Bland Liver Tumor Embolization Complicated by Hepatic Abscess

Omar H. Elsayed-Ali, BS¹ Andrew J. Lipnik, MD¹ Daniel B. Brown, MD¹

¹Department of Radiology and Radiological Sciences, Vanderbilt University Medical Center, Nashville, Tennessee

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Address for correspondence Daniel B. Brown, MD, Department of Radiology and Radiological Sciences, Vanderbilt University Medical Center, 1161 21st Avenue South, MCN - Room CCC-1118, Nashville, TN 37232-2675 (e-mail: daniel.b.brown@vanderbilt.edu).

Case Report

A 64-year-old man with metastatic pancreatic acinar cell carcinoma featuring BRCA2 mutation was referred to the authors' Interventional Oncology (IO) section to discuss treatment options for an enlarging left hepatic mass. In 2008, he underwent resection of locally advanced disease including Whipple procedure with total pancreatectomy, splenectomy, and partial left colectomy. He was placed on adjuvant therapy starting with FOLFOX until he developed dose-limiting toxicity. He then received gemcitabine as monotherapy followed by the addition of Abraxane until 2011. He developed liver metastases in 2012 and was placed on FOLFIRI prior to right hepatectomy with Roux-en-Y hepaticojejunostomy. In 2013, additional metastatic disease developed in his liver remnant and did not respond to carboplatin/taxol, or irinotecan/panitumumab. At the time of consultation, he was receiving irinotecan and panitumumab infusions and PO temozolomide.

In clinic, he was appearing healthy and fully participating in work and activities of daily living (ECOG 0). His postpancreatectomy diabetes was well controlled. He denied hypertension, shortness of breath, chest pain, or other signs/symptoms. Review of imaging demonstrated a single large hypervascular left hepatic lobe mass measuring 12 cm × 10 cm. There were postsurgical changes from the patient's prior right hepatectomy including pneumobilia. The portal vein was patent (►Fig. 1).

Treatment options including radioembolization and bland embolization were discussed with the patient, as were the potential complications. The consult included a focused discussion on the increased risk of liver abscess in the setting of the patient's bilioenteric anastomosis. Radioembolization was ultimately selected, as the patient preferred the outpatient recovery and lesser potential postembolization syndrome.

Planning mesenteric angiogram with technetium-99m macroaggregated albumin (Tc99m-MAA) was performed. This demonstrated postsurgical changes from prior right

hepatectomy, with otherwise standard arterial anatomy. Both mapping angiography and cone-beam computed tomography (CT) confirmed a hypervascular tumor blush in the left lateral lobe, supplied by the segment 3 hepatic artery (►Fig. 2). The microcatheter tip was positioned in the segment 3 hepatic artery, no arterial supply to extrahepatic structures was identified, and 4 mCi of Tc99m-MAA was administered from this location. SPECT/CT was then performed that demonstrated uptake in the hepatic metastasis. Unfortunately, there was a hepatic to pulmonary shunt fraction of 37.3% (►Fig. 3). Given the large pulmonary shunt fraction, radioembolization was deferred in favor of bland embolization.

The authors' routine prophylactic antibiotic protocol for patients with bilioenteric anastomoses was prescribed, which included 400 mg moxifloxacin (Avelox, Bayer HealthCare, Seattle, WA) for 3 days prior to the procedure, followed by an additional 17 days post-procedure. This prophylaxis is used for all patients with a disrupted sphincter of Oddi undergoing any arterial or ablative procedure for hepatic malignancy.

Two weeks following mapping angiography, the patient returned for a percutaneous biopsy and bland tumor embolization. Immediately prior to bland embolization, a CT-guided biopsy of the hepatic mass was performed to bank tissue for future molecular testing (►Fig. 4). Five 18-gauge core samples were acquired. Bland embolization was then performed under fluoroscopic guidance with moderate sedation. As with the mapping, a microcatheter was advanced into the segment 3 hepatic artery supplying the tumor, and embolization was performed with one vial of 100 to 300 µm microspheres and one vial of 300 to 500 µm microspheres (Embosphere, Merit Medical, South Jordan, UT). Postembolization angiography demonstrated elimination of tumor blush (►Fig. 5). The patient was discharged the following day in good condition with instructions to complete his moxifloxacin course, and plans for a 1-month follow-up CT.

