Case Report

# Spontaneous rupture of hepatocellular carcinoma

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## ABSTRACT

Hepatocellular carcinoma is the most common malignancy among males and the 7th among female patients in the Kingdom of Saudi Arabia. This is due to the endemicity of hepatitis B and hepatitis C. Spontaneous rupture of hepatocellular carcinoma is rare. We report 4 cases of spontaneous rupture of hepatocellular carcinoma. Initial control of bleeding was achieved surgically in 3 patients and by embolization in the 4th patient. All patients had very good hepatic reserve as reflected by Child-Pough scoring (A & B). We found that the incidence of ruptured hepatocellular carcinoma among 85 patients was 4.7%. The prognosis of this subgroup of patients is poor as reflected by the low median survival ranging from 6-16 weeks.

**Keywords:** Hepatocellular carcinoma, hemoperitoneum, spontaneous rupture, embolization.

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Hepatocellular carcinoma (HCC) is a common malignancy in the Kingdom of Saudi Arabia (KSA) with the majority of patients presenting at late stages where any effective therapy is precluded by the advanced nature of the tumor. The prognosis is generally dismal,[1] and the mortality is high.[2,3] Rupture of HCC is the 2nd common cause of spontaneous hemoperitoneum at 24% following gynecological diseases at 44%.[4] Among complications due to HCC, spontaneous rupture is uncommon. In this article, we report our experience of treating 4 cases of spontaneous rupture of HCC in cirrhotic livers due to hepatitis C, hepatitis B and schistosomiasis. The total number of patients with proven HCC was 85 admitted to King Abdul-Aziz Hospital and Oncology Center between 1990 and 1999. The bleeding was controlled in 3 patients by packing and suturing and in one patient by embolization of the left hepatic artery. One patient died during the same admission, 2 patients died 2 and 4 months after the first presentation and the 4th patient died 6 weeks after embolization. The Child-Pough scoring was A, A, B, and B. All patients had re-bleeding from the tumor. Liver function tests were not significantly altered. There was no evidence of clinical or sub-clinical coagulopathy. There were no specific sites of rupture in the liver. Three patients had re-bleeding confirmed by the presence of hemoperitoneum as shown by computerized tomography (CT) scan and paracentesis. The 4th patient died of hepatic encephalopathy. The incidence of ruptured HCC in our study is 4.7%. The mortality rate was 1.2%. Packing-suturing and embolization are effective methods of controlling the initial bleeding. However, a multi-modality approach is recommended to control further bleeding and probably improve the quality of life of patients.

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Case Report. ***Patient One.*** A 49-year-old male patient was admitted with 2 days complaint of left hypochondrial pain that was dull, localized, increased by lying flat and relieved after passage of stool. It was associated with watery diarrhea. He is known to be hypertensive and cirrhotic secondary to hepatitis C infection. On examination, patient looked fairly well. His temperature was 37.7°C, pulse 80 beats/min and blood pressure 100/70 mmHg. General examination revealed a tinge of jaundice, spider nevi, bilateral gynecomastia, bilateral pitting edema of the legs and ecchymosis over knees. Abdominal examination revealed slight tenderness in the left hypochondrial area and ascites. Bowel sounds were normal. Investigations revealed: Hemoglobin (Hb) 11.5 (14 - 18 g/dL), packed cell volume (PCV) 37.7 (42 - 52), WBC 15.5 (4.8 -10.8 x $10^9$/l), platelets 150 x $10^9$ (130-400 x $10^9$/l), serum glutamic-oxaloacetic transaminase (SGOT) 183 (5-50 iu/L), serum glutamic pyruvic transaminase (SGPT) 126 (5-55 iu/L), gamma glutamyl transferase (GGT) 213 (5-55 iu/L), hepatitis C positive antibodies, alpha-fetoprotein 60.1 (0-5.8 ng/ml), total serum bilirubin 24 (5-17 umol/l), serum albumin 36 (35-50 g/L), international normalized ratio (INR) 1.2 and partial thromboplastin time (PTT) 36.6/32.3. The Child-Pough scoring was A. Abdominal ultrasound showed multiple hepatic nodules and hemoperitoneum. Laparotomy revealed hemoperitoneum and cirrhotic liver with 3 soft nodules in the right and left lobes of the liver profusely bleeding. Packing and suturing did not control the bleeding, so the common hepatic artery was isolated and ligated; the bleeding stopped (**Figure 1**). Post-operatively, the liver decompensated and the patient bled massively intra-peritoneally as demonstrated by paracentesis. The patient died on the 9th post-operative day. Histopathology showed necrotic poorly differentiated HCC arising in a cirrhotic liver.

