Hepatoma Rupture following Drug-Eluting Bead Chemoembolization

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Rupture of hepatocellular carcinoma (HCC) represents a devastating and potentially fatal complication of both the underlying disease and the tumor posttransarterial treatment. Early recognition of the complication and aggressive management is usually mandatory to effectively treat the hemorrhagic sequelae arising from the rupture. A low threshold for suspicion of rupture is mandatory in any patient presenting with significant abdominal pain, particularly if sudden in onset, and/or hemodynamic instability. The following article describes two cases of HCC rupture postchemoembolization (transarterial chemoembolization [TACE]) as well as a brief literature review of this disease process.

Case Presentation

A 79-year-old African American woman was referred by the hepatology service to the interventional radiology (IR) clinic to discuss treatment options for HCC. She had a long-standing history of hepatitis C, and on a screening computed tomographic (CT) examination was diagnosed with HCC. Her history was otherwise noncontributory other than a long-standing history of medically controlled hypertension.

On presentation to the IR clinic, the patient was anxious but otherwise in no apparent distress. She was ECOG 1 due to generalized fatigue, but otherwise had no signs or symptoms related to her liver tumor. Review of her CT demonstrated cirrhotic changes and a segment IV 4.5 cm enhancing nodule with portal venous washout diagnostic for HCC (►Fig. 1). Her portal vein was patent, and there was no evidence for extrahepatic disease. Her laboratory evaluation demonstrated no significant abnormalities, and she was graded to a Child–Pugh class A.¹ She was not a transplant candidate due to her age, and the goal of therapy as explained to the patient was to provide a survival benefit with the proposed IR procedure. Due to the size and subcapsular location of the tumor, oily chemoembolization (cTACE) was decided upon as the most appropriate and timely treatment for the tumor.

Within a few days, the patient underwent cTACE using 50 mg doxorubicin emulsified in 10 mL lipiodol. Embolization was performed following selection of the segment IV hepatic artery (►Fig. 2), and embolization was performed to near stasis. No embolic agent other than lipiodol was used (e.g., no particles or Gelfoam (Pfizer/Pharmacia & Upjohn Co., New York, NY) to follow the oily embolization). The procedure was performed before the general use of cone-beam CT in the authors' angiography suites, but a spot film obtained after the embolization demonstrated what appeared to be a good angiographic result (►Fig. 3). The patient was admitted overnight per institutional protocol, then discharged the next day.

Three days following cTACE, the patient presented to the emergency department with obtundation and hypotension (systolic blood pressure < 90 mm Hg). Before her admission, while at home the patient had described sudden and severe abdominal pain. An emergent CT scan without contrast was performed, which demonstrated new-onset abdominal fluid suggestive of HCC rupture (►Fig. 4). The patient was transferred emergently to the IR suite, where a paracentesis (►Fig. 5) confirmed the presence of hemoperitoneum. Angiography of the hepatic artery failed to demonstrate acute hemorrhage, but given the presumptive diagnosis of ruptured HCC the segment IV hepatic artery was embolized with Gelfoam slurry (►Fig. 6). Due to persistent hemodynamic instability following selective segment IV embolization, the entire hepatic artery distribution was then embolized with Gelfoam slurry. Although the patient stabilized following the embolization procedure, she died several days later from multiorgan failure.

Companion Case

A 67-year-old African American man with a past medical history of hepatitis C virus and alcohol-induced liver cirrhosis as well as HCC presented to the emergency department for evaluation of weakness, fatigue, and abdominal pain for

Fig. 1 Contrast-enhanced (a) axial, (b) sagittal, and (c) coronal CT scans demonstrating the 4.5 cm enhancing hepatocellular carcinoma in segment IV of the liver (arrows).

2 days. The patient was initially diagnosed with HCC 4 years earlier, and while he had previously undergone three TACE sessions, his tumor burden had progressed to multinodular bilobar disease.

At the time of presentation, the patient was tachycardic (heart rate 100–110 beats per minute) but had a normal blood pressure (120–130/70–80 mm Hg). Physical examination was significant for abdominal distension with a fluid wave but no rebound tenderness or other peritoneal signs. Laboratory investigation revealed profound anemia, with a hemoglobin level of 5.2 mg/dL (reduced from prior baseline of 10–11 mg/dL), as well as new onset of liver (bilirubin 6.4 mg/dL, albumin 1.8 g/dL, international normalized ratio [INR] 2.4) and renal (creatinine 3.2 mg/dL) insufficiency; the patient's Child–Pugh score was 12 (class C). A diagnostic paracentesis in the emergency department yielded frankly bloody ascites, and a noncontrast CT scan (→**Fig. 1**) confirmed intraperitoneal hemorrhage. The patient was transfused 4 units of packed red

blood cells, with appropriate increase in hemoglobin level to 9.1 mg/dL. IR was consulted for possible intervention, and given a high suspicion for a hepatic tumoral source of bleeding, arteriography with possible embolotherapy was recommended and pursued.

