Spontaneous Hemoperitoneum Resulting from Rupture of Hepatocellular Carcinoma

James T. Loynes, MD

Hepatocellular carcinoma (HCC) is a common neoplasm worldwide. The incidence of HCC is highest in Africa and Asia, where it exceeds 20 cases per 100,000 persons. In Mozambique, HCC occurs in 103.8 per 100,000 men.[1] The neoplasm is much less common in the United States, but its rate of occurrence has been increasing.[2]

Intraperitoneal hemorrhage (ie, hemoperitoneum) resulting from rupture of HCC can cause anemia, orthostasis, increasing abdominal fullness, hypotension, and shock. Throughout Africa and Asia, HCC frequently ruptures spontaneously, often leading to death.[3] Spontaneous hemorrhage from HCC is reported infrequently in the United States.[4] This article presents a case report and review of the literature on HCC.

CASE PRESENTATION

A 50-year-old African American man comes to the emergency department reporting a 3-day history of lethargy, dizziness, abdominal pain, and increased thirst. Because of hypotension, progressive hypoxia, and a change in mental status, he is intubated emergently and admitted to the hospital.

History

Medical history is significant for alcoholism, hepatitis B, variceal hemorrhages, splenorenal shunt, coagulopathy, anemia, and Child's class B cirrhosis. There is no known family history of cancer. Medications include magnesium oxide, vitamin K, folic acid, and vitamin B_{12} (cyanocobalamin). He drinks 12 beers and smokes 1 pack of cigarettes daily. He lives by himself in an apartment.

Physical Examination

Physical examination reveals a thin man with no evidence of head trauma. Blood pressure is 84/60 mm Hg, pulse is 125 bpm, and respiratory rate is 24 breaths/min. Pupils are equal, round, and reactive to light; the sclera of both eyes is icteric. He has poor dentition and dry mucous membranes. There is no evidence of cervical lymphadenopathy, thyromegaly, or jugular venous distention. Cardiac examination shows tachycardia; lung sounds are coarse. His abdomen is distended, and he had decreased bowel sounds; abdominal tenderness is difficult to evaluate because of his decreased level of consciousness. There is no evidence of hepatosplenomegaly. Results of a guaiac test for occult blood are positive, but there is no melena or hematochezia. Examination of the extremities reveals 1+ edema.

Laboratory and Radiographic Evaluation

Hematologic findings include a hematocrit of 9%, a leukocyte count of $15.9 \times 10^3/mm^3$, a partial thromboplastin time of 92.5 seconds, and an international normalized ratio of 5.8. Laboratory tests additionally yield the following serum values: carbon dioxide, 6.5 mEq/L; blood urea nitrogen, 30 mg/dL; creatinine, 2.4 mg/dL; glucose, 117 mg/dL; albumin, 1.2 g/dL; total bilirubin, 2.6 mg/dL; alkaline phosphatase, 229 U/L; and alanine aminotransferase (ALT, SGPT), 80 U/L. The patient is transferred to the medical intensive care unit where he is given fresh frozen plasma and packed red blood cells. When a nasogastric tube is placed, an aspirate that is not grossly bloody is obtained.

Abdominal ultrasonography, performed because of increasing abdominal distension, shows intraperitoneal fluid and a previously undiagnosed hepatic tumor measuring 7.5×6.5 cm. A tentative diagnosis of HCC is made. The patient remains severely hypotensive and requires fluid and pressor support. Paracentesis is performed, and analysis of the aspirated fluid reveals frank blood, a hematocrit of 18%, and a total protein level of 5.0 g/dL.

Clinical Outcome

A surgical consultation determines that the patient is not a suitable candidate for surgery because of his

Dr. Loynes is a Fellow in Hematology/Oncology, Dartmouth-Hitchcock Medical Center, Lebanon, NH.

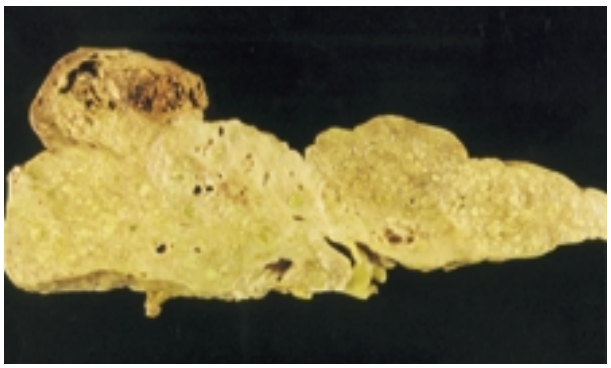

Figure 1. Necrotic tumor measuring 7.5 × 6.5 × 4.5 cm in the right hepatic lobe with dissection to the peritoneal surface. Multiple smaller nodules are visible within the liver.