***Patient 2.*** A 40-year-old male patient was hospitalized through the Emergency Department due to sudden onset of epigastric pain of 10 hours duration, which then became generalized and associated with vomiting. The patient had no history of previous similar attacks, and had schistosomiasis in the past. On examination, blood pressure was 100/60 mmHg, pulse was 98 beats/min. The epigastric region was tender with guarding. There was ascites and bowel sounds were absent. Hemodynamically, the patient was stable with Hb 13.0 (14 -18 g/dL), PCV 36.0 (42-52), WBC 24.3 (4.8-10.8 x $10^9$/l), platelets 126 X $10^9$ (130 - 400 x $10^9$/l), total serum bilirubin 23 (5-17 umol/l), serum albumin 23 (35-50 g/l), SGOT 65 (5-50 iu/L, SGPT 55 (5-55 iu/L), GGT 165 (5-55 iu/L), INR 1.3, PTT 38/36. Patient's serology for hepatitis B surface antigen (HBsAg) and hepatitis C virus antibody HCV-Ab was negative. Alpha-fetoprotein was 350 (0-5.8 ng/ml). The Child-Pough scoring was A. Upper gastro-intestinal endoscopy revealed non-bleeding esophageal varices. Abdominal ultrasound showed a mass in the right lobe of the liver and ascites. Computerized tomography scan demonstrated a large tumor in the right lobe of the liver and huge hemoperitoneum. Laparotomy revealed hemoperitoneum and cirrhotic liver with a large mass measuring 10x8 cm in the right lobe of the liver. The mass was oozing blood. Packing and suturing controlled bleeding. Histopathology showed well-differentiated HCC (**Figure 2**). The patient was discharged well on the 7th post-operative day. Two months later, the patient was re-admitted because of hypovolemic shock. Abdominal CT scan demonstrated replacement of the right lobe of the liver by the tumor which also invaded the chest wall, diaphragm, porta hepatis, transverse colon, gallbladder with hemoperitoneum. The patient died 2 months after the first presentation.

***Patient 3.*** A 72-year-old male patient was admitted through the Emergency Department due to left hypochondrial pain, fatigability and sweating of 3 days duration. He was anorexic and constipated. He denied vomiting and hematemesis. The patient was known to be hypertensive, chronic hepatitis B virus (HBV) carrier, cirrhotic with a mass arising from the left lobe of the liver and fundal varices. Biopsy of the hepatic lesion was planned but not accomplished because of technical difficulties. On examination he was fully conscious. He looked pale, ill and in pain. He was not jaundiced. His pulse was 86 beats/min and his blood pressure was 90/50 mmHg. General examination revealed bilateral gynecomastia and bilateral pitting lower limb edema. On abdominal examination there was generalized gaseous distension and generalized tenderness but no rigidity. He had reducible paraumbilical and inguinal hernias. Bowel sounds were normal. His investigations on admission were as follows: Hb 10.3 (14-18 g/dL); WBC 11.3 (4.8 -10.8 x $10^9$/l); platelets 169 x $10^9$ (130 - 400 x $10^9$/l); serum albumin 28 (35-50 g/L); SGOT 245 (5 - 50 iu/L); SGPT 231 (5-55 iu/L), GTT 91 (5-55 iu/L), total serum bilirubin 5 (5-17 mmol/L); INR 1.4, PTT 38/30 and alpha-fetoprotein 4.3 (0-5.8 ng/dl). The Child-Pough scoring was B. Abdominal x-rays showed markedly dilated small and large bowel loops, no air-fluid levels and no free gas under the diaphragm. The patient was managed conservatively. Within 24 hours the patient's pain worsened and he was more distended and tender all over the abdomen. His blood pressure was maintained but he had tachycardia (Pulse: 110 beats/minute). His Hb dropped to 6.1 g/dl. Emergency laparotomy revealed cirrhosis, hemoperitoneum and ruptured cystic swelling in the left lobe of the liver which was still bleeding. The contents of the swelling were removed and sent for histopathology. The bleeding was

