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**World Journal of Clinical Cases**

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### ABOUT COVER

Editorial board member of *World Journal of Clinical Cases*, Dr. Kvolik is a Professor in the School of Medicine, Osijek University, Croatia. She obtained her MD degree, with specialization in the field of anesthesiology, resuscitation and intensive care from the Zagreb Medical School, Croatia. Afterwards, she undertook postgraduate training in Clinical Pharmacology at the same institution, defending both a Master’s thesis and PhD thesis. In 2006, she joined the Osijek University Medical Faculty as a lecturer and was promoted to Professor in 2009. In 2012, she was elected Head of the Department of Anesthesiology, Resuscitation, Intensive Care and Pain Therapy, a position she occupies to this day. She is also the current Head of the Intensive Care Unit at the Osijek University Hospital, Croatia. (L-Editor: Filipodia)

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*WJCC* mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

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E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com
Concurrent hepatocellular carcinoma metastasis to stomach, colon, and brain: A case report

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Author contributions: Kim R was the patient’s surgeon, reviewed the literature, and contributed to manuscript drafting; Song J performed the pathological analyses and interpretation; Kim SB was responsible for the revision of the manuscript and for important intellectual content; all authors issued final approval for the version to be submitted.

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Abstract

BACKGROUND
Extrahepatic metastasis (EHM) from hepatocellular carcinoma (HCC) occurs in 10%–15% of cases following initial treatment. The most frequent sites of EHM are the lung, lymph nodes, and bone. Gastrointestinal or brain metastasis from HCC is rarely reported. Here, we report a rare case of concurrent HCC metastases to the stomach, colon, and brain.

CASE SUMMARY
A 72-year-old male with a history of alcohol induced HCC presented with multiple intrahepatic recurrences and tumors lesions in the stomach and ascending colon. Three years earlier, he underwent right hemihepatectomy, and 1 year ago, he had a video-assisted thoracoscopic wedge resection for pulmonary metastasis of HCC. We decided on surgical resection of the new metastases because of massive gastric bleeding and concern for possible colonic obstruction. The patient underwent gastric wedge resection and right hemicolecotomy. Two weeks later, the patient developed dysarthria and mild cognitive disorder. Magnetic resonance imaging of the brain revealed a left frontal lobe lesion, and he underwent resection of a metastatic brain tumor. Unfortunately, he died 6 weeks after the last surgery due to hepatorenal syndrome.

CONCLUSION
Decision of surgery was carefully recommended in this case and may extend survival in other metastatic HCC patients with well-preserved hepatic function.

Key words: Hepatocellular carcinoma; Extrahepatic metastasis; Stomach; Colon; Brain;
Case report

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Core tip: This was a very unusual case of concurrent stomach, colon, and brain metastasis of hepatocellular carcinoma. Extrahepatic metastasis of hepatocellular carcinoma has a poor prognosis. However, deteriorated hepatic function due to intrahepatic metastases is more often the cause of death than is extrahepatic metastasis. Treatment of extrahepatic metastases is still suggested to control tumor progression. Surgical resection of these metastases may extend survival and quality of life and should be considered in patients with well-preserved hepatic function.

INTRODUCTION

Extrahepatic metastasis (EHM) from hepatocellular carcinoma (HCC) occurs in 10%-15% of cases of recurrence following initial treatment[1-6]. The most frequent sites of EHM are the lung, lymph nodes, and bone[1-7]. Hematogenous and lymphatic spreading patterns seem to be the most important mechanisms of EHM[5].

Gastrointestinal metastasis is rarely reported for HCC[6-9]. In one autopsy study, there was just one case each of gastric or colonic metastasis from HCC[9]. Another recent case reported HCC metastasis to the ascending colon and stomach[9].

The incidence of brain metastases from HCC is also extremely rare, with a reported incidence of 0.2%-2.2%[10,11]. Because of this rarity, the prognosis and treatment strategies for patients with HCC brain metastases are still under investigation[10]. Here, we report the first known case of synchronous HCC metastases to the stomach, colon, and brain.

CASE PRESENTATION

Chief complaints

A 75-year-old male with a history of alcoholic liver cirrhosis and HCC presented to our hospital for transarterial chemoembolization (TACE). He complained of melena and mild dyspnea.

History of present illness

Patients reported intermittent melena episodes 1 wk ago and worsened over two to 3 d.

History of past illness

The patient underwent right hemihepatectomy for HCC 3 years ago. One year ago, he had a left lower lung wedge resection for pulmonary metastasis of HCC. 5 mo ago, he had multiple intrahepatic HCC recurrence and underwent transarterial chemoembolization (TACE). The gastric and colonic metastases were not prominent radiologic findings at the time. 4 mo ago, other intrahepatic recurrences developed and intestinal lesions were prominent.

Personal and family history

The patient had diabetes and hypertension. There was no family history of cancer.

Physical examination

Hypotension and tachycardia were present at admission, and the patient recovered after hydration and transfusion. The abdominal was soft and tenderness or rebound tenderness was not observed. The rectal examination showed melena, but no
hematochezia. 2 wk after gastrectomy and colectomy, he complained of dysarthria and mild cognitive disorder.

**Laboratory examinations**
The hemoglobin level was 7.1 g/dL and recovered to 9.4 g/dL after two RBC transfusions. The prothrombin time (international normalized ratio, INR) was 1.04 (normal range 0.86–1.14). The total bilirubin was 0.3 mg/dL (normal range 0.3 –1.2), and the albumin was 2.8 g/dL (normal range 3.5–5.2). The aspartate aminotransferase was 27 U/L (normal range < 35), and the alanine aminotransferase was 26 U/L (normal range < 45). The serum levels of protein induced by vitamin K absence or antagonist II (PIVKA-II) and α-fetoprotein were not elevated, at 15 mAU/mL (normal range < 40 mAU/mL) and 2.3 ng/mL (normal range < 7.0 ng/mL), respectively.

**Imaging examinations**
A computed tomography (CT) scan showed intramural wall thickening of the stomach body and luminal narrowing of the ascending colon (Figure 1). Magnetic resonance imaging (MRI) of the brain 2 wk after abdominal surgery showed a 38 mm lesion in the left frontal lobe with hemorrhagic features (Figure 2).

**Further diagnostic work-up**
Endoscopy and colonoscopy revealed a bleeding, fungating mass in the lesser curvature of the stomach body, and an ulcerofungating tumor of the ascending colon that was suspicious for partial obstruction. Biopsies of both lesions confirmed metastatic HCC (Figure 3).

**FINAL DIAGNOSIS**
The patient was diagnosed with concurrent metastatic HCC of the stomach, colon, and brain.

**TREATMENT**
Although the optimal treatment option was sorafenib, we decided to perform surgical resection because of massive gastric bleeding and concern for possible colonic obstruction. The patient underwent gastric wedge resection and right hemicolectomy. 2 wk later, he underwent brain tumorectomy.

**OUTCOME AND FOLLOW-UP**
The postoperative course after abdominal surgery was uneventful. After the brain operation, his cognitive impairment and dysarthria recovered. Ten days after the brain surgery, his urinary output was decreased and weight gain had developed. The size and number of intrahepatic recurrent tumors were slightly increased, and a large number of ascites were detected by CT. Despite the use of diuretics, the control of ascites became difficult and the azotemia aggravated. We recommended dialysis to the patient, but the patient refused further treatment. Unfortunately, the patient suffered hepatorenal syndrome after brain surgery and died 6 wk after the brain operation.

The pathologic findings of the gastric and colonic specimens showed metastatic HCC with mucosal to serosal invasion, without involvement of adjacent lymph nodes. Analysis of the brain specimen showed metastatic HCC with hemorrhage invading the normal brain issue. In the immunohistochemical analyses between the primary liver tumor and all metastatic lesions, CD44, p53, and Ki-67 were strongly positive in the metastatic tissues. E-cadherin, glypican-3 (GPC-3), and hepatocyte paraffin 1 (HepPar1) were positive in the primary tumor tissue. Vimentin was negative in both the primary tumor and metastatic lesions. (Figure 4 and Figure 5 and Table 1).

**DISCUSSION**
Extrahepatic metastasis from HCC has extremely poor prognosis[1-5,12]. However,
Table 1 Summary of immunohistochemical expression in the primary tumor and metastatic lesions

<table>
<thead>
<tr>
<th>Markers</th>
<th>Primary liver</th>
<th>Stomach</th>
<th>Colon</th>
<th>Brain</th>
</tr>
</thead>
<tbody>
<tr>
<td>HepPar1</td>
<td>P</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>p53</td>
<td>N</td>
<td>P</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>Ki-67</td>
<td>5%</td>
<td>60%</td>
<td>60%</td>
<td>60%</td>
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<tr>
<td>E-cadherin</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Vimentin</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>GPC-3</td>
<td>P</td>
<td>N</td>
<td>WP</td>
<td>N</td>
</tr>
<tr>
<td>CD44</td>
<td>N</td>
<td>P</td>
<td>P</td>
<td>P</td>
</tr>
</tbody>
</table>

N: Negative expression; P: Positive expression; WP: Weakly positive expression; GPC-3: Glypican-3.

Figure 1 Abdominal computed tomography. The computed tomography shows a lesion thickening the lateral wall of the stomach and another lesion partially obstructing the ascending colon (orange circle).

Extrahepatic progression is reported as the cause of death in less than 10% of the patients with EHM from HCC\[1-6\]. Rather, the control of intrahepatic tumor lesions is the prognostic factor in these cases\[1-3,12\]. In fact, deteriorated hepatic function was strongly considered as a cause of death in the present case. Although tumor factors at the time of hepatectomy strongly influence prognosis, treatment of EHM is important to delay extrahepatic tumor progression\[9\]. A surgical approach should be considered for patients with resectable extrahepatic metastasis from HCC.

Cheng et al\[7\] reviewed 11 cases of gastrointestinal metastasis from HCC. In their study, the initial presentations were massive bleeding from the GI tract and epigastric discomfort. Most patients presented with large tumor size and high tumor marker levels. The metastatic pattern of most cases was direct invasion from the subserosal to mucosal layer. In contrast, recent GI metastasis cases were described with the hematogenous spread pattern rather than direct invasion\[8,9\]. In our patient, the metastatic pattern was hematogenous spread without surrounding lymph node involvement. Most reports\[8,9\] indicate that patient’s symptoms, radiologic findings, and elevated tumor markers were important for the detection of GI metastasis. However, tumor markers in our case were not elevated at the time the GI metastases were detected. Therefore, detailed radiologic interpretation and annual endoscopic evaluation are advisable for HCC patient follow up.

Almost all patients with brain metastases present with neurologic symptoms such as headache, motor weakness, aphagia, ataxia, blurred vision or hemiparesis/hemiplegia\[10,11\]. Our patient complained of cognitive disorder and dysarthria, without headache or motor weakness. Patients with EHM from HCC who show any neurologic disorder should have radiologic evaluation with a neurologic specialist. In addition, most patients with HCC brain metastases also present with simultaneous pulmonary metastases. In fact, pulmonary metastasis may be a key sign of brain metastases and should be an indication for brain CT\[10-16\]. After assessment for brain metastasis, further evaluation for other extrahepatic metastases also should be considered.

The tumor biology between the primary HCC and metastatic lesions showed...
different characteristics. It showed the possibility of an HCC primary tumor acquiring a new metastatic mechanism due to stimulation by the tumor microenvironment. E-cadherin repression is essential for disassembling intercellular junctions, which is known to facilitate hematogenous metastasis[9]. CD44, as a cancer stem cell marker, is stimulated by the mesenchymal markers[13,14]. Epithelial-mesenchymal transition is also a key mechanism of hematogenous metastasis. The variation of numerous proteins in the metastasis of HCC is one reason why therapy targeted to specific proteins is not effective. It might be the reason that multi-kinase inhibitors, such as sorafenib and lenvatinib, had efficacious results for the patient with HCC metastasis. Therefore, it is important to study the characteristics of tumors and plan the treatment direction by considering differences between metastatic lesions and the primary tumor.

In brain metastases of various tumors, angiogenesis was identified as an important mechanism, demonstrating the possibility of neo-angiogenetic therapy[17]. There are two case reports using sorafenib in brain metastasis[18,19]. Sorafenib treatment for patients with brain metastases from thyroid cancer or renal cell carcinoma increased survival by more than one year. However, these cases were not hepatic metastases and liver function was normal. In addition, the improvement of symptoms after treatment took more than 1 mo. There is still a lack of randomized controlled trial studies for neo-angiogenetic therapy for brain metastasis. Therefore, comparing the therapeutic effects of surgical treatment with chemotherapy in brain metastases still requires further study.
Figure 4  Immunohistochemical results. A: Liver; B: Stomach; C: Colon; D: Brain. CD44 expression in metastatic lesions is strongly positive compared to the primary tumor.

CONCLUSION

The most common cause of death in EHM from HCC is not progression of EHM, but hepatic functional deterioration by recurrent intrahepatic HCC. Although our patient died due to hepatorenal syndrome 6 wk post-surgery, we cautiously suggest that a surgical approach for EHM could result in longer survival and improved quality of life in selected patients with well-maintained hepatic function.
Figure 5  Immunohistochemical results. A: Liver; B: Stomach; C: Colon; D: Brain. E-cadherin expression of primary tumor is strongly positive compared to metastatic lesions.

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Kim R et al. Concurrent hepatocellular carcinoma metastasis