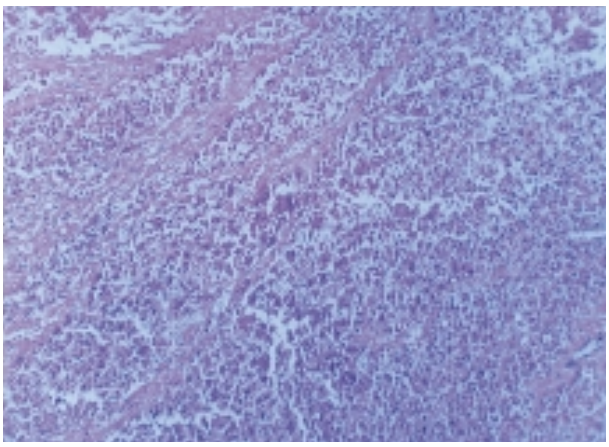

Figure 2. Photomicrograph of liver parenchyma demonstrating tumor infiltration.

underlying cirrhosis, now classified as Child's class C. Despite aggressive supportive care, the patient's condition continues to worsen. The option of arterial embolization, the procedure of choice in patients with advanced liver disease, significant coagulopathy, and hemoperitoneum, is discussed with the family. However, on the basis of the patient's prior wishes, his poor baseline performance status, and his severely critical condition, the family decides on a "do not resuscitate" order; no further interventions are performed, and the patient dies 3 days after admission.

Autopsy Findings

An autopsy authorized by the family reveals a 2200-g liver with evidence of micronodular cirrhosis. There is a necrotic hemorrhagic tumor (7.5 × 6.5 × 4.5 cm) in the right hepatic lobe with dissection to the peritoneal surface and an adherent hematoma (**Figure 1**); microscopic evaluation shows a tumor consistent with hepatocellular carcinoma (**Figure 2**). There also are multiple smaller tumor nodules in the liver and on the adjacent diaphragm, as well as approximately 2 L of bloody ascites. His splenorenal shunt is intact with no evidence of thrombus. The pancreas is characterized by a soft hemorrhagic parenchyma suggestive of acute pancreatitis. There is evidence of concentric left ventricular hypertrophy, congested lungs, acute gastritis, and unruptured varices in the distal third of the esophagus.

DISCUSSION

Case Patient

The case patient had the classic symptoms of spontaneous hemoperitoneum resulting from hepatocellular carcinoma. His initial examination revealed hypotension, anemia, and abdominal distension in the setting of cirrhosis caused by hepatitis B and alcoholism. There was no obvious source of blood loss. Abdominal ultrasonography revealed a liver mass and fluid in the peritoneum. Although previously suspected, the final diagnosis of HCC with a spontaneous hemoperitoneum was not confirmed until autopsy.

Epidemiology

HCC, a common neoplasm and a common cause of death from cancer, is 3 times more likely to occur in men than in women.[2] There are approximately 1 million deaths resulting from HCC worldwide each year. It currently is unclear whether HCC is preventable by treating underlying hepatitis B or C with interferon.[5]

Spontaneous rupture of HCC with acute hemoperitoneum is more common in Africa, Asia, and parts of Europe than in the United States. In an Italian study, the authors presented a retrospective review of 518 patients with HCC admitted to their institution between 1982 to 1993.[6] Approximately 2% of these patients had spontaneous rupture of their tumors. Other causes of spontaneous hemoperitoneum in hospitalized patients were ruptured ovarian cyst (44%), acute pancreatitis (9%), ruptured abdominal aortic aneurysm (6%), necrosis of the gall bladder (3%), ruptured liver (in cases of eclampsia) (3%), ruptured spleen (3%), necrosis of the uterine tube (3%), cancer of the uterus (3%), ectopic pregnancy (3%), and (more rarely) metastatic disease such as gestational trophoblastic disease.[6]

As previously indicated, the incidence of spontaneous hemoperitoneum in the United States is much smaller than that reported in Africa and Asia. Although the reasons behind this finding are not clear, differences in access to heath care might play a role. In the largest US study of HCC, only 1.6% of patients had

intraperitoneal bleeding caused by hepatic rupture.[4] Additionally, whereas the age-specific incidence of HCC in the United States has shifted to patients age 75 to 79 years,[2] the average age reported for patients with spontaneous hemoperitoneum resulting from HCC in the Italian study was 62 years.[6]

Etiology

HCC is the cause of noncritical blood-tinged ascites in approximately 33% of patients with this finding.[7] It also has been associated with smaller amounts of blood in the abdominal cavity. Intraperitoneal hemorrhage most likely occurs when tumor necrosis leads to rupture of blood vessels. The dissecting blood reaches the liver surface, causes interruption of the hepatic capsule, and results in intraperitoneal bleeding.

Noncritical bloody ascites can be differentiated from acute hemoperitoneum, a potentially fatal intraperitoneal hemorrhage, by evaluating the ascitic fluid. If analysis of the ascitic fluid in a patient with bloody ascites shows an erythrocyte count greater than $1 \times 10^6/mm^3$ and a hematocrit greater than 3%, then acute hemoperitoneum most likely is present.[6]

In contrast to most metastatic diseases, which generally have a poor blood supply, HCC is a very vascular tumor,[8] receiving its blood supply from the hepatic artery.[9] HCC can present as a single mass (massive HCC), as multiple nodules (nodular HCC), or as diffuse liver involvement (diffuse HCC). The microscopic growth pattern is trabecular, solid, tubular, sclerosing, or fibrolamellar. The fibrolamellar variant is associated with young patients without cirrhosis who have alpha-fetoprotein (AFP) levels within normal limits; this variant is often surgically resectable and has a good prognosis.

Clinical, Laboratory, and Radiographic Findings

The most common initial symptoms of intraperitoneal hemorrhage are abdominal pain, acute blood loss, and acute shock.[6] Other signs and symptoms include right upper quadrant pain, hypotension, evidence of peritoneal irritation, and increasing abdominal girth.[7] Abdominal tenderness, abdominal distension, hypotension, and tachycardia are common physical examination findings in patients with spontaneous hemoperitoneum. HCC with spontaneous intraperitoneal hemorrhage should be suspected in any patient with a history of cirrhosis who has anemia and hypotension, even when there is an absence of melena and hematochezia and a nasogastric aspirate shows no blood.

Paraneoplastic manifestations occurred in 12 of 121 patients with HCC in one study.[4] Common paraneoplastic symptoms in these 12 patients included fever (7 patients), hypoglycemia (2 patients), hypercalcemia (2 patients), and erythrocytosis (1 patient). Hypercholesterolemia is another paraneoplastic symptom of HCC.

Serum tumor markers are common in patients with HCC. Chlebowski and colleagues found serum AFP levels to be elevated in 76% of patients with HCC.[4] In 63% of these patients, serum AFP levels were greater than 1000 ng/mL, and in 75%, greater than 25 ng/mL. Hepatitis B surface antigen (HBsAg) levels were elevated in 52% of the patients evaluated, and 63% of patients had elevated levels of carcinoembryonic antigen.[4]

HCC generally presents as an area of low attenuation on computed tomography (CT) scans, which are abnormal in 79% to 81% of patients with this neoplasm.[6,7] In a previously cited study, spontaneous hemoperitoneum could be diagnosed in only 13% of patients on the basis of abdominal CT scans and abdominal ultrasound studies.[6] Ruptured HCC has been detected using gray-scale and Doppler ultrasonography.[10]

Management

Surgical resection with complete removal of the tumor is the only option that can provide long-term survival in cases of HCC.[11] For those undergoing surgical resection, long-term survival is improved if they are HBsAg negative rather than HBsAg positive.[12]

In many patients with such severe underlying liver disease, however, surgery is not an option. For them, the current mainstay of therapy is arterial embolization.[13] This procedure is safe and effective and, if the tumor is discrete, allows for surgical resection once the patient is stabilized. A retrospective study of 12 consecutive emergency hepatic artery embolization procedures performed because of spontaneous hemoperitoneum showed that hemostasis was achieved in all patients,[14] with a mean length of survival of 149 days. An earlier study reported that hepatic artery embolization in 17 patients with spontaneous rupture of their HCC led to hemostasis in all patients, 14 of whom survived the procedure; survival generally ranged from 16 to 386 days, but 1 patient was alive 15 months after undergoing the procedure.[15]

