Chemoembolization with Drug-Eluting Beads Complicated by Intrahepatic Biloma

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ABSTRACT

Chemoembolization with drug-eluting beads is a type of locoregional therapy currently being used for the treatment of hepatocellular carcinoma and metastatic disease to the liver. This treatment has proven effectiveness in controlling tumor growth, extending survival time, and improving quality of life. Chemoembolization with drug-eluting beads have been shown to be safe, but like any other invasive procedure, can have associated complications. The authors present a case of intrahepatic biloma formation occurring as a result of treatment with drug-eluting beads.

KEYWORDS: Biloma, drug-eluting beads, DEBs, chemoembolization

CASE REPORT

A 70-year-old woman with primary neuroendocrine tumor of the lung and metastatic disease involving the liver presented for discussion of treatment options. She was diagnosed in November of 2009 and had been receiving monthly Sandostatin[®] (Novartis Pharmaceuticals, East Hanover, NJ) injections. The injections had resulted in a decrease in size of her lung nodules, but had not improved the disease in the liver. She complained of fatigue, nausea, and intermittent right upper quadrant abdominal pain radiating to her back and left side. The patient was referred to the interventional oncology service for liver-directed therapy.

Her past medical history was significant for hypercholesterolemia, hypertension, benign breast biopsy, depression, and a multinodular goiter. In addition to Sandostatin[®], significant medications included promethazine and ondansetron as needed for nausea, and hydrocodone APAP as needed for pain. Review of systems was negative for symptoms suggestive of carcinoid syndrome, and physical examination findings were unremarkable. The patient's prior imaging was

reviewed, which demonstrated metastatic disease involving the right and left hepatic lobes (Fig. 1).

The patient was determined to be a good candidate for chemoembolization of the right and left hepatic lobes with drug-eluting beads. The right hepatic lobe treatment was scheduled with the plan to treat the left hepatic lobe ~6 weeks later. Chemoembolization of the right hepatic lobe was performed with a combination of 100–300 and 300–500 micron beads loaded with doxorubicin (DC bead, Biocompatibles UK, Farnham, Surrey, UK). One vial of the 100–300 micron beads was split between the right hepatic artery distal to the cystic artery origin and the middle hepatic artery, followed by about vial of the 300–500 micron beads split between the two as well. The embolization resulted in near complete stasis of flow (Fig. 2). Approximately 43 cc of doxorubicin were administered into right hepatic artery and 29 cc of doxorubicin into the middle hepatic artery.

The patient was seen in clinic 1-month postchemoembolization with drug-eluting beads. She reported persistent mild to moderate right upper quadrant pain, extreme fatigue, and occasional low-grade temperatures

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Figure 1 Contrast-enhanced axial computed tomography images demonstrating numerous hypoenhancing lesions in the right and left hepatic lobes, consistent with metastatic neuroendocrine tumor.

up to 100.3°. Magnetic resonance imaging (MRI) revealed a partial tumor response to treatment in the right hepatic lobe according to WHO, EASL, and RESIST criteria.¹ However, there had been interval development of dilated biliary ducts within the mid and peripheral aspects of the right hepatic lobe with large fluid collections, concerning for intrahepatic bilomas (Fig. 3). Some of the tumors in the left hepatic lobe had progressed in size since the prior examination.

The patient was admitted to the hospital for intravenous antibiotics. The largest collection was sampled percutaneously under computed tomography (CT) guidance (Fig. 4). The presence of bilirubin confirmed the diagnosis of an intrahepatic biloma. Cultures were negative for infection, but the patient was still treated with a 1-month course of Avelox[®] (Bayer, Morristown, NJ).

At follow-up 1 month later, the patient reported increased energy. She continued to have occasional nausea, deep mid-abdominal pain, and intermittent low-grade fevers (never greater than 100°F). She also complained of gas pain and bloating, which she attributed to the long-term antibiotics. On physical exam, she had lost 7 pounds since her last visit. Her temperature was 97.8°F. The abdominal exam was significant for a palpable mass in the right upper quadrant, which corresponded to the largest liver metastasis on imaging. Her abdomen was otherwise soft and nontender. Repeat MRI revealed a decrease in size of the intrahepatic bilomas (Fig. 5). Stable posttreatment changes were noted to the right hepatic lobe metastases with partial necrosis of the large metastatic lesion spanning the right and left hepatic lobes. Some of the other smaller lesions

showed necrosis or partial necrosis. The left hepatic lobe lesions were stable in size. An additional follow up MRI was scheduled for 3 months with the plan to chemoembolize the left hepatic lobe if the intrahepatic bilomas continued to decrease in size.

DISCUSSION

Several locoregional therapies are presently available for the treatment of HCC and metastatic disease to the liver in patients with nonoperative disease. These treatments have proven effectiveness in achieving local tumor control, improving quality of life, and extending overall survival time.²⁻⁴ These therapies include transcatheter intraarterial chemoembolization with or without drug-eluting beads and radioembolization with Yttrium-90. Treatment approaches have symptomatic, palliative, adjuvant, and potentially curative goals. They rely on the dual blood supply of the normal liver (portal vein 75% and hepatic artery 25%) and predominant arterial supply of tumors (hepatic artery 90%).

Chemoembolization with drug-eluting beads represents a new and clinically proven delivery device that can deposit a chemotherapeutic agent in the liver with minimal release into adjacent tissues.⁵ The chemotherapeutic agent, typically doxorubicin (DEBDOX) or irinotecan (DEBIRI[®], Biocompatibles UK), is loaded onto beads to minimize systemic diffusion by embolizing the terminal capillaries,⁶ and thereby minimizing systemic effects. Studies have shown that treatment with drug-eluting beads is generally well tolerated.^{2,7-9} Reported complications of chemoembolization with

Figure 2 (A, B) Nonselective celiac axis angiograms prior to embolization demonstrating hepatic arterial anatomy and diffuse hepatic tumor blush. (C) Selective right hepatic artery angiogram following embolization with drug-eluting beads demonstrating pruning of the arterial vasculature and near-complete stasis of flow.

drug-eluting beads include adverse events involving the gastrointestinal tract and liver, such as liver toxicity (3%), pancreas and gallbladder pathology (6%), gastrointestinal bleeding (2%), abscess and infection (1%), gastrointestinal ulcer (1%), ascites (1%), hospitalization for transjugular intrahepatic portosystemic shunt (TIPS) (1%), and hospitalization for intratumoral bleeding (1%). Other complications of chemoembolization with drug-eluting beads are attributable to side effects of the chemotherapeutic agent and include alopecia (1%), mucositis (3%), marrow suppression (5%), and skin discoloration (2%).¹⁰ Martin et al discovered several risk factors to be associated with adverse events of drug-eluting beads, including lack of pretreatment with hepatic arterial lidocaine, 3 or more treatments, achievement of complete stasis, treatment with > 100 mg DEBIRI in a single treatment, and bilirubin > 2.0 mg/dL with > 50% liver involvement.¹¹

Biloma formation is a well-known complication of several surgical and interventional procedures including biliary surgery, liver transplantation, percutaneous cholangiography, biliary drainage, liver biopsy,^{12–14} chemoembolization, chemoinfusion therapy, radiofrequency

ablation,^{14–26} cholecystectomy,^{14,27,28} endoscopic retrograde cholangiopancreatography (ERCP), percutaneous ethanol injection,¹⁴ and radioembolization.²⁹ A biloma is an encapsulated bile collection outside the biliary tree due to bile leakage.³⁰ It results from a bile duct leak caused by insult to the biliary tree and can be solitary or multiple. Because the biliary tree is supplied primarily by arterial blood alone,³¹ the proposed mechanism of injury to the bile ducts in the setting of chemoembolization or radioembolization is ischemia resulting in bile duct necrosis followed by stricture and subsequent biloma formation. Biloma formation secondary to regional damage to the peribiliary plexus and/or cholestasis may resolve spontaneously. Otherwise, percutaneous drainage should be considered.²⁹

In one of the largest studies to analyze the occurrence of biloma associated with chemoembolization, Sakamoto et al¹⁶ chemoembolized 972 patients with gelatin sponge and anticancer drugs and reported a 3.6% overall incidence of biloma formation (3.3% in patients with HCC and 9.6% in patients with metastatic liver disease). Miyayama et al³² also reported on the complications of chemoembolization for HCC. Following initial