The patient was brought to the IR suite. After sterile site preparation and administration of intravenous moderate sedation, routine arterial access was gained via the common femoral artery using direct sonographic guidance. The percutaneous access was dilated to a 5-French vascular sheath (Pinnacle; Terumo, Somerset, NJ). Next, celiac arteriography was performed using a 5-French Sos Omni Selective catheter (AngioDynamics; Queensbury, NY), and hepatic arteriography was performed after placement of a coaxial 3-French Renegade Hi-flo microcatheter (Boston Scientific, Natick, MA). The microcatheter was advanced into the segmental distribution of a large subcapsular right hepatic lobe tumor, which showed active hemorrhage as confirmed using digital

Fig. 2 Image from segment IV digital subtracted angiogram demonstrating hypervascular blush corresponding to the hypervascular mass noted on CT scan in →**Fig. 1**.

Fig. 3 Radiograph obtained following completion of the chemoembolization procedure demonstrating lipiodol staining of the mass (open black arrow). Lipiodol staining of the gallbladder wall is incidentally noted (white arrow).

Fig. 4 Representative noncontrast-enhanced CT scan images (a and b) demonstrate lipiodol staining of the previously embolized mass (black arrow). Lipiodol staining of the remainder of the segments IV and III vascular distributions is incidentally noted (white arrows). Also note the significantly increased intraperitoneal fluid collections in the abdomen and pelvis (stars).

subtraction angiography (►Fig. 2). Given the finding, bland particle embolization was performed using 100 to 300 tris-acryl gelatin microspheres (Embosphere; Biosphere Medical, Rockland, MA). Particles were injected as a suspension in iodinated contrast material under direct fluoroscopic observation, and infusion was continued until tumor staining was seen fluoroscopically and no further tumor vascular blush was present on postembolization arteriography (►Fig. 2). Finally, all devices were removed, and hemostasis was achieved using a vascular closure device (Perclose Proglide; Abbott Vascular, Abbott Park, IL).

Following embolization, the patient's hemoglobin remained stable and he required no further transfusions. However, he suffered progressive worsening of both liver and renal function during his hospital inpatient stay, with bilirubin increase to 17.0 mg/dL, INR rise to 3.7, and creatinine elevation to 3.6 mg/dL. Given this gradual multiorgan deterioration, the patient and his family elected to pursue palliative supportive care. The patient was discharged to a hospice facility 13 days after hospital admission, and expired 11 days later (►Figs. 7 and 8).

Fig. 5 Ultrasound image obtained during paracentesis demonstrating significant nonoculated ascites (star).

Discussion

HCC is the fifth most common cancer and third leading cause of cancer mortality worldwide.² Despite potential cures with surgical resection and transplantation, 70 to 80% of patient with HCC present with advanced disease, hepatic impairment, or are nonsurgical candidates.³ TACE has been proven as an effective, first-line treatment for patients with unresectable tumors as well as a bridging therapy until transplantation can be performed.⁴ In addition, TACE improves 1- and 2-year survival rates compared with systemic treatment or best supportive care.⁵

There is no uniformly accepted regimen for TACE, though the basic principle remains consistent; the delivery of tumor-icidal medications locally to hepatic tumors paired with decreased hepatic arterial blood supply.^{1,6} Various chemotherapeutic agents can be delivered in either a viscous oil emulsification or suspended within drug-eluting beads, and the chemotherapeutic agents can be followed by the delivery of various embolic agents to further decrease hepatic arterial supply to tumors.

Despite the lack of uniformity in treatment regimens, TACE remains a safe, first-line treatment choice for HCC. Minor complications rates range from 10 to 12%, which include postembolization syndrome, impaired hepatic function, and leukopenia.⁶ Major complications following TACE occur in approximately 2.6 to 5.3% of cases, and predominately include liver failure, abscess formation, bile duct injury, upper gastrointestinal bleed, acalculous cholecystitis, pulmonary embolism, hepatic arterial spasm, and acute renal failure.¹ Treatment-related mortality after TACE has decreased over the past two decades, likely attributable to newer techniques and advancements in equipment, and now reported treatment-related mortality rates range from 4.1 to 0.5%.^{3,7}

Tumor rupture following TACE represents a rare though potentially fatal complication, as severe bleeding can be difficult to control in cirrhotic patients with the associated coagulopathy.⁸ The incidence ranges from 0.1 to 1.5% with

Fig. 6 Representative angiographic images obtained during second embolization procedure. (a) Image obtained during common hepatic artery angiography demonstrating attenuated appearance of all vessels due to hypotension (arrow—segment IV artery). (b) Segment IV selective angiogram before Gelfoam embolization to stasis. (c) Post-embolization proper hepatic angiogram demonstrating complete stasis of all hepatic arteries.

Fig. 7 Noncontrast CT scan reveals 5.2 subcapsular right hepatic lobe HCC (arrow) in liver segment VI and evidence for intraperitoneal blood, seen as high attenuation layering material (arrowhead) in right paracolic gutter. CT, computed tomography; HCC, hepatocellular carcinoma.

Fig. 8 Selective right hepatic arteriogram (a) demonstrates active extravasation of iodinated contrast material (arrowheads) from large subcapsular tumor (arrows), indicating active bleeding. Postembolization right hepatic arteriogram (b) shows cessation of active hemorrhage and no further vascular supply to embolized tumor (arrowheads).

traditional oily TACE, though one small study experienced a 4% rate of tumor rupture.^{1,3,9} In addition, tumor rupture following TACE with drug-eluting beads has been reported, with a 3.3% rupture rate reported in small study of 30 treated tumors.¹⁰ Despite its rarity, tumor rupture remains the third leading cause of treatment-related death behind liver failure and cancer-related mortality, and death has been reported to occur in one-third to one-half of cases of tumor rupture.^{3,8}

Tumor rupture following TACE should be suspected in patients who present with severe abdominal pain, abdominal distension, bloody paracentesis, shock or hemodynamically instability, or a greater than 2 g/dL drop in hemoglobin. Although tumor rupture may occur in the hours immediately following TACE, it may take several days to weeks to occur.^{1,6,8–11}

The mechanism of tumor rupture following TACE remains unknown, though many explanations have been theorized.⁸ These include increased pressure secondary to edema or ischemia from treatment within a friable tumor, tumoral or capsular necrosis secondary to the chemotherapeutic agents, infection or inflammation related to either tumor or chemotherapeutic agents, vessel trauma secondary to mechanical manipulation, or hepatic venous occlusion with resultant edema.^{8,11} In addition, HCC is a highly vascular tumor and any increased vascular load may cause rupture of hepatic artery branches that are likely diseased due to cirrhosis and/or portal hypertension.⁸ This theory is supported by the presence of intrahepatic aneurysm formation following TACE in 2 to 4% of patients with cirrhosis.³

Once tumor rupture has been identified, treatment options must be weighed appropriately for each patient. Although in some cases, surgical debridement can be lifesaving, many patients undergoing TACE are nonsurgical candidates. Bland embolization can be performed during angiographic evaluation of hepatic rupture, with varying success rates. In addition, conservative management can be pursued in certain clinical scenarios, with several cases of patient survival with supportive/conservative measures alone.⁸

Although no randomized, controlled studies have been performed specifically to identify risk factors for tumor rupture, several observations have been made when analyzing these cases. Most described cases of tumor rupture published in the literature describe tumor location as either subcapsular, superficial, peripheral, exophytic, or protruding from the liver surface. In addition, many reported cases have involved large or infiltrating tumors, with one series reporting a median size of 13.2 cm.⁸ Another risk factor for the occurrence of tumor rupture may be the use of higher doses of lipiodol, with several cases of tumor rupture involving doses from 18 to 30 mL. However, a review of 8,510 Japanese patients treated with TACE had a 0.8% rate of tumor rupture despite stating that most tumors treated with TACE in this study involved tumors less than 5 cm and used doses of lipiodol 10 mL or less.⁷ However, specific sizes and doses of lipiodol for these cases of tumor rupture were not available, and may in fact have been outside the expected tumor size or dose.⁷ Other observations for tumor rupture following TACE included involvement of the right hepatic lobe and male sex,

which was seen in two of two cases and in six of six cases reported by Battula et al and Jia et al, respectively.^{3,8} In addition, rupture after TACE has been reported to occur predominately following the first TACE treatment.⁹

In comparison to HCC rupture following TACE, spontaneous rupture of HCC has been more extensively studied.¹² In western countries, the incidence of spontaneous HCC rupture has been reported at a rate of less than 3%; however, eastern countries report much higher rates of spontaneous HCC rupture; approximately 12 to 14%, with some reports as high as 50%.¹³ A large multivariate analysis from Japan demonstrated that the risk factors for spontaneous rupture include age younger than 60 years, larger tumor diameter, higher Child–Pugh classification, des-gamma-carboxy prothrombin levels, platelet count, and Massive tumors by Eggel classification. In addition, patients with spontaneous rupture of HCC had significantly lower survival compared with non-ruptured HCC patients, with a 6-month survival rate of 54% in cases of ruptured HCC compared with 90% in nonruptured HCC.¹² Treatment strategies for the spontaneous rupture of HCC revolve around hemostasis, and can be achieved with bland embolization or TACE, as well as local ablation or surgical resection. In fact, emergent TACE followed by resection has become the treatment of choice in Japan for spontaneous rupture of HCC.¹²

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