Sunderland and colleagues reported another alternative method of treating patients with ruptured HCC.[16] Nine patients with ruptured HCC underwent laparotomy with injection of alcohol. One patient died when the procedure failed, but 8 patients survived and left the hospital 8 to 21 days postoperatively.[16]

Another option for patients in this situation is supportive care without intervention. However, in a study of 63 patients with ruptured HCC, such conservative

management resulted in an overall mortality rate of 84% versus a mortality rate of 53.8% in patients having surgical intervention.[8]

SUMMARY

Spontaneous hemoperitoneum is an uncommon manifestation of hepatocellular carcinoma in the United States. However, the diagnosis should be considered in patients with a known history of cirrhosis or hepatocellular carcinoma whose symptoms and physical examination findings are consistent with acute blood loss despite no evidence of gastrointestinal bleeding. Although abdominal CT scans can diagnose HCC in 79% to 81% of patients with the neoplasm, only 13% of spontaneous hemorrhages from HCC can be detected. An ultrasound-guided paracentesis can be performed to confirm hemoperitoneum. Intra-arterial selective embolization is an effective treatment strategy, while other options include surgical intervention with resection or alcohol injection. **HP**

REFERENCES

1. Higginson J. The geographic pathology of primary liver cancer. Cancer Res 1963;23:1624–33.
2. El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med 1999;340:745–50.
3. Dunham LJ, Bailar JC 3rd. World maps of cancer mortality rates and frequency ratios. J Natl Cancer Inst 1968;41:155–203.
4. Chlebowski RT, Tong M, Weissman J, et al. Hepatocellular carcinoma. Diagnostic and prognostic features in North American patients. Cancer 1984;53:2701–6.
5. Baffis V, Shrier I, Sherker AH, Szilagyi A. Use of interferon for prevention of hepatocellular carcinoma in cirrhotic patients with hepatitis B or hepatitis C virus infection. Ann Intern Med 1999;131:696–701.
6. Vivarelli M, Cavallari A, Bellusci R, et al. Ruptured hepatocellular carcinoma: an important cause of spontaneous haemoperitoneum in Italy. Eur J Surg 1995;161:881–6.
7. Clarkston W, Inciardi M, Kirkpatrick S, et al. Acute hemoperitoneum from rupture of a hepatocellular carcinoma. J Clin Gastroenterol 1988;10:221–5.
8. Chearanai O, Plengvanit U, Asavanich C, et al. Spontaneous rupture of primary hematoma: report of 63 cases with particular reference to the pathogenesis and rationale treatment by hepatic artery ligation. Cancer 1983; 51:1532–6.
9. Breedis C, Young G. Blood supply of neoplasms in liver. J Pathol 1954;30:969.
10. Ishida H, Konno K, Hamashima Y, et al. Sonographic and color Doppler findings of rupture of liver tumors. Abdom Imaging 1998;23:587–91.
11. Chiappa A, Zbar A, Audisio RA, et al. Emergency liver resection for ruptured hepatocellular carcinoma complicating cirrhosis. Hepatogastroenterology 1999;46: 1145–50.
12. Wu CC, Ho WL, Chen JT, et al. Hepatitis viral status in patients undergoing liver resection for hepatocellular carcinoma. Br J Surg 1999;86:1391–6.
13. Acunas B, Rozanes I. Hepatocellular carcinoma: treatment with transcatheter arterial chemoembolization. Eur J Radiol 1999;32:86–9.
14. Boyer JC, Zins M, Vilgrain V, et al. Hemoperitoneum caused by spontaneous rupture of hepatocellular carcinoma. Value and prognostic factors of hepatic artery embolization [in French]. J Radiol 1995;76:365–9.
15. Hseih JS, Huang CJ, Huang YS, et al. Intraperitoneal hemorrhage due to spontaneous rupture of hepatocellular carcinoma: treatment by hepatic artery embolization. AJR Am J Roentgenol 1987;149:715–7.
16. Sunderland GT, Chisholm EM, Lau WY, et al. Alcohol injection: a treatment for ruptured hepatocellular carcinoma. Surg Oncol 1992 Feb;1:61–3.