After the embolization, the patient experienced typical symptoms of postembolization syndrome including several

Fig. 1 Axial contrast-enhanced CT image demonstrating a large hypervascular hepatic mass in the left lateral segment (black arrows). Pneumobilia is also present (black circle).

Fig. 2 (a) Digital subtraction angiogram and (b) axial cone-beam CT image obtained during mapping angiography by injecting contrast through a microcatheter positioned in the segment 3 hepatic artery (black arrow). The hypervascular hepatic mass in the left lateral segment is seen (white arrows and black arrowheads).

Fig. 3 Anterior planar image from Tc-99m MAA scan. Intrahepatic lung shunt fraction was calculated to be 37.3%. Note the marked uptake in the lungs (roi3).

days of nausea, vomiting, and low-grade fevers. However, on postprocedure day 9, the patient was admitted to an outside hospital for worsening symptoms and disorientation. The patient was diagnosed with *Escherichia coli*-related sepsis, and was transferred to the authors' institution. Upon admission his white blood cell (WBC) count was more than 50,000,

Fig. 4 Axial noncontrast CT image obtained during percutaneous biopsy of the hepatic mass (white arrows). An 18-gauge core biopsy needle (white arrowheads) was placed coaxially through a 17-gauge guiding needle (black arrowheads) and five core biopsy samples were obtained with CT guidance.

Fig. 5 (a) Digital subtraction angiogram of the segment 3 branch of the left hepatic artery demonstrates a hypervascular tumor blush in the left lateral segment prior to embolization. (b) Digital subtraction angiogram after bland embolization with calibrated microspheres demonstrates no further tumor blush.

and a noncontrast CT showed interval development of gas throughout the tumor, with an associated air–fluid level (► **Fig. 6**). No other fluid collections or other imaging findings to explain his septicemia were identified. CT-guided drainage was performed with placement of an 8F pigtail drain. Culture of the abscess fluid grew *E. coli* (a gram-negative facultative anaerobic rod) and *Veillonella* species (a gram-negative anaerobic cocci), both resistant to ciprofloxacin and levofloxacin. The patient clinically improved after drainage of the abscess and was ultimately discharged with a 14-day course of intravenous piperacillin/tazobactam.

The patient required four additional drain-related procedures including revisions, upsizing, and repositioning, during which communication between the abscess and biliary tree was noted (► **Fig. 7**). Prolonged antibiotics and multiple changes in regimen were required to manage recurrent fevers and bacteremia. Final imaging demonstrated an increasing size of the left lobe tumor, with a small residual central fluid collection (► **Fig. 8**). Ultimately the drain was removed after 4 months, and the patient was referred to hospice shortly thereafter. Repeat drainage was not required and he died several weeks later.

Fig. 6 (a) Axial noncontrast CT image obtained 10 days after bland embolization demonstrates interval development of gas throughout the tumor (white arrows). (b) A more cephalad image from the same study demonstrates an air/fluid level (white arrows).

Fig. 7 Spot radiograph during an exchange of the percutaneous hepatic abscess drain demonstrates a large residual collection communicating with the biliary tree (black arrowheads) which drain into the small bowel across the bilioenteric anastomosis (black arrow).

Fig. 8 Axial contrast-enhanced CT image obtained 4 months after bland embolization demonstrates a large residual enhancing mass (black arrows), with decreased size of intratumoral fluid collection (white arrows) after removal of the percutaneous abscess drain.

Discussion

Hepatic artery embolization (HAE) is a well-established procedure for the palliation of both primary and secondary liver malignancies.¹ Complications of HAE range from transient postembolization syndrome (fever, pain, and nausea) to life threatening (liver failure and death). Hepatic abscess following hepatic artery embolization is a well-described complication. In patients with a competent sphincter of Oddi, the risk of hepatic abscess is less than 1%¹⁻⁴; however, in patients with bilioenteric anastomosis or an incompetent sphincter of Oddi from prior biliary stenting or sphincterotomy, the risk increases dramatically, ranging from 8 to 86%.²⁻⁶

