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Yttrium-90 Complications: Prevention and Management

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Radioembolization has become a more prevalent treatment for both primary and secondary liver of the liver. Radioembolization is a relatively safe procedure with major complications being rare. Understanding how to identify the potential complications and their treatment can help make the procedure even safer and mitigate the risk of severe life threatening complications. In this article, we will review the most common complications, how to identify them, and how manage them.
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Introduction

Radioembolization (RE) is a radiation-based locoregional therapy delivered via resin or glass microspheres currently available for the treatment of hepatocellular carcinoma (HCC) and liver metastases. Depending on patient performance status, liver function, and tumor characteristics, there are multiple curative and palliative treatment options available to patients in the treatment of HCC and liver metastases. RE with 90-yttrium has a growing role in the treatment of patients with early, intermediate, and late stage HCC.[1]

RE is a relatively safe procedure. While a large minority of patients is likely to experience mild adverse effects such as self-limited fatigue or abdominal pain, RE is associated with low major complication rates. The more common complications of RE can be roughly divided into liver parenchymal, nontarget embