Case Report

Hemorrhagic Brain Metastasis as an Initial Presentation of Hepatocellular Carcinoma in a Patient With Alcohol-Related Liver Cirrhosis: A Case Report and Review of Literature

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Abstract

Hepatocellular carcinoma (HCC) is the most common primary hepatic cancer. Although it usually presents as a liver mass, rarely HCC can have an initial presentation at an extrahepatic site before the diagnosis of the primary lesion in the liver. Even rarely was that brain metastasis as initial extrahepatic presentations. Furthermore, the initial presentation of HCC as brain metastases has been with most cases being secondary to hepatitis-related hepatoma. In this case report, we are presenting a rare and unusual case of hemorrhagic cerebral metastasis as an initial extrahepatic presentation of an alcohol-related hepatoma. Our case is the second case in the English literature that has been presented in such a way. Due to the uncommonness of presentation, there can be diagnostic dilemmas and delay in treatment. Therefore, a high level of suspicion is needed in the high-risk patients of HCC who present with unexplained or new neurological signs and symptoms. More exploration is warranted for clinical research and treatment guidelines for brain metastases of HCC to help improve survival and quality of life.

Keywords
hepatocellular carcinoma, brain metastasis, hemorrhagic metastases

Introduction

Globally, hepatocellular carcinoma (HCC) is the fifth most common cause of cancer and the second most common cause of cancer-related deaths.1 Studies have shown that extrahepatic metastasis of HCC occurs in about 30% to 50% of cases, with the common sites being the lungs, lymph nodes, bones, and adrenal glands.2-4 The clinical presentation of metastatic HCC is most often associated with features of the primary lesion.5 Metastasis, which represents the advanced stage, in some rare cases, is present before the primary liver tumor is found.5-10 Brain metastasis from HCC is rare—occurring in approximately 0.2% to 2.2% of cases,11 and represents a sign of a very dismal course of the disease.12 As such, brain metastasis as the initial presentation of HCC is even far less common. More so, such presentation from alcohol-related liver cirrhosis is very rare. Upon review of current literature, we found 2 cases of HCC with initial presentation as brain metastasis related to hepatitis B virus (HBV) infection, and 2 other cases reported in the 1988 Surgical Neurology Journal with unknown risk factors.13,14,15

We report a case of HCC with hemorrhagic brain metastasis as an initial presentation in a patient with alcohol-related liver cirrhosis. To the best of our knowledge, only one other case has been reported as secondary to alcohol-related HCC.16 As such, we will be reporting the second case of alcohol-related HCC with initial manifestation as a hemorrhagic brain metastasis.

Case Report

A 74-year-old Spanish male with a past medical history of heavy alcohol use with chronic liver disease (CLD), hypertension, diabetes, benign prostatic hyperplasia, dementia,

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coronary artery disease with coronary artery bypass graft (placed in 2004), C3-C7 laminectomy with posterior fusion presented to the emergency department with weakness of lower extremities and altered mental status. He was able to walk and drive independently until 4 months before the presentation. Then he gradually began to lose strength in all 4 extremities. The patient stated that he had head trauma recently and had noticed significant unintentional weight loss. On initial physical examination, he was oriented only to self. The nervous system exam was significant for bilateral upper and lower extremity weakness with motor power in the left upper and lower extremities 0/5 and 1/5, respectively. The motor power of the right upper and lower extremities was 3/5. Other exams were unremarkable. Initial laboratory tests were significant for hemoglobin: 13.8 g/dl, hematocrit: 42.2%, white cell count: 8.3 × 10³/µl, platelet count: 363 × 10³/µl, aspartate aminotransferase: 221 U/L, alanine transaminase: 91 U/L, alkaline phosphatase: 430 U/L, total bilirubin: 1.3 mg/dl, direct bilirubin: 0.5 mg/dl, albumin: 4.4 g/dl, partial thromboplastin time: 34.8 seconds, prothrombin time: 11.6 seconds, international normalized ratio: 1.02. Serum electrolytes and kidney function were within the normal range. On imaging, magnetic resonance imaging (MRI) of the brain revealed a hemorrhagic, lobulated, heterogeneous mass with surrounding vasogenic edema measuring approximately 2.9 × 2.0 × 2.2 cm in posterior parietal lobes, while in the left mid posterior parietal lobe it measured 1.7 × 1.9 × 1.7 cm (Figure 1). Based upon MRI findings, hemorrhagic metastatic disease was suspected. He was started on levetiracetam for seizure prophylaxis and dexamethasone 4 mg every 6 hours for brain edema.

Computed tomography (CT) chest/abdomen/pelvis with and without contrast was performed for staging of the tumor which showed signs of pulmonary metastasis (Figure 2), and mild fatty infiltration of the liver with ill-defined masses in both lobes suspicious for primary versus metastatic disease (Figure 3).

Magnetic resonance imaging of the cervical, thoracic, and lumbar spine was negative for bone metastasis. After a multidisciplinary discussion, the decision was made to proceed with the right craniotomy and stereotactic resection of hemorrhagic brain mass. Pathology of the brain lesion was consistent with metastatic HCC. On immunohistochemistry, tumor cells expressed Arginase-1, Hepatocyte, and Glypican-3. Ki67 proliferation marker showed brisk mitotic activity (40-50%; Figure 4,5). Also, the alfa fetoprotein (AFP) level was elevated at 349 400 ng/ml. Carcinoembryonic antigen (CEA) was normal. Hepatitis B virus antigen and hepatitis C virus (HCV) antibody were negative. The patient was planned for stereotactic body radiotherapy followed by treatment with monoclonal antibody atezolizumab and vascular endothelial growth factor inhibitor bevacizumab. However, the patient developed status epilepticus on postoperative day 8 and had to be intubated for airway protection. His clinical course was further complicated by a progressive decline in neurological status and aspiration pneumonia. Given
multiple comorbidities and poor prognosis, goals of care were discussed and code status was changed to do not resuscitate/do not intubate with comfort measures. He expired shortly after that.

**Discussion**

Etiologies of HCC vary according to geographical distribution. The incidence is highest in Asia and Africa due to the high prevalence of hepatitis B and C. Most cases of HCC (approximately 80%) are associated with chronic HBV or HCV infections. Approximately, 13% to 23% of cases of HCC are related to alcohol-use disorders, considering alcohol to be a well-recognized carcinogen. Chronic alcohol intake induces steatosis, steatohepatitis, and cirrhosis in the liver. The earliest stage is steatosis, which occurs in more than 90% of drinkers who consume 4 to 5 standard drinks per day over decades. By the time the next stage of steatohepatitis is reached, the morphology of the liver can rarely go back to normal, even after alcohol cessation. Possible mechanisms by which alcohol contributes to hepatocarcinogenesis include oxidative stress and the direct mutagenic effect of acetaldehyde. The aberrant deoxyribonucleic acid (DNA) or hepatocyte protein methylation may also play a role in the pathogenesis. Non-alcoholic fatty liver disease (NAFLD) is also a common risk factor for HCC, particularly in Western countries, due to obesity and metabolic syndrome. Other risk factors include exposure to toxins, such as aflatoxins and aristolochic acid. All of these are potentially preventable risk factors of HCC, which signifies that the prevention of these risk factors can decrease the incidence of HCC.

Clinical presentation varies depending on the extent of the tumor, preserved hepatic function at the time of diagnosis, and a risk factor that led to HCC. Cirrhotic patients frequently present with signs and symptoms of chronic liver disease such as ascites, jaundice, hepatic encephalopathy, variceal bleeding, etc. The clinical presentation also varies with geographic regions. For instance, many patients with HCC related to HBV and HCV infections in high prevalent locations (sub-Saharan and Asia) have severe hepatic decompensation at presentation. On the other hand, in the United States and other Western countries with a

**Figure 3.** Axial computed tomography image through the liver showing heterogeneous attenuation of the liver parenchyma caused by multiple ill-defined hypodense liver lesions infiltrating both lobes.

**Figure 4.** (A) Metastatic carcinoma in brain: At intermediate magnification (100×), the carcinoma cells form nests around the veins (indicated by arrow), infiltrate within the cerebral parenchyma (indicated by arrowhead). (B) At high magnification (400×), the carcinoma cells demonstrate marked pleomorphism, vesicular nuclei, high nuclear cytoplasm ratio, irregular nuclear membranes.
low incidence of hepatitis infections, most patients present normally after routine laboratory screening for HCC and as a result, roughly 40% of patients are asymptomatic at the time of diagnosis, just like our patient. In such cases, it is very challenging to diagnose HCC at an early stage because HCC grows silently.

The metastatic pattern after HCC with initial liver presentation includes the portal and hepatic veins in a contiguous invasion, with regional lymph nodes. Subsequently, it can spread to the lungs, bones, and adrenal glands hematogenously. However, HCC does not always present in the liver as the initial presentation. A case report done by Punia et al. showed multiple cranial nerve palsies (extrahepatic metastasis) as the initial presentation of HCC. In a review of published cases, there were unusual extrahepatic metastatic sites in which HCC could be found as the initial presentation. A study done by Helal et al. in HCV-positive Egyptian patients, metastatic HCC with no known liver primaries was found in bones (36%), lymph nodes (19%), soft tissue (15%), omentum (15%), maxillary sinus (4%), adrenal gland (4%), brain (4%), and skin (2%).

Hepatocellular carcinoma presenting with brain metastases is rare, occurring only in around 0.2% to 2.2% of cases, and represents a critical stage. Hepatocellular carcinoma very rarely can even present as initial cerebral metastatic manifestations before the primary lesion itself. Table 1 shows previous case reports with cerebral metastasis as the first presentation of HCC. As per our literature search, our case is the second case in the English literature where hemorrhagic cerebral metastasis was the initial presentation of HCC. Therefore, a high index of suspicion for HCC is warranted for high-risk patients who present with unexplained or new neurological signs and symptoms.

Hepatocellular carcinoma surveillance should be performed in all patients with cirrhosis and high-risk patients with chronic HBV infections. This includes Asian hepatitis B carriers (over age 40 years for males and over 50 years for females), hepatitis B carriers with a family history of HCC, and African and/or

Table 1. Case Reports With Cerebral Metastasis as First Presentation of HCC.

| Author           | Risk factor         | Case presentation                                                                 |
|------------------|---------------------|-----------------------------------------------------------------------------------|
| Loo et al<sup>13</sup> | Hepatitis B virus infection | 38-year-old previously healthy Chinese man with intracerebral hemorrhagic brain metastasis as initial presentation of HCC. |
| Loo et al<sup>13</sup> | Hepatitis B virus infection | 71-year-old Chinese woman with good past health with intracerebral hemorrhagic brain metastasis as initial presentation of HCC. |
| Peres et al<sup>16</sup> | Alcohol            | 43-year-old white man presented with hemorrhagic cerebral metastasis as initial presentation of HCC. (Case reported in South America.) |
| Lee et al<sup>14</sup>  | Unknown             | 58-year-old Chinese woman presented with progressive bulging mass over the high vertex of her head and progressive weakness of her right leg. She was found to have metastatic hemorrhagic intracranial carcinoma identical to hepatoma. |
| Lee et al<sup>14</sup>  | Unknown             | 59-year-old Chinese man presented with weakness and numbness of his left upper arm, headache and vomiting followed by weakness in his left side and altered mentation. He was found to have extensive intracerebral hemorrhage in CT head. Biopsy showed metastatic carcinoma identical to hepatoma. |

Abbreviations: HCC, hepatocellular carcinoma; CT, computed tomography.
North American blacks with hepatitis B.29,30 Ultrasonography (US) is the primary HCC surveillance method as it provides inexpensive, real-time, and simple detection.31 The sensitivity and specificity of ultrasound exceed 90% for any stage of HCC, but only less than half of early-stage HCC is detected by ultrasound. Adding AFP to ultrasound surveillance is associated with significantly improved sensitivity.32 However, using US presents limitations for obese patients as well as patients with NAFLD. Abdominal CT or MRI may be beneficial as the primary screening modality in these patients.30

Unfortunately, the overall prognosis of patients with brain metastases from HCC is extremely poor, with the median survival time being only 8 weeks.33,34 There are no standard guidelines regarding treatment modalities specifically for brain metastases from HCC. Current treatment modalities include surgery, whole-brain radiation therapy (WBRT), stereotactic radiosurgery, chemotherapy, targeted agents, immunotherapy, and supportive measures. However, aggressive treatment sometimes might not be beneficial in patients with brain metastasis. Stratification of prognostic factors would play a significant role in guiding physicians to make optimal treatment decisions for their patients. Some of the prognostic factors include recursive partitioning analysis, Child-Pugh classification, performance status, and serum AFP.11,35 According to the goals of care, patients with favorable prognostic factors might benefit from aggressive treatment; however, for those with unfavorable prognosis, stabilizing BMs and palliative care are preferable options.35 A study done by Han et al36 demonstrated that patients treated with surgical resection with/without postoperative WBRT had a longer median survival time than patients treated with gamma knife radiosurgery (GKS) followed by WBRT/GKS/WBRT only or those treated with only steroids (25.3 weeks vs 10.4 weeks vs 1.0 week, P < .001). Other studies show that surgical excision of the intracranial metastatic mass, followed by radiotherapy, can improve the quality of life and prolong survival time for patients.37

**Conclusion**

Because of the atypical presentation, and poor prognosis in patients with intracerebral metastases from HCC, it is important to be familiar with risk factors, surveillance strategies, prognostic factors, and clinical presentation of brain metastasis from HCC. Timely and effective screening and surveillance can prevent HCC tumor burden and late diagnosis significantly. On the other hand, it is paramount to explore further clinical research and treatment guidelines for BM of HCC which can help improve survival and quality of life.

**Author Contributions**

C.T. wrote the manuscript, collected data, literature review; A.P. collected data, edited the manuscript; L.S. collected patient data, helped editing manuscript, took care of patient; V.J. collected data; J.C.W. designed and mentored original draft, writing and editing.

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**Ethics Approval**

Ethics approval to report this case was obtained from Brookdale Hospital Institutional Review Board. Our institution does not require ethical approval for reporting individual case reports.

**Informed Consent**

Patient expired before consent could be taken. Brookdale Hospital Institutional Review Board does not need consent for publishing case reports.

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