A retrospective study by Kim et al of 157 patients who underwent chemoembolization (TACE) demonstrated an odds ratio of 894 for liver abscess formation in patients with prior bilioenteric anastomosis despite a 5-day course of prophylactic antibiotics (IV cefazolin 1 g and metronidazole 500 mg periprocedurally until discharge, followed by 5 days of oral amoxicillin/clavulanate or 500 mg ciprofloxacin).² In a retrospective study of 971 patients using a similar bland embolization technique to that employed in the patient described here, Mezhir et al reported that 11 of 34 patients (33%) with bilioenteric anastomosis and 2 of 21 patients (10%) with biliary stent or sphincterotomy developed hepatic abscesses after embolization, in comparison to 1 of 916 patients (0.1%) with an intact sphincter of Oddi. Again, these infections occurred despite prophylactic antibiotics (piperacillin/tazobactam or cefotetan IV; followed by 5 days of oral antibiotics).³

The diagnosis of hepatic abscess after HAE can be challenging, as the symptoms overlap with those of postembolization syndrome, as seen in the current patient. Fever, abdominal pain, and nausea are nonspecific, although when attributable to postembolization syndrome typically resolve within a week. Prolonged, severe, or new symptoms beyond this time frame should prompt further evaluation, as

hepatic abscesses usually present at least a week after embolization.^{2,3,7}

Although imaging findings of new gas or fluid in the treated tumor can occur with sterile necrosis, the presence of clinical symptoms, leukocytosis, or bacteremia is suggestive of hepatic abscess formation. Ultimately, fluid sampling is necessary to confirm the diagnosis. Initial treatment is typically a combination of percutaneous drainage and broad-spectrum antibiotics, which can subsequently be tailored to the results of bacterial cultures and sensitivities. The potential for prolonged abscess drainage should not be underestimated, which in this palliative population in the setting of a nonhealing biliary fistula can be required for the remainder of the patient's life. Communication with the biliary tree was identified in our patient but eventually closed spontaneously. Despite aggressive treatment, mortality also remains significant, with up to 12% of patients dying of associated sepsis.⁶

Several regimens have been developed to reduce the risk of postembolization abscess in at-risk patients, including more aggressive antibiotic regimens both with and without bowel preparation. A retrospective study by Geschwind et al⁸ identified 8 at-risk patients undergoing TACE among 258 total patients over a 7-year period. Seven had bilioenteric anastomoses and one had undergone sphincterotomy. Four of these patients received prophylaxis with 1 g IV cephalexin (before December 2000). The other four patients (after December 2000) were prophylaxed with 3.375 g piperacillin/tazobactam every 6 hours for 3 days before surgery. This second group also received a bowel preparation (45 mL oral fleet phospho-soda, 1 g oral neomycin, 1 g oral erythromycin, four tablets of oral bisacodyl, and one rectal suppository of bisacodyl) the day before TACE. All patients prophylaxed with cephalexin developed hepatic abscesses, whereas no patient prophylaxed with piperacillin/tazobactam and bowel preparation developed an abscess.⁸ A retrospective study by Patel et al⁷ evaluated a prolonged periprocedural antibiotic course combined with a bowel preparation in comparison to historical controls. Sixteen TACE procedures were performed in seven patients with prior biliary intervention (four with endoscopic biliary stents, two following Whipple procedures, and one with percutaneous biliary drains). Prophylaxis with 500 mg oral levofloxacin and 500 mg oral metronidazole was initiated 2 days prior to TACE and continued for 2 weeks after discharge. Bowel preparation consisting of 1 g oral neomycin and 1 g oral erythromycin was given at 1, 2, and 11 PM the day before the TACE. This resulted in 2 of 7 patients (28.6%) developing hepatic abscesses after 2 of 16 total procedures (12.5%), compared with their prior experience of 6 of 7 patients (86%) developing hepatic abscesses after 6 of 14 procedures (42%). Although impressive, these findings did not reach statistical significance against the historical controls from the same institution ($p = 0.1$).^{2,7}

Recently, a retrospective review evaluating a prolonged antibiotic course without a bowel preparation demonstrated promising results in a series of 10 patients with compromised sphincter of Oddi (3 patients with prior Whipple, 6 patients with biliary stents, and 1 patient with a biliary stent and

choledochojunostomy) undergoing a total of 25 embolization procedures. Patients received 400 mg Moxifloxacin orally beginning 3 days before HAE and continued for 17 days after the procedure. No patient developed a hepatic abscess during the follow-up period (range: 43–503 days).⁹ This regimen is appealing for the following three reasons. First, moxifloxacin has a high level of biliary excretion with activity against both aerobes and anaerobes. Second, it is orally absorbed, easing outpatient administration. Finally, moxifloxacin appears effective without a bowel preparation, eliminating a source of patient discomfort and the potential electrolyte abnormalities that can result from bowel preparations. It may be notable that both the bacterial strains isolated from the hepatic abscess mentioned earlier were resistant to ciprofloxacin and levofloxacin (moxifloxacin sensitivity is not routinely evaluated at the authors' institution). Whether this implies that moxifloxacin was not adequate prophylaxis for this patient or the strains developed subsequent resistance is uncertain.

