Case Report

Contrast-enhanced ultrasonography for the diagnosis of spontaneous necrosis of hepatocellular carcinoma: A report of 2 cases

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A B S T R A C T

Spontaneous necrosis of hepatocellular carcinoma (HCC) is rare and difficult to diagnose preoperatively if it occurs before the definitive diagnosis of HCC; this is because spontaneous necrosis of HCC exhibits various patterns in imaging studies. We compared imaging and pathological findings, and examined the possibility of diagnosing spontaneous necrosis of HCC using contrast-enhanced ultrasonography (CEUS). We experienced 2 cases of spontaneous necrosis of HCC. In case 1, spontaneous necrosis occurred after HCC diagnosis, while in case 2 it occurred before the first admission. The tumor in case 2 contained internal nodules and outer fibrous tissue. CEUS revealed a vascular spot in the hypovascular area during the vascular phase and a complete defect during the Kupffer phase. These findings accorded with the pathological findings and may be important for diagnosing spontaneous necrosis of HCC.

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary cancer of the liver. New systemic therapeutics have recently become available, including several multigated tyrosine kinase and immune checkpoint inhibitors [1]. Although diagnostic techniques have advanced [2], HCC is often difficult to diagnose. Spontaneous necrosis of HCC makes the diagnosis difficult. Spontaneous necrosis occurs in several types of tumors, particularly renal cell carcinoma, melanoma, and neuroblastoma [3]. Spontaneous necrosis of HCC is a rare event (estimated incidence of 0.4%) [4]. Herein, we present 2 cases of spontaneous necrosis of HCC. Because it exhibits various patterns in imaging studies, it is difficult to diagnose spontaneous necrosis of HCC if it occurs before the definitive diagnosis. Therefore, we compared contrast-enhanced ultrasonography (CEUS) images and pathological findings, and show that preoperatively diagnosing spontaneous necrosis of HCC using CEUS is possible.

Case presentation 1

A male patient in his 70s with hepatitis B virus-associated chronic hepatitis presented at our hospital in June 2018 with a liver tumor. The patient had consumed approximately 50 g of alcohol per day for 50 years but had completely stopped drinking after the HCC diagnosis. The serum alpha-fetoprotein (AFP) and Lens culinaris agglutinin-reactive AFP isofrom 3 (AFP-L3) tests were negative, but protein induced by vitamin K absence-II (PIVKA-II) was slightly elevated, at 42 mAU/mL. Multiphasic contrast-enhanced computed tomography (CECT) and CEUS with Sonazoid (GE Healthcare, Waukesha, WI, USA) were performed for the qualitative diagnosis (Fig. 1). The CECT showed a 2 cm, well-defined round tumor in the right hepatic lobe. The tumor was enhanced during the arterial-dominant phase (Fig. 1B) and washed out during the late venous phase (Fig. 1D). CEUS revealed hyperenhancement during the vascular phase (Fig. 1F) and a defect during the Kupffer phase (Fig. 1C). As these findings were suggestive of HCC, we scheduled surgical resection. The tumor enhancement on CECT was lost in the arterial-dominant phase in July before the surgery (Fig. 1I) and spontaneous necrosis was suspected. However, as persistence of a malignant tumor could not be excluded, the patient underwent surgical resection. Unfortunately, no CEUS assessment was conducted after the spontaneous necrosis.

The heptically resected specimen contained a tumor, the cut surface of which revealed a yellowish mass with a fibrous capsule (Fig. 2A). The entire tumor had undergone coagulative necrosis, and ghosts of tumor cells were arranged in a trabecular pattern. Viable cancer cells were observed in one region of the tumor (Fig. 2B, C). The surrounding liver parenchyma was chronic hepatitis tissue. These findings were suggestive of HCC with spontaneous necrosis.

Case presentation 2

A male patient in his 70s with Parkinson's disease, high blood pressure, and diabetes mellitus was admitted to another hospital in February 2021 because of choledocholithiasis. A computed tomography (CT) scan on admission revealed common bile duct stones, gallbladder stones, and a tumor in the right hepatic lobe. The patient underwent endoscopic retrograde cholangiography with removal of the choledocholithiasis. The common bile duct was compressed by gallbladder stones in June, resulting in Mirizzi syndrome. The patient was referred to our hospital for an elective cholecystectomy and further evaluation of the liver tumor in July. The patient had no history of alcohol consumption. Blood analysis and liver function tests were abnormal due to cholestasis. Serum AFP was negative but the AFP-L3 percentage was 24.7%, and serum PIVKA-II was elevated (1094 mAU/mL). The patient was negative for hepatitis B and C virus markers.

A 4-cm low-density tumor was observed on an abdominal CT scan (Fig. 3A), and the tumor exhibited some internal nodules. The internal nodules were heterogeneously enhanced during the arterial-dominant phase (Fig. 3B) and washed out insufficiently during the late venous phase (Fig. 3D). CECT also revealed gallstone cholecystitis (Fig. 3E), extrinsic compression of the common bile duct by the gallbladder stones (Fig. 3F), and dilation of the intrahepatic bile duct (Fig. 3G). Magnetic resonance imaging (MRI) revealed the tumor, which was mainly hypointense on T1-weighted imaging (Fig. 4A) and hyperintense on diffusion-weighted imaging (Fig. 4C). The enhanced pattern of Gd-EOB-DTPA was the same as that on CECT (Fig. 4D, E), and the tumor exhibited a defect during the hepatobiliary phase (Fig. 4F). A B-mode scan showed that the mass that contained mixed hypoechoic and hyperechoic areas (Fig. 5A), and CEUS revealed internal blood flow during the vascular phase (Fig. 5B), followed shortly thereafter by a vascular spot in the hypovascular area (Fig. 5C). The mass appeared as a complete destructive lesion of the inner and outer nodules during the Kupffer phase (Fig. 5D). Based on these imaging and hematological findings, atypical HCC or inflammatory pseudotumor-like nodule due to Mirizzi syndrome or cholangitis were considered. Ultrasound-guided needle biopsy of the liver tumor was performed to confirm the diagnosis. The needle biopsy revealed necrotic tissue mixed with some normal hepatocytes but no obvious cancer cells (Fig. 6A, B). Because a malignant tumor could not be completely ruled out, the patient underwent surgical resection.

The cut surface of the hepatically resected specimen revealed several yellowish nodules and a grayish white area replaced by fibrotic tissue (Fig. 6C). The yellowish nodules were mainly composed of necrotic tissue and a fibrous capsule surrounding the nodules (Fig. 6D). Viable cancer cells remained in the nodules and were arranged in a thick trabecular pattern (Fig. 6E, F). Only fibrous tissue was observed outside the fibrous capsule. The histological changes in the surrounding liver were unremarkable. These findings indicated moderately differentiated HCC with spontaneous necrosis. The nodules had been replaced by fibrotic tissue on the outside through a prolonged process after necrosis.
Fig. 1 – Abdominal contrast-enhanced computed tomography (CECT) (A-D) and contrast-enhanced ultrasonography (CEUS) with Sonazoid (E-G) for the initial diagnosis, and preoperative CECT (H-K). (A, H) Plain, (B) I arterial-dominant phase, (C) J portal venous phase, and (D) K late venous phase of CECT. (E) B-mode, (F) vascular phase, and (G) Kupffer phase of CEUS. Abdominal CECT on first admission showed a well-defined, approximately 2-cm round tumor (arrowheads) in segment 8 of the right hepatic lobe (A). A high-density region was noted inside the tumor during the arterial-dominant phase (B), while a low-density region was noted during the portal venous phase (C) and late venous phase (D). A B-mode scan showed a 2-cm hypoechoic nodule (E; arrowheads). CEUS showed hyperenhancement during the vascular phase (F) and a defect during the Kupffer phase (G). Abdominal CECT before surgery showed a lack of enhancement in the arterial-dominant phase (I) and low density during all phases (H-K).
Fig. 2 – Macroscopic and histological images of the resected specimen. (A) Macroscopic findings, (B) microscopic findings of the red-bordered section in A (hematoxylin-eosin stain; magnification ×40), and (C) microscopic finding of the green-bordered section in B (hematoxylin-eosin stain; magnification ×100). The hepatically resected specimen contained a tumor measuring 2.5 × 1.9 × 1.7 cm (A). The tumor was encapsulated with a thick fibrous capsule, and the entire region within the tumor was necrotized. The histopathological findings revealed ghosts of tumor cells arranged in a trabecular pattern and some viable cancer cells remaining in the tumor (B, C).

Discussion

Some mechanisms for spontaneous necrosis of HCC have been proposed, including reduced blood supply due to the fibrous capsule or arterial thrombosis [5–7], an immune reaction [3,8], abstinence from alcohol consumption [9,10], cholecdocholithiasis [11], the use of herbal medicines [12,13], and tumor hypoxia or systemic inflammation [14]. In our patients, the main mechanism of spontaneous necrosis was speculated to be an immune reaction, for example due to abstinence from alcohol (case 1) or cholecdocholithiasis (case 2). A disturbance in the blood supply by the fibrous capsule may also have played a role. It was easy to diagnose spontaneous necrosis in the first case because the patient had a definitive diagnosis of HCC. However, the second case had already undergone spontaneous necrosis when the imaging studies were performed at first admission. Diagnosis becomes quite difficult if spontaneous necrosis occurs before definitive diagnosis, because the imaging features of sponta-
Abdominal CECT for the initial diagnosis. (A) Plain, (B) arterial-dominant phase, (C, E-G) portal venous phase, and (D) late venous phase. Abdominal CECT shows an approximately 4-cm round tumor in segment 8 of the right hepatic lobe (A; arrowheads). Heterogeneous enhancement was seen inside the tumor during the arterial-dominant phase (B), with insufficient washout during the portal venous phase (C) and late venous phase (D). Abdominal CECT also revealed gallstone cholecystitis (E; arrows), extrinsic compression of the common bile duct by the gallbladder stones (F; arrows) and intrahepatic bile duct dilation (G).
neous regression of HCC are not uniform. Because the usefulness of CEUS for spontaneous necrosis after a definitive diagnosis has been reported [15], we compared the CEUS images with the pathological finding of spontaneous necrosis, and assessed the possibility of preoperative diagnosis using CEUS.

Patients with HCC and spontaneous necrosis before the first admission have a long history of necrosis, as in our second case. Hence, it is possible that the fibrous tissue was replaced after necrosis, and that residual viable cancer cells were growing within that fibrous tissue. The CEUS marker of spontaneous necrosis was a vascular spot in the internal nodules during the vascular phase, and a complete defect without any difference between the inner and outer nodules during the Kupffer phase. However, HCC with a nodule-in-nodule appearance is often detected, and is considered as a transient stage of multistep hepatocarcinogenesis between well-differentiated and dedifferentiated HCC [16]. Therefore,
Fig. 5 – CEUS with sonazoid. (A) B-mode scan, (B) vascular phase at 25 s, (C) vascular phase at 29 s, and (D) the Kupffer phase. The B-mode scan showed a 4-cm mass containing mixed hypoechoic and hyperechoic areas (A; arrowheads). CEUS revealed a vascular spot in the hypovascular area during the vascular phase (B, C) and complete defect during the Kupffer phase (D).

Enhancement differences between the inner and outer nodules are seen during the Kupffer phase because of the relationship between the distribution of Kupffer cells and cellular differentiation in HCC [17]. Thus, the CEUS findings were a typically hypoechoic nodule within an isoechoic nodule during the Kupffer phase, and no complete defect. The complete defect during the Kupffer phase differentiated it from the nodule-in-nodule type of HCC and may be an important finding for diagnosing spontaneous necrosis. Although preoperative radiological images are atypical for HCC, CEUS findings of spontaneous necrosis should be noted in the presence of other factors, such as abstinence from alcohol or cholangitis due to choledocholithiasis.

Conclusion

We present 2 rare cases of spontaneous necrosis of HCC confirmed by surgical resection and pathological evaluation. The cause of the spontaneous necrosis was presumed to be abstinence from alcohol or cholangitis due to choledocholithiasis, along with a disturbance in the blood supply because of a thick fibrous capsule. Spontaneous necrosis at the time of the first radiological image is an atypical finding for HCC. However, a vascular spot in the hypovascular area during the vascular phase and complete defect during the Kupffer phase may be important CEUS findings aiding diagnosis.
Fig. 6 – Macroscopic and histological images of the resected specimen and needle biopsy. (A, B) Microscopic findings of the needle biopsy (hematoxylin-eosin stain; magnification x 100). (C) Macroscopic findings of the resected specimen. (D) Microscopic findings of the red–bordered section in C (hematoxylin-eosin stain; magnification x 40). (E) Microscopic findings of the green–bordered section in D (hematoxylin-eosin stain; magnification x 100). (F) Microscopic findings of the blue–bordered section in D (hematoxylin-eosin stain; magnification x 100). The needle biopsy shows some normal hepatocytes without cytologic atypia (A) and necrotic tissue (B). The hepatically resected specimen contained a tumor measuring 3.9 × 3.0 × 2.2 cm (C). The cut surface of the tumor revealed several yellowish nodules and a grayish-white area replaced by fibrotic tissue. The yellowish nodules were mainly composed of necrotic tissue and surrounded by a fibrous capsule (D). Viable cancer cells remained in the nodules and were arranged in a thick trabecular pattern (E, F).
Patient consent

Patient consent was obtained for being included in the article.

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