Clear Visualization of Extravasation on Angiography Using Carbon Dioxide in a Case of Hepatocellular Carcinoma Rupture with Unclear Visualization Using Iodine Contrast Agent

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Abstract

A 62-year-old woman with hepatocellular carcinoma (HCC) and asthma presented with acute abdominal pain and a decreased hemoglobin level. Peritoneal fluid was detected around the lesion, and rupture was suspected based on the findings of computed tomography. Extravasation of the HCC tumor was not detected on angiography with iodine contrast agent; however, such extravasation was clearly observed on angiography with carbon dioxide (CO₂). CO₂ angiography is sometimes utilized in patients with arterial bleeding. This modality be more effective and safe than angiography with iodine contrast agent for assessing potential ruptured HCC lesions.

Key words: hepatocellular carcinoma, carbon dioxide, angiography, therapeutic embolization, rupture, bleeding

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Introduction

Spontaneous rupture is a life-threatening complication of hepatocellular carcinoma (HCC) associated with a high rate of mortality, as it most commonly occurs in patients with a poor functional liver reserve (1). Therefore, rapid diagnosis of the site of bleeding and the prompt administration of treatment (e.g., hepatic surgery or transcatheter arterial embolization) are required.

Spontaneous HCC rupture can be diagnosed via contrast-enhanced computed tomography (CE-CT) and angiography with iodine contrast agent. However, iodine contrast agents cannot be used in patients with contrast allergies or those with nephropathy or asthma. Moreover, the site of bleeding is not always detected on CE-CT (2), which is not a real-time imaging modality, and the source of bleeding from ruptured HCC lesions is not always localized on angiography with iodine contrast agent (3, 4).

Carbon dioxide (CO₂) was employed as an intravascular contrast agent in the 1950’s (5, 6) and is safe for use in patients with iodine contrast agent allergies, nephropathy or asthma. Recently, the ability to depict the hepatic artery using CO₂ has improved due to the use of digital subtraction angiography (DSA). In several cases, angiography with CO₂ has been reported to detect bleeding sites that are not otherwise noted on angiography with iodine contrast agent in trauma patients (7-9). Therefore, angiography with CO₂ may be more effective than angiography with iodine contrast agent for detecting the source of bleeding from ruptured HCC lesions.

Case Report

A 62-year-old woman was admitted to Ehime University Hospital for the treatment of HCC in June 2011. She had been treated by her primary care physician for liver cirrhosis caused by hepatitis C virus infection and bronchial asthma.
guided abdominal paracentesis was therefore performed, and revealed high-density ascites around the liver (Fig. 2). US-10.8 to 8.1 g/dL. At that time, her blood pressure was 89/53 mmHg and her pulse rate was 74 bpm, and abdominal CT revealed high-density ascites around the liver (Fig. 1).

Twenty days after admission, the patient developed severe abdominal pain, and the hemoglobin level decreased from 11.3 g/dL to 10.8 g/dL. Therefore, emergency ultrasonography (US) screening was subsequently identified, and embolization with a gelatin sponge contrast agent (Fig. 3). The site of bleeding was subsequently identified, and embolization with a gelatin sponge contrast agent was performed from the A2 hepatic artery to prevent vascular spasms that may otherwise interfere with the diagnosis of bleeding. CO2 was aspirated from a CO2 catheter (2.0- or 4.0-Fr) by hand. Massive extravasation from the A2 hepatic artery was clearly visualized by CO2-DSA, although this finding was not depicted by the iodine contrast agent on angiography with a minimum volume (8 mL) of iodine contrast agent due to the patient’s asthma. A contrast study with contrast agent was performed from the celiac artery and to the A2 hepatic artery only. Deep cannulation of the A2 hepatic artery was not performed in order to prevent vascular spasms that may otherwise interfere with the diagnosis of bleeding. CO2 was aspirated from a CO2 cylinder into a 2.5- or 5.0-mL syringe and injected into the catheter (2.0- or 4.0-Fr) by hand. Massive extravasation from the A2 hepatic artery was clearly visualized by CO2-DSA, although this finding was not depicted by the iodine contrast agent (Fig. 3). The site of bleeding was subsequently identified, and embolization with a gelatin sponge (Gelpart, Astellas Pharma, Tokyo, Japan) was performed. The extravasation disappeared after embolization (Fig. 4).