At least 90% of patients with a bilioenteric anastomosis have retrograde colonization of their bile ducts with intestinal bacteria, which is reflected in the polymicrobial nature of most hepatic abscesses in this patient population.¹⁰ The peribiliary capillary plexus to the biliary tree is primarily supplied by the hepatic arteries—the same arteries that are targeted during HAE. Thus, treating to the angiographic endpoint of complete embolization will include the vascular supply of the colonized bile ducts. The tumoricidal effect of radioembolization with Y-90 is dependent on radiation-induced effects from β -emission rather than ischemia, and angiographic stasis is rarely encountered during treatment with glass microspheres and in only up to 20% with resin microspheres using sterile water.^{11,12} With this consideration in mind, a recent study by Chola-pranee et al retrospectively evaluated the frequency of hepatic abscess in 16 patients with an incompetent sphincter of Oddi (11 patients with bilioenteric anastomosis and 5 patients with biliary stents) undergoing 24 radioembolization procedures with Y-90 resin microspheres. This was compared with a reference cohort of 13 patients (5 patients with bilioenteric anastomosis and 8 patients with biliary stents) who underwent TACE. Despite the same aggressive antibiotic prophylaxis, no radioembolization patient developed a hepatic abscesses compared with 3 of 13 patients (23%) who underwent TACE.¹³ Another retrospective study of 143 patients evaluated a subset of 9 patients with preexisting bilioenteric anastomosis who underwent radioembolization, none of whom developed a liver abscess.¹⁴

For the patient described here, radioembolization was initially planned; however, a high lung shunt fraction (37.3%) caused a change in the treatment plan to bland embolization to avoid pulmonary toxicity from Y90. While adjunctive techniques such as hepatic vein balloon occlusion catheter placement have been described to reduce lung shunting, these are anecdotal events and, given the very large shunt percentage in our patient, the authors did not feel comfortable trying this type of manipulation.¹⁵

Along with the prior Whipple procedure, this patient had two additional risk factors for infectious complications: prior

splenectomy and diabetes mellitus (a result of his prior total pancreatectomy). The spleen has a well-known immunological role, particularly with respect to encapsulated bacteria; this patient had received the recommended vaccines including pneumococcal polyvalent (Pneumovax 23, Merck, Kenilworth, NJ), meningococcal polysaccharide conjugate (Menactra, Sanofi Pasteur, Swiftwater, PA), and Haemophilus b conjugate (ActHIB, Sanofi Pasteur) following his splenectomy. To the authors' knowledge, no specific data exist regarding associations with hepatic abscess and HAE in patients after splenectomy, although it is conceivably a contributing factor. Patients with poorly controlled diabetes are also considered to be relatively immunocompromised and could be at higher risk for infectious complications after HAE. However, in a recent retrospective study, Woo et al evaluated multiple risk factors for hepatic abscess formation in 25 patients with a bilioenteric anastomosis undergoing 65 TACE procedures, and diabetes was not among the statistically significant risk factors.⁶

The risk of hepatic abscess after HAE in patients with a compromised sphincter of Oddi is clearly significantly elevated, and remains problematic despite the application of various aggressive antibiotic prophylaxis and bowel preparation regimens. Recent data from radioembolization with Y-90 are promising in this patient population, although a randomized study comparing it with TACE is unlikely to occur based on the sample size necessary as calculated by Chola-pranee et al.¹³ Although transarterial therapies have become an accepted part of the treatment algorithm for many hepatic tumors, acquiring data to guide proper patient selection is an ongoing project. Regardless of the method of transarterial treatment selected, and prophylactic antibiotic regimen employed, close clinical follow-up with a high index of suspicion remains necessary in this patient population to minimize the significant risk of this potentially lethal complication.

Disclosure Statement

D. B. is a consultant for Cook Medical, Medtronic, Vascular Solutions, and Onyx Pharmaceutical. O. E. and A. L. have nothing to disclose.

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