Figure 3 Postcontrast axial T1-weighted (A and B) and T2-weighted fat-saturation (C and D) images demonstrating developing of several fluid collections in the right hepatic lobe, consistent with intrahepatic bilomas.

treatment, they reported main bile duct stricture in 4.0% of patients, with biloma occurring in 22.2% of these. The overall incidence of biloma formation was < 1%. However, in patients requiring more than 1 treatment session, biloma formation occurred in 13.3%. Thus, the overall incidence of biloma formation for the entire patient population was 1.6%. Of the patients that developed bilomas, treatment was required in 43%. Interestingly, all patients who developed bilomas in this study had 1 to 2 tumors near the hepatic hilum fed by arterial branches

supplying the caudate lobe or segment 4. This was also true of the case presented here following chemoembolization with drug eluting beads, as the middle hepatic artery was selectively treated. These branches supply the central bile ducts, and thus embolization can lead to necrosis and subsequent biloma formation.

Regarding radioembolization, Atassi et al²⁹ reported < 1% incidence of biloma formation following this therapy. In this series, all patients were treated with percutaneous drainage. Similar to experiences with chemoembolization, Atassi et al found the incidence of biliary sequelae to be higher in patients with metastatic disease to the liver compared with HCC, and theorized that previous systemic chemotherapy may have increased susceptibility to biliary injury by disrupting the usual hepatic vasculature (and occasionally the biliary vasculature) to some degree.

Because bilomas typically develop in the setting of biliary stricture, clinical indicators include jaundice, right upper quadrant abdominal pain, and elevated liver function tests. If infection of the biloma is present, other signs such as fever and elevated white blood cell count may be present.¹⁴ Diagnosis may be suggested by noninvasive imaging modalities such as ultrasound, CT, MRI, or magnetic resonance cholangiopancreatography (MRCP). However, unless communication between the fluid collection and biliary tree can be established, the imaging appearance of bilomas is nonspecific and indistinguishable from other cystic liver lesions. Other imaging modalities, such as ^{99m}Tc-HIDA cholescintigraphy,

Figure 4 Axial noncontrast computed tomography image demonstrating percutaneous sampling of one of the intrahepatic fluid collections, consistent with a biloma. Cultures were negative for infection.

Figure 5 Postcontrast axial T1-weighted (A and B) and T2-weighted fat-saturation (C and D) images demonstrating an interval decrease in size of the intrahepatic bilomas at 1 month follow-up.

percutaneous cholangiography, or ERCP may be more helpful in making a definitive diagnosis, as they are better suited to demonstrate a connection between the fluid collection and biliary tree. Definitive diagnosis can also be made by detection of bilirubin within the lesion following percutaneous sampling.

Once the diagnosis of a biloma is made, treatment options include conservative management, percutaneous or endoscopic drainage, bile duct stenting, or surgical intervention. Small bilomas measuring only a few centimeters may be monitored, but the majority of bilomas require drainage.³³ Indications for treatment include large or increasing size, presence of biliary stricture or obstruction, presence of symptoms (jaundice, pain, fever, etc.), or elevated white blood cell count or liver function tests. Most bilomas are treated successfully with percutaneous or endoscopic drainage with surgery reserved for refractory or more complicated cases.^{33,34} Drainage allows the bile duct leak to heal spontaneously with subsequent resolution of the biloma. Drain catheters are usually left in place until output ceases,³⁵ indicating the leak has resolved. Follow-up imaging with ultrasound, CT, or MRI can be used to further evaluate for residual biloma. Healing of the bile duct leak can take a variable amount of time depending on the size of the leak, varying from a few days to several weeks.^{36–38} Leaks that do not resolve may require endoscopic or percutaneous bile duct stenting to divert bile flow and provide the opportunity for leakage healing.^{35,39,40} In rare instances, the bile leak persists and surgical repair

may be necessary.³³ With appropriate treatment, the overall prognosis in the setting of biloma formation is excellent.³³

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