Hepatic Radioembolization Complicated by Radiation Cholecystitis

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ABSTRACT

Biliary complications following yttrium-90 (⁹⁰Y) radioembolization are rare, and radiation-induced cholecystitis requiring intervention represents an even smaller proportion of these complications, reportedly occurring in fewer than 1% of patients treated with ⁹⁰Y [1]. However, its implications are serious, as the treatment of radiation cholecystitis may require cholecystectomy in patients otherwise considered poor surgical candidates. While biliary complications such as intrahepatic biliary strictures or bilomas may be unavoidable in the course of treating hepatic malignancies due to local field effects of radiation, radiation cholecystitis results from non-target embolization of radioactive microspheres. Meticulous attention to anatomic detail and catheter position may be adequate in preventing this avoidable complication. Herein we discuss the clinical, radiographic, and pathologic findings, as well as the outcome, of a patient who experienced radiation cholecystitis following ⁹⁰Y radioembolization.

KEYWORDS: Radioembolization, Y90, radiation cholecystitis

CASE REPORT

The patient is a 68-year-old woman who had been diagnosed with stage IIB ER+, PR-, Her-2/neu negative invasive ductal carcinoma 2 years prior, for which she underwent mastectomy and received Adriamycin (doxorubicin), Cytoxan (cyclophosphamide), and Taxol (paclitaxel), in addition to radiation therapy and Arimidex (anastrozole). Approximately 15 months later, she was found to have a liver lesion that was biopsy-proven ER+ adenocarcinoma, consistent with metastatic breast cancer, and Aromasin (exemestane) was added to her treatment regimen. Due to progressive hepatic disease several months later, she was referred to our interventional oncology clinic for locoregional therapy of the liver metastasis.

At the time of presentation to the interventional oncology clinic, she was deemed to be a good candidate

for yttrium-90 glass microsphere radioembolization. At the time of treatment, she had an Eastern Cooperative Oncology Group (ECOG) score of zero. Her liver function tests revealed an albumin of 2.5 mg/dL and a prothrombin time (PT) of 11.1 seconds, corresponding to an international normalized ratio (INR) of 0.9. Her total bilirubin was 0.7 mg/dL.

She received a 100 Gy dose of ⁹⁰Y glass microspheres to both the right and left hepatic lobes via the right and left hepatic arteries, respectively, for bilobar treatment according to the protocol of a study in which she had enrolled. She tolerated the procedure well without immediate complications and was discharged with a 5-day course of oral ciprofloxacin in accordance with our departmental practice guidelines for right lobar treatments in patients who still have a gallbladder.

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Figure 1 Axial contrast-enhanced computed tomography image acquired 3 days following ^{90}Y treatment to both right and left hepatic lobes demonstrating marked gallbladder wall thickening and pericholecystic fluid consistent with acute cholecystitis.

Beginning on the first postprocedural day, however, she noted right upper quadrant pain and developed low-grade fevers. An abdominal CT 4 days later revealed a distended gallbladder with a thickened wall and pericholecystic fluid, consistent with cholecystitis (Fig. 1). At that time, she underwent percutaneous cholecystostomy. Nonetheless, despite adequate decompression of the gallbladder and demonstration of cystic and common duct patency on follow up cholangiography, she had continued right upper quadrant pain and intermittent low-grade fevers. Because of her persistent symptoms, she was referred to the transplant/hepatobiliary surgical service for cholecystectomy.

Approximately 7 weeks after ^{90}Y radioembolization, she underwent laparoscopic cholecystectomy. Intraoperatively, the gallbladder was noted to be extremely thickened and edematous with gross inflammatory reaction. Surgical pathology reported an edematous gallbladder with a denuded wall and prominent vasculature. Histologically, there was mural fibrosis with chronic inflammatory changes. Microspheres were present within the histologic specimens (Fig. 2).

The patient tolerated surgery well and was discharged home on her first postoperative day. She recovered well from surgery and had complete resolution of her right upper quadrant pain and fevers.

DISCUSSION

We present a clinical case with classic findings of radiation cholecystitis. Specifically, the patient presented

Figure 2 High-powered photomicrograph acquired following laparoscopic cholecystectomy in the same patient approximately 7 weeks later demonstrating fibrosis and chronic inflammatory changes, as well as a glass microsphere (arrow).

with persistent fever and right upper quadrant abdominal pain shortly following treatment with ^{90}Y radioembolization. As this patient's symptoms did not improve with conservative therapies, surgery was ultimately required for definitive management.

Complications related specifically to the gallbladder following ^{90}Y radioembolization are rare. The spectrum ranges from biliary dyskinesia to cholecystitis. In the largest published series of 327 patients evaluating biliary sequelae of ^{90}Y radioembolization, Atassi et al report 6 patients with increased gallbladder wall enhancement (1.8%) and 3 patients with asymptomatic gallbladder wall disruption (0.9%), of whom 2 (0.6%) required cholecystectomy.¹

Radiation-induced cholecystitis results from nontarget embolization of radioactive microspheres into the capillary network supplying the gallbladder wall via the cystic artery. The cystic artery most commonly arises from the right hepatic artery (>60%), with the common hepatic, left hepatic, gastroduodenal (GDA), superior mesenteric and superior pancreaticoduodenal arteries representing variant sites of origin in order of decreasing frequency.² Collateral perforators to the gallbladder body also arise from hepatic parenchyma and the GDA.³

Although some might raise concern that radiation from microspheres in adjacent liver tissue may cause cholecystitis, we consider this unlikely given that the mean penetration of the emitted β particles is 2.5 mm, with a maximum penetration of 10 mm.⁴

Careful attention to angiographic anatomy and catheter position relative to the cystic artery, both during mapping procedures and dose delivery, can prevent inadvertent infusion of microspheres into the cystic

artery. In addition, confirmation of adequate forward flow prior to radioembolization may help prevent reflux of microspheres into the cystic artery from a distally placed catheter.

However, radioembolization from a position distal to the cystic artery is occasionally either not possible or not ideal. Optimal tumor targeting with radioembolization relies on flow-dependent distribution of microspheres, requiring that ^{90}Y microspheres be administered from a location with adequate antegrade flow to allow admixture of the ^{90}Y microspheres. Furthermore, an origin of the cystic artery from the more distal right hepatic artery may require increasingly selective catheterization to avoid the cystic artery. Yet this carries with it the risk of becoming too selective and incompletely perfusing targeted tumors, as well as increasing procedure and fluoroscopy time, and splitting lobar ^{90}Y doses into separately delivered segmental doses.⁵

Prophylactic embolization of the cystic artery may be considered, but the possibility and risk of ischemic cholecystitis must be carefully weighed against the possibilities and risks of radiation cholecystitis or suboptimal microsphere distribution. If the cystic artery is large and appears to be the dominant arterial supply to the gallbladder, embolization should be avoided as the risk of ischemic cholecystitis is presumed to be quite high. On the other hand, a diminutive cystic artery implies collateral blood supply to the gallbladder, and the risk of ischemic cholecystitis from cystic artery embolization may be lower.⁵

The diagnosis of radiation-induced cholecystitis relies largely on the clinical profile of the patient, as imaging findings have not shown to correlate with clinical severity or the need for surgical intervention. Indeed, some patients may have worrisome findings at follow-up imaging but remain asymptomatic.¹ The spectrum of radiation-induced gallbladder injury can range from biliary dyskinesia to cholecystitis. Biliary dyskinesia is typically characterized by postprandial right upper quadrant pain, whereas cholecystitis presents with persistent right upper quadrant pain, fever, and nausea/vomiting. Although findings at ultrasound, CT, or MRI do not correlate with severity or the need for intervention, features such as gallbladder wall thickening, enhancement and/or disruption may help confirm the clinical diagnosis.

Histologic findings of radiation-induced cholecystitis range from inflammatory lymphocytic infiltration and fibrosis, representing acute-on-chronic cholecystitis, to extensive, often transmural, necrosis of the gallbladder wall in the setting of acute gangrenous cholecystitis. Intravascular microspheres in the gallbladder wall, often with a surrounding foreign body giant cell/granulomatous response, may be considered the sine qua non for the histopathologic

diagnosis of radioactive-microsphere-induced cholecystitis.^{6,7}

The treatment of radiation-induced cholecystitis initially includes supportive care, including adequate hydration and nutrition, antibiotics, and pain medication. Refractory or persistent right upper quadrant pain and tenderness, or the ongoing need for narcotic pain medication, warrants surgical intervention. As nearly all patients receiving ^{90}Y radioembolization have some degree of underlying hepatic dysfunction, consultation with specialized hepatobiliary or transplant surgeons skilled in the management of such patients should be considered. With regard to the safety of operating on patients recently treated with ^{90}Y microspheres, the half-life of ^{90}Y is ~64 hours, with radiation exposure considered negligible at 2 weeks.⁴ Surgical intervention is not recommended prior to 2 weeks, as conservative therapy should be the initial management.

The prognosis of radiation-induced cholecystitis essentially depends on the clinical severity and the response to supportive care. Based on the published series cited previously, a minority of patients with either clinical or radiographic concern for cholecystitis required surgical intervention. Outcomes for patients requiring cholecystectomy depend on the severity of their underlying disease and their ability to tolerate general anesthesia and surgery. Patients with metastatic disease to the liver may have an increased bleeding risk due to liver-related coagulopathy. Patients with HCC, and therefore commonly cirrhosis, are subject to increased operating times, more bleeding complications and higher overall morbidity compared with patients without cirrhosis.⁸ Although surgical morbidity rates may be higher in the patient population treated with ^{90}Y radioembolization as a result of their underlying liver disease, cholecystectomy in the setting of radiation cholecystitis is considered wholly curative.

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