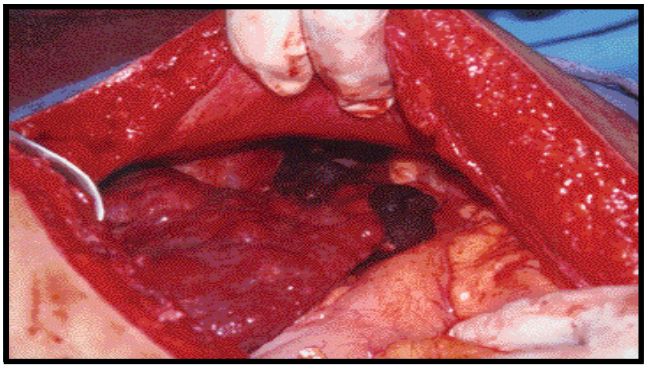

**Figure 1 -** Operative field showing cirrhotic liver and the bleeding sites were controlled by packing-suturing.

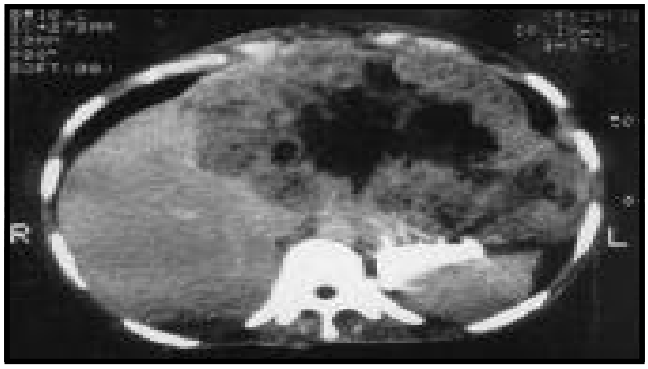


**Figure 3 -** CT scan abdomen showing a huge mass in the left lobe of the liver and extending to the right lobe with central necrosis.

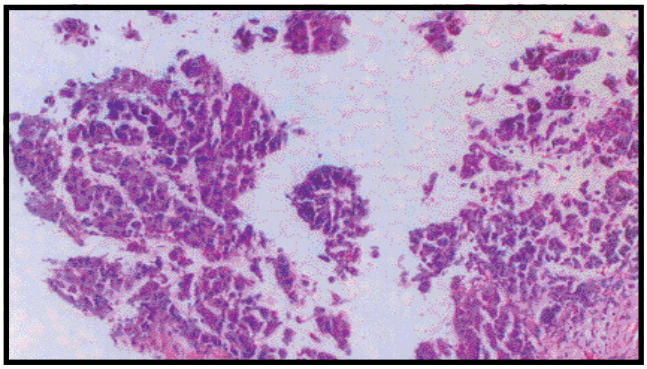

**Figure 2 -** Poorly differentiated hepatocellular carcinoma showing an area of capsular rupture (Hematoxylin & Eosin x 250).

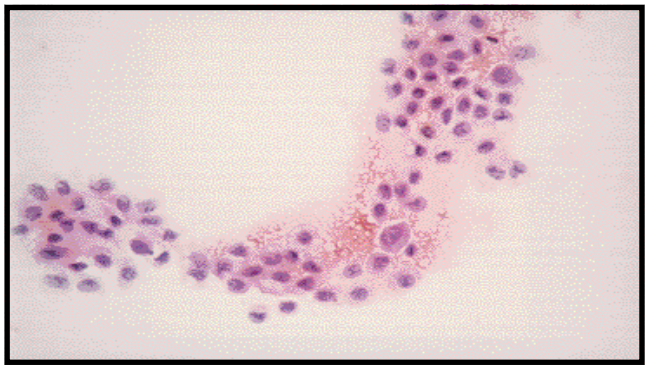

**Figure 4 -** Peritoneal cytology demonstrating clusters of malignant hepatocytes (Hematoxylin & Eosin x 200).

stopped with packing of the cyst with surgicel and suturing of the edges. On the 2nd postoperative day he developed deep vein thrombosis which was proved by doppler scan. He was anticoagulated with heparin 5000 iu subcutaneously twice daily. The patient was discharged home on the 14th postoperative day in good condition. Histopathology of the content of the cystic swelling showed necrotic HCC. After 2 months, the patient was re-admitted for chemoembolization. Magnetic resonance image at that time revealed a 7.8 x 6.4 cm mass in the right lobe of the liver and another mass measuring 3.8 x 2.4 cm in segment VI. Chemoembolization was tried but the patient became unwell with elevation of his blood pressure, so the procedure was terminated. Subsequently the patient developed a drop in his Hb with ascites and an elevation of his serum potassium. Abdominal paracentesis showed bloody ascites. The patient died 4 months after the initial presentation.

***Patient 4.*** A 30-year-old female patient was referred to our oncology center as a case of HCC for further treatment. She gave a history of epigastric pain of 3 months duration. The pain was dull and localized. It was not associated with vomiting, hematemesis, melena, fever or jaundice. There was no past history of blood transfusion or alcohol intake. Three weeks after admission she started to develop abdominal discomfort with respiratory embarrassment. Abdominal paracentesis with free drainage was carried out. There was hemorrhagic ascitic fluid. Urgent embolization of the left hepatic artery was carried out and the Hb level rose to 11.0 g/l. The patient was discharged on supportive therapy. On initial examination, the patient looked ill. Her vital signs were stable. There was pallor but no jaundice or signs of chronic liver diseases. Abdominal examination revealed a huge epigastric mass. There was no ascites. Her investigations were as follows: Hb 7.2 (14 - 18g/dL), PCV 25.2 (42 - 52), mean corpuscular volume 66.4 (80 - 94 fL), mean corpuscular Hb 19 (27 - 31 pg), mean corpuscular Hb Concentration 28.7 (33 - 37 g/dL), WBC 6.7 (4.8 - 10.8 x $10^9$/l), platelets 232 x $10^9$ (130-400 x $10^9$/l), SGOT 39 (5-50 iu/l), SGPT 40 (5-55 iu/l), GGT 165 (5-55 IU/L), positive HBsAg, alpha-fetoprotein > 5000 (0 - 5.8 iu/ml), serum albumin 29 (35-50 g/l), INR 1.2, PTT 28.4/25.4. The Child-Pough scoring was B. Contrast CT scan of abdomen showed a large (18.0 x 11.0 cm) mass in the left lobe of the liver and extending to the right lobe with central necrosis. The mass reached the anterior and left lateral abdominal walls, and encroached significantly on the porta

hepatis with mild indentation on the portal vein. It also compressed the gastric fundus. The peri-pancreatic and para-aortic lymph nodes were enlarged (**Figure 3**). Urgent embolization of the left hepatic artery with polyvinyl alcohol particles (PVC) was carried out until 95% of the tumor bed was embolized. The peritoneal cytology showed clusters of malignant hepatocytes with large hyperchromatic nuclei, multiple nucleoli and ample eosinophilic cytoplasm with increased nuclear/cytoplasmic (N/C) ratio (**Figure 4**). Review of the tru-cut liver biopsy which was carried out 2 months prior to her admission demonstrated, HCC, chronic active hepatitis Grade II and peri-portal fibrosis Stage II. Because of the extensive and metastatic nature of the tumor, there was no justification for surgical intervention. The patient was discharged on supportive therapy with Hb 11.5 g/dl, and 6 weeks after discharge, the patient died of hepatic encephalopathy.

Discussion. Hepatocellular carcinoma (HCC) is very common in KSA. According to the local tumor registry (1996) it is ranked the first malignant tumor among male adults and the 4th among female adults.[5] Rupture of HCC is a well known catastrophic complication which may be spontaneous or following transcatheter arterial embolization (TAE),[6-9] interferon therapy,[10] trans-jugular intrahepatic porto-systemic shunt (TIPS)[11] or abdominal trauma.[12] The relative incidence of spontaneous rupture of HCC ranges between 2% to 26%;[4,13] being low in the western hemisphere[4,14] and high in Southeast Asia.[13,15] The incidence in our study is (4/85) 4.7%. The mechanism of spontaneous rupture is not clear but it seems to be due to rapid expansion of the tumor secondary to bleeding from within its substance.[16] It may also be due to an area of acute inflammation with consequent bleeding, coagulopathy or tumor necrosis.

Rupture of HCC was predominantly in the left lobe.[3,13] Computerized tomography scan and arteriogram are the most effective diagnostic modalities but arteriogram has the advantage of its therapeutic potential;[17] color-doppler sonography is helpful in detecting the rupture site by demonstrating a high-velocity jet flow from it.[18]

Various methods of treatment strategies have been described. These include supportive measures,[16,19,20] hepatectomy,[15,20-22] hepatic arterial ligation,[4,16,22] packing and suturing,[16,22] argon beam coagulation,[16] microwave,[16] absolute ethanol,[16] TAE[2,16,20,23-27] and staged hepatectomy after TAE.[16,25,26,28] The results of various therapeutic modalities are variable.

In our patients, hemostasis was achieved in one by packing, suturing and hepatic arterial ligation, in 2 by packing and suturing only and in one by embolization of the left hepatic artery. The first patient had hepatitis C infection with advanced cirrhosis and poorly-differentiated HCC. He died on the 9th post-operative day. The 2nd patient had schistosomiasis, cirrhosis and a solitary well-differentiated tumor. The 3rd patient was a HBV carrier with cirrhosis and necrotic HCC. The 4th patient had hepatitis B with chronic active hepatitis, peri-portal fibrosis and HCC.

Early diagnosis is vital for management. Conservative measures may be used for selected patients in extremely poor condition.[16,29] Long-term survival has been achieved following hepatic resection.[15,19,21,22,25,29] Transcatheter arterial embolization is highly effective and is the treatment of choice for initial hemostasis.[2,16,23,24,27] Selective surgery seemed better than TAE although the difference was not statistically significant.[30] However, TAE has the lowest hemostatic failure rate (20%).[20] At present in the majority of patients with ruptured HCC, TAE followed by hepatectomy (if the lesion is resectable) seems the most appropriate treatment.[16,25,26,28] Wakahara et al demonstrated no viable tumor cells following combined TAE and resection.[31] The post-operative mortality following left lobectomy, right lobectomy, excesion, hepatic arterial ligation and direct hemostesis is high 45.5%.[3]

Rupture of HCC leads to intra-peritoneal recurrence which necessitates re-operation.[32,33] A few patients have long-term survival after resection of implanted metastasis.[33] However, there was no difference in the rates of peritoneal dissemination between ruptured and non-ruptured HCC.[34] This study demonstrates that initial control of bleeding by packing, suturing, hepatic arterial ligation and embolization is feasible but is not enough to prevent further bleeding or the progression of the disease since all our 4 patients died after short intervals, 9 days, 8 weeks, 16 weeks and 6 weeks respectively. Additionally, long-term survivors have not been reported.[29] The median survival following hepatectomy ranges between 30-375 days,[20,26] while following TAE alone was 149-202 days.[20,24] In our study, the 4th patient who underwent embolization survived 6 weeks only.

Patients with cirrhosis or HCC should have periodic surveillance with liver ultrasound and serum alpha-fetoprotein to monitor the progression of the disease and the development of metastasis. Why some patients with HCC rupture spontaneously is not well understood. Further trials should look for factors predicting patients who are at high risk of spontaneous rupture of HCC. It is apparent from our analysis that the spontaneous rupture has no relation to the underlying cause or to the degree of hepatic reserve. Therefore, prophylactic measures such as TAE could be employed timely to avoid this catastrophic complication.

In conclusion, spontaneous rupture of HCC is a serious complication with an incidence of 4.7% and overall mortality of 1.2%. Packing-suturing, hepatic

arterial ligation and embolization can achieve initial control of bleeding. It should be emphasized that this approach is not adequate to prevent subsequent re-bleeding or advancement of the disease, which affects the quality of life. Elective surgery on selected patients after initial hemostasis gives a better expectancy than emergency laparotomy. Staged hepatectomy after TAE is the rational treatment for the majority of patients. Predicting factors for spontaneous rupture should be evaluated, since this might improve the management and survival of these patients.

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