Diffuse Intraperitoneal Metastasis After Spontaneous Rupture of Hepatocellular Carcinoma

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Rupture of hepatocellular carcinoma (HCC) is a fatal complication. Intraperitoneal metastasis after rupture of HCC is rare. We report a case of diffuse intraperitoneal metastases after rupture of HCC. A previously asymptomatic 32-year-old man was admitted because of massive ascites due to ruptured HCC. Poor liver reserve limited the therapeutic options. Transarterial chemoembolization was performed. Cytology was positive for HCC. It is rare for HCC to develop intraperitoneal metastases in as short as 3 months. [J Formos Med Assoc 2006;105(7):577–582]

Key Words: hepatocellular carcinoma, peritoneal seeding, rupture

Hepatocellular carcinoma (HCC) may invade the portal and hepatic venous system, but intraperitoneal metastasis is rare.¹ In Asia, spontaneous rupture of HCC occurs in 10.2–22% of patients.²,³ In Taiwan, the incidence is up to 26%.⁴ However, intraperitoneal metastasis after rupture of HCC is seldom noted. We report a case of HCC rupture with diffuse intraperitoneal metastases identified by echo-guided aspiration cytology 3 months later.

Case Report

A previously asymptomatic 32-year-old man had a 10-year history of chronic hepatitis B. Liver cirrhosis with ascites developed in 2001. General malaise and fatigue developed in late November 2003. A hepatic tumor was noted in December 2003. Bilateral leg edema, progressive abdominal distension, and decreased urine output led to admission for further evaluation in January 2004.

On examination, blood pressure was 100/70 mmHg, pulse rate was 110/minute, respiratory rate was 24/minute, body temperature was 36.3°C, and his body weight was 76.2 kg. Physical examination revealed pale conjunctiva and mildly icteric sclera. The abdomen was distended with shifting dullness. The bowel sound was normoactive and the liver was not palpable. The spleen was palpable two finger breadths below the left subcostal margin along with the left midaxillary line. The extremities were freely movable with pitting edema. Laboratory results disclosed normocytic anemia (Hb 3.5 g/dL, MCV 80 fl) and high levels of serum alpha-fetoprotein (AFP) (29,042 ng/mL). Other biochemistry data and coagulation profile were as

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Received: June 23, 2005
Revised: July 28, 2005
Accepted: September 13, 2005

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follows: total/direct bilirubin 2.0/0.6 mg/dL, AST/ALT 47/45 U/L, albumin/globulin 3.5/2.5 g/dL, and PT 17.6 seconds (international normalized ratio, 1.5). Component therapy with packed RBC was given for the anemia. Abdominal ultrasound revealed cirrhosis of the liver with massive ascites, gallstones, marked splenomegaly, and a 3.0 × 2.7 cm hypoechoic tumor at Couinaud’s segment 6. Diagnostic abdominal tapping obtained non-coagulable bloody ascites. Ascites routine revealed WBC 900/μL (L:N:M = 50:45:5), RBC 720,000/μL. Abdominal contrast-enhanced computed tomography (CT) scan (Figure 1A and B) showed a moderately enhanced, 3 cm diameter lesion protruding from the right hepatic tip compatible with HCC. High-density fluid collection was noted around the tumor. Massive ascites was noted to extend from the upper abdomen to the pelvis. Ruptured HCC was diagnosed. Endoscopy showed esophageal and gastric varices without active bleeding. Surgical intervention was not indicated due to high risk of hepatic failure. Liver biopsy was not done because of massive ascites and coagulopathy. Hepatic angiogram (Figure 1C) showed an ill-defined hypervascular tumor with heterogeneous staining in the right hepatic tip. Transarterial chemoembolization (TACE) was performed in February 2004 for the ruptured HCC. Follow-up post-TACE abdominal CT 1 week later revealed partial lipiodol retention (Figure 1D). AFP level decreased from 29,042 to 25,731 ng/mL. The patient was discharged in a stable condition with hemoglobin level 12.4 g/dL in early March.

During follow-up, the patient complained of orthostatic dizziness and increasing abdominal distension soon began about 14 days after

![Figure 1. Contrast-enhanced CT scan at first admission. (A) A protruded lesion, about 3 cm in diameter, (large arrow) with moderate enhancement at the right hepatic tip compatible with HCC. High-density fluid collection is apparent around the tumor. Gallstones (small arrow) are also visible. (B) Massive ascites from the upper abdomen extending to the pelvis. (C) Hepatic angiogram shows an ill-defined hypervascular tumor with heterogeneous staining in the right hepatic tip (arrow). (D) CT scan 1 week after transarterial chemoembolization shows partial lipiodol retention (large arrow) in the HCC. Most of the tumor was poorly enhanced. Gallstones (small arrow) were also noted.](image)
discharge. Hemoglobin level was 4.8 g/dL in April 2004. Tarry stool passage developed. Endoscopy disclosed three F3Cb esophageal and gastric varices with nipple signs. Histoacryl injections to the gastric varices were performed. Higher AFP level (> 87,500 ng/mL) was noted. He was admitted again for further evaluation. Diagnostic paracentesis did not show bloody ascites. Ascites routine showed WBC 200/μL; RBC 0/μL; L:N:M = 90:03:7. Another episode of HCC rupture was not considered likely. Thus, the decrease in hemoglobin level during this admission was considered likely due to variceal bleeding.

Abdominal CT in May showed diffuse tumor metastases in the peritoneum, especially in the pelvic cavity (Figure 2). Cytology of echo-guided aspiration from the suprapubic area was positive for HCC (Figure 3). The history, together with cytology of echo-guided aspiration, indicated that the rapidly diffuse peritoneal metastasis had occurred secondary to the HCC rupture. An oncologist was consulted for further chemotherapy. However, due to poor liver reserve (Child–Pugh class C) and extensive extrahepatic metastases, chemotherapy was not recommended. The patient survived for 4 months under conservative treatment.

Discussion

The most common sites of HCC metastases are the intrahepatic, local lymph node, lung, bones, brain, adrenal glands, etc. Intraperitoneal metastases are rare in nonruptured HCC.

![Figure 2](image1.png)

**Figure 2.** Contrast-enhanced CT scan 3 months after rupture reveals: (A) two small well-enhanced nodules (arrows) in the greater omentum, and (B) extensive peritoneal implantation (arrows) in the lower abdominal wall and pelvic cavity.

![Figure 3](image2.png)

**Figure 3.** Peritoneal aspiration cytology of (A) cellular aspirate specimen shows a feeding blood vessel (small arrow) and tumor nests (big arrow). The malignant cells have polygonal outlines, central nuclei, and high nuclear/cytoplasmic (N/C) ratios. The cytoplasm has well-defined cell boundaries. Trabeculae are represented by disorderly thick plates and lined by sinusoidal endothelial cells with elongated nuclei (Riu’s stain, 400×). (B) The malignant hepatocytes are larger than the neutrophils. Numerous naked nuclei are visible. The background of the smear is clean and inflammation is scant (Riu’s stain, 400×).
Nakashima et al noted that metastases to the pouch of Douglas occurred in 6.2% of 232 consecutive autopsy cases of HCC. Such metastases in patients with nonruptured HCC seem to occur only in the late stage of the disease.\(^5\)

Several mechanisms have been postulated to explain spontaneous HCC rupture, including: venous hypertension caused by obstruction of venous flow by direct tumor invasion, central necrosis caused by rapid tumor growth, coagulopathy such as thrombocytopenia and disturbed prothrombin synthesis, slight trauma or compression by the diaphragm associated with respiratory movement, and vascular injury giving rise to hemorrhage and subsequent rupture.\(^6\)–\(^8\) The diagnosis of HCC rupture was based on blood-stained ascites plus imaging studies and symptoms.\(^1\) Yeh et al\(^9\) found that the clinical picture in patients with ruptured HCC is different from those without rupture in four aspects: (1) they have symptoms such as sudden attack of severe abdominal pain and signs of bleeding during physical examination; (2) a lower hemoglobin level is observed; (3) there is a higher AST (aspartate aminotransferase) concentration; and (4) greater blood loss is observed during hepatic resection. They concluded that sudden-onset abdominal pain is the only independent indicator of ruptured HCC. From imaging studies, enucleation sign on helical CT could be more specific for ruptured HCC.\(^10\)

Treatment of ruptured HCC is aimed at controlling hemorrhage and resection. Miyamoto et al\(^3\) recommended a two-stage therapeutic approach. First, it is important to accomplish hemostasis. Widely used techniques include TACE, gauze tamponade, or hepatic artery ligation. TACE is the preferred method to arrest tumor bleeding.\(^11\) Second, it is advisable to perform a two-stage hepatectomy. Both 3-month cumulative survival rate and mean survival period following two-stage hepatectomy were significantly higher than with other treatments. Yoshida et al reported similar results.\(^12\) Liu et al\(^13\) and Mizuno et al\(^14\) also claimed that second-stage hepatic resection in selected patients can achieve prolonged survival. However, hepatectomy was not performed in our patient due to poor liver reserve. In addition to the above management for ruptured HCC, Ng et al reported that ruptured HCC could be treated by radio-frequency ablation as a salvage procedure.\(^15\)

HCC rupture with intraperitoneal hemorrhage is an acute and potentially fatal complication. The prognosis is very poor, and long-term survival can be expected in very few patients.\(^16\) Implanted metastases usually do not become clinically apparent because most of these patients die within several weeks after HCC rupture.\(^17\) Peritoneal metastases following rupture of HCC were first reported by Ong et al in 1965.\(^18\) The peritoneal metastases were thought to be due to hematogenous spread with implantation to peritoneum.\(^19\) Peritoneal metastases after HCC rupture were not mentioned in several large series of spontaneous rupture of HCC.\(^2\)–\(^4\),\(^20\) Only sporadic case reports have been published. Of the case reports discussing survival after HCC rupture, metastases were found 1–105 months after rupture (Table).\(^5\),\(^17\),\(^19\),\(^21\)–\(^25\) Most reported cases of peritoneal metastases were documented 8 months after rupture.\(^5\),\(^17\),\(^19\),\(^22\)–\(^24\) A single metastatic tumor was the most frequent presentation. Resection was the treatment of choice for peritoneal metastasis if possible and might offer long-term survival benefit.\(^17\),\(^22\)–\(^25\) Shirabe et al reported a patient who had previously undergone hepatic resection for ruptured HCC but developed a solitary peritoneal recurrence at the incision site 105 months later.\(^22\) The peritoneal recurrence was proven to be identical to the primary tumor by using Ki-67, DNA ploidy pattern, and DNA index identification. However, this patient did not undergo surgical treatment due to poor liver reserve (Child–Pugh class C) and extensive peritoneal metastasis.

Our patient developed diffuse intraperitoneal metastases, which were documented 3 months after spontaneous HCC rupture. Since the peritoneum does not provide an adequate environment for HCC to grow quickly, carcinomatosis peritoneum of HCC is unusual.\(^1\) The clinical presentation of our patient is unusual in terms of the rapid growth in the peritoneum. Kim et al reported metastasis of multiple small size nodules in the
peritoneum 50 days after HCC rupture. In contrast, our patient had multiple and larger tumors implantation.

Because few cases of peritoneal metastases after ruptured HCC are reported, data are lacking on the viral etiologies (HBV vs. HCV), AFP level, cell differentiation, and patient age. However, it was interesting to note that all reported cases have been male (Table). In addition, most of these patients underwent surgical resection for their primary tumors.

In conclusion, HCC rupture is a fatal complication. Multiple large intraperitoneal metastases may develop as early as 3 months after rupture of HCC. However, further studies are required to clarify the underlying mechanisms for such rapid growth of HCC in the peritoneum.

**Acknowledgments**

This study was supported by grants from the Liver Disease Prevention and Treatment Research Foundation, Taiwan.

**References**


### Table. Case reports of peritoneal metastases after ruptured HCC

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N/A = not available; M = male; TACE = transarterial chemoembolization.