regarding the topic of this paper.

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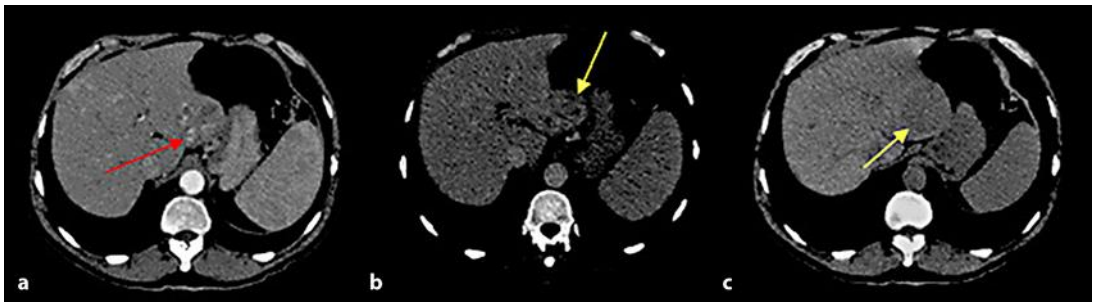

Fig. 1. Triple-phase CT scan. **a** Arterial phase of contrast enhancement showing neovascularity (red arrow) in a low-density hepatic mass in the left lobe. **b**, **c** Portal and excretory phases are shown, respectively; there is a hypodensity (yellow arrow) in the same topography. These findings are commonly referred to by radiologists as "arterial enhancement with washout" and they have high accuracy in the diagnosis of HCC (sensitivity of 83% and specificity of 91% [39]).

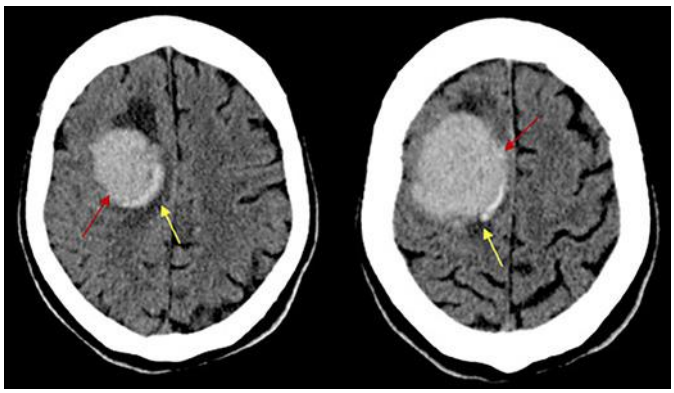

Fig. 2. CT scan of the brain demonstrating an intraparenchymal hemorrhage area (red arrow) in the right frontal lobe. There is a surrounding edema (yellow arrow) associated with the lesion.

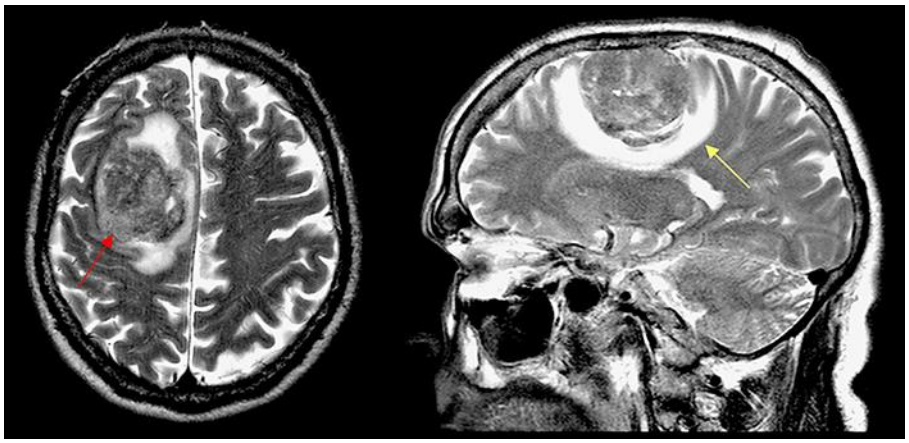

Fig. 3. Cranial angioresonance demonstrating a massive lesion located in the skull in the frontal region (red arrow), 4.5 × 4.2 × 3.3 cm in size, that presents a predominantly hypointense signal on T2 sequence. Vasogenic edema surrounding (yellow arrow) the brain parenchyma with areas of hemorrhage can be seen.

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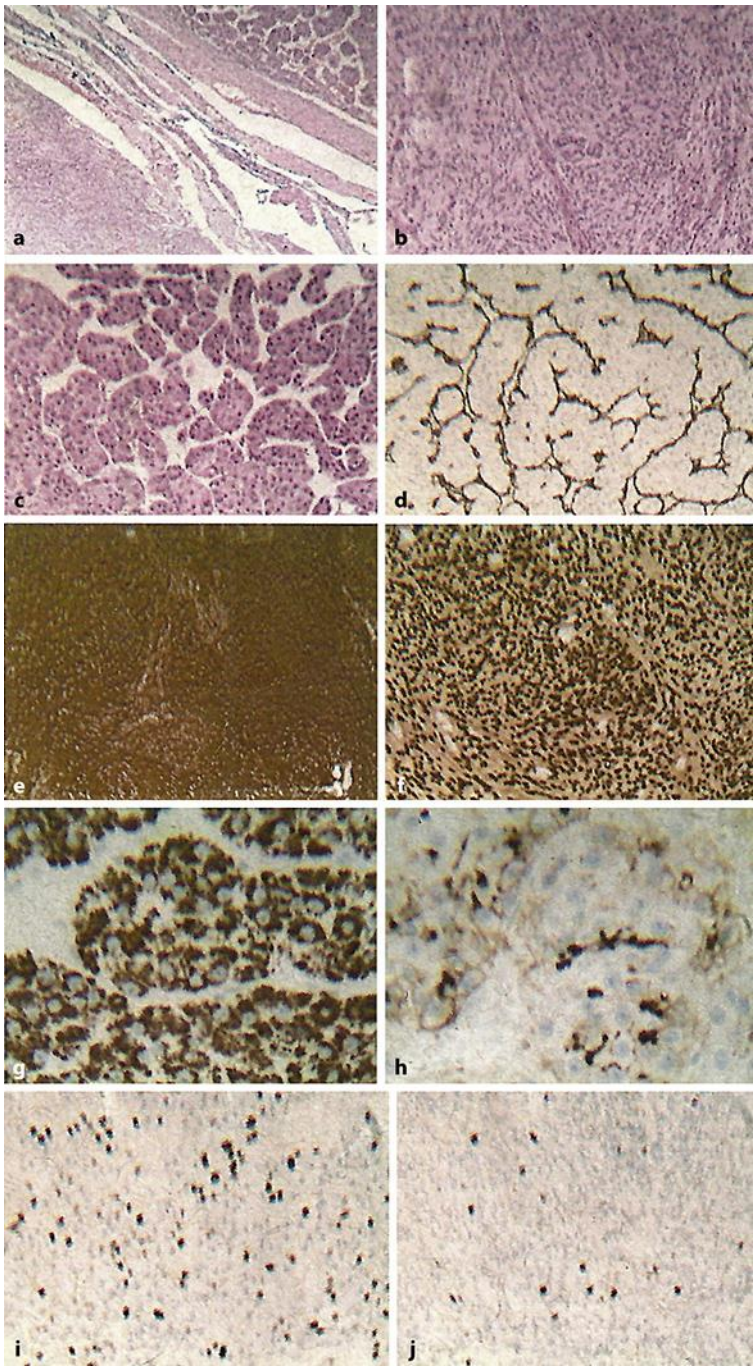

Fig. 4. Microscopic findings. **a** Transition. HE. ×400. **b** Meningioma. HE. ×400. **c** HCC. HE. ×400. **d** HCC. Vimentin. ×400. **e** Meningioma. Vimentin. ×400. **f** Meningioma. Progesterone receptor. ×400. **g** HCC. HepPar-1. ×400. **h** HCC. CD10. ×400. **i** HCC. Ki67. ×400. **j** Meningioma. Ki67. ×400.

Table 1. Immunohistochemistry panel

Antibody	Result
Cytokeratin 7 (OV-TL 12/30)	Negative
Cytokeratin 20 (Ks20.8)	Negative
Ki67 (MIB-1)	Positive in 5% of meningioma cells and 25% of HCC cells
Cytokeratin 18 (DC-10)	Positive in HCC
CDX-2: intestine-specific transcription factor (DAK CDX-2)	Negative
Vimentin (V9)	Positive in meningioma
TTF-1: thyroid transcription factor-1 (8G7G3/1)	Positive in HCC (cytoplasmic labeling)
Hepatocyte: Hep Par-1 (OCH1E5)	Positive in HCC
Progesterone receptor (PgR636)	Positive in meningioma
Chromogranin A (DAK-A3)	Negative
CD10 (56C6)	Positive in HCC (canalicular pattern)

HCC, hepatocellular carcinoma.