Hepatectomy was carried out 30 days after admission. The patient’s postoperative course was good, and she was discharged without adverse events.

Despite receiving medical therapy, the patient experienced occasional asthmatic attacks. A hepatic tumor was subsequently detected in the second segment of the liver on routine ultrasonography (US) screening.

Upon admission to our hospital, a physical examination showed a blood pressure of 125/63, pulse rate of 80 bpm and pedal edema. However, no wheezing was noted. The laboratory results obtained on admission are summarized in Table. After admission, gadolinium-ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance imaging (MRI) revealed HCC in one segment of the liver (Fig. 1).

Twenty days after admission, the patient developed severe abdominal pain, and the hemoglobin level decreased from 10.8 to 8.1 g/dL. At that time, her blood pressure was 89/53 mmHg and her pulse rate was 74 bpm, and abdominal CT revealed high-density ascites around the liver (Fig. 2). US-guided abdominal paracentesis was therefore performed, and hemorrhagic ascites was aspirated. Hence, spontaneous rupture of the HCC lesion was suspected. CO2 was used as a contrast agent on angiography with a minimum volume (8 mL) of iodine contrast agent due to the patient’s asthma. A contrast study with contrast agent was performed from the celiac artery and to the A2 hepatic artery only. Deep cannulation of the A2 hepatic artery was not performed in order to prevent vascular spasms that may otherwise interfere with the diagnosis of bleeding. CO2 was aspirated from a CO2 cylinder into a 2.5- or 5.0-mL syringe and injected into the catheter (2.0- or 4.0-Fr) by hand. Massive extravasation from the A2 hepatic artery was clearly visualized by CO2-DSA, although this finding was not depicted by the iodine contrast agent (Fig. 3). The site of bleeding was subsequently identified, and embolization with a gelatin sponge (Gelpart, Astellas Pharma, Tokyo, Japan) was performed. The extravasation disappeared after embolization (Fig. 4).

Hepatectomy was carried out 30 days after admission. The patient’s postoperative course was good, and she was discharged without adverse events.

**Table. Laboratory Data at the Time of Admission**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tbody>
<tr>
<td>WBC (×10^9/L)</td>
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</tr>
<tr>
<td>RBC (×10^12/L)</td>
<td>393</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
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</tr>
<tr>
<td>PLT (×10^9/L)</td>
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</tr>
<tr>
<td>T.Bil (mg/dL)</td>
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</tr>
<tr>
<td>AST (U/L)</td>
<td>34</td>
</tr>
<tr>
<td>ALT (U/L)</td>
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<tr>
<td>ALP (U/L)</td>
<td>500</td>
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<tr>
<td>γ-GTP (U/L)</td>
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</tr>
<tr>
<td>Alb (g/dL)</td>
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<td>Cr (mg/dL)</td>
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<tr>
<td>AFP-L3 (%)</td>
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<td>PIVKA-II (mAU/mL)</td>
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</tr>
</tbody>
</table>


**Figure 1.** Gd-EOB-DTPA-enhanced magnetic resonance imaging reveals HCC in a segment of the liver in the hepatocyte-specific phase (arrow). Gd-EOB-DTPA: gadolinium-ethoxybenzyl diethylenetriamine pentaacetic acid, HCC: hepatocellular carcinoma.

**Figure 2.** Abdominal CT revealed high-density ascites around the liver (arrow). CT: computed tomography.

**Discussion**

Patients with advanced HCC may develop hemoperitoneum, a major cause of acute abdomen (10). In Japan, the annual number of deaths due to liver cancer is 30,000 (11), and spontaneous rupture of HCC is associated with a mortality rate of 10% (12). Surveillance of HCC had resulted in a decrease in the rate of spontaneous rupture, although this phenomenon remains a severe complication (13). HCC rupture is ranked as a T4 complication according to the Tumor, Nodes, Metastasis (TNM) staging system of HCC based on the fifth edition of the Liver Cancer Study Group of Japan (LCSGJ) classification. Spontaneous rupture occurs in patients with advanced HCC and a poor liver function and is associated with poor outcomes. For example, in one study, the 1-, 3- and 5-year overall survival rates were 41.4%, 21.1% and 13.3%, respectively, among HCC patients with rupture, compared with 84.1%, 63.0% and 45.8%, respec-
in deterioration of the patient’s condition (16). Transcatheter failure to stop bleeding on the first attempt will likely result in the first try in patients with spontaneous rupture of HCC, as and safety in a patient with asthma. bleeding is not always visualized on angiography with io-

source of bleeding on angiography. However, the site of HCC rupture (3, 17). Therefore, it is important to detect the success for stopping bleeding in patients with spontaneous arterial embolization (TAE) is associated with a rate of high limited in those with a history of contrast allergies, nephro-

pathy or asthma. In addition, a history of asthma is associ-

ated with an increased likelihood of having a contrast reaction (14). A previous study described the utility of both contrast-enhanced ultrasonography and CO2-angiography in a case of HCC rupture (15). In the present case, we also performed CO2-angiography and confirmed its usefulness and safety in a patient with asthma.

Leung et al. reported that bleeding must be stopped on the first try in patients with spontaneous rupture of HCC, as failure to stop bleeding on the first attempt will likely result in deterioration of the patient’s condition (16). Transcatheter arterial embolization (TAE) is associated with a rate of high success for stopping bleeding in patients with spontaneous HCC rupture (3, 17). Therefore, it is important to detect the source of bleeding on angiography. However, the site of bleeding is not always visualized on angiography with iodine contrast agent, as experienced in the present case. Soyer et al. reported that angiography showed extravasation of contrast agent in only two of 12 patients with HCC rupture (4), while Ngan et al. found extravasation of contrast agent from HCC lesions on angiography in six of 33 patients (18.2%) (3).

In the present case, CO2 was very effective for detecting the site of bleeding, which was not identified on angiography with iodine contrast agent. CO2 was used as a contrast agent for abdominal angiography by Hawkins in the 1970’s (9). One advantage of CO2 is that it can be used safely in patients with contrast media allergies or nephropa-

thy. CO2 is also 20 times more soluble in blood than iodine contrast medium and is excreted promptly via respiratory exhalation. In contrast, the viscosity of CO2 is 400 times less than that of iodine contrast medium (9). Although the ability to depict blood vessels using conventional angiography with CO2 is suboptimal, the development of DSA has improved the capacity to visualize blood vessels. For example, in the present case, the fourth peripheral branch of the common hepatic artery was visible on CO2-DSA. In addition, CO2 is economically valuable, as it is less expensive than iodine contrast agent.

While angiography with iodine contrast agent provides better peripheral visualization of blood vessels, CO2-DSA yields more useful information than DSA with iodine con-

trast agent in some situations. For example, CO2-DSA is su-

perior with respect to identifying the site of bleeding from arteries (5), and the low viscosity of CO2 allows it to flow into large arteriovenous shunts and/or vascular injury lesions more easily than iodine contrast agent. Furthermore, the hepatic parenchyma is not enhanced in the arterial or portal phase during CO2 angiography, allowing for clear depiction of the bleeding site. Spontaneous rupture of HCC often in-

volves bleeding from small arteries (18), and the low viscos-

ity of CO2 allows it to reach the source of bleeding via small arteries more easily than iodine contrast agent.

Nevertheless, CO2 angiography is associated with a risk of several side effects, including embolism and central neuro-

logical manifestations. For example, Cardi et al. reported side effects in seven of 1,200 cases of CO2 angiogra-

Figure 3. A: Angiography via the common hepatic artery with iodine contrast agent. Extravasation of contrast agent is unclear. B: Angiography via the common hepatic artery with carbon dioxide. Marked extravasation of carbon dioxide is seen (arrow).

Figure 4. The extravasation of CO2 disappeared after embolization. CO2: carbon dioxide
In order to prevent adverse effects, the total amount of CO₂ on angiography should be limited to less than 200 mL, with an upper limit for the rate of application of 25 mL/s (20).

In conclusion, CO₂ angiography is very effective for assessing ruptured HCC lesions, and CO₂ may be used safely in patients with intolerance to iodine contrast agent. Therefore, CO₂ may be the preferred agent for performing angiography to detect HCC rupture.

The authors state that they have no Conflict of Interest (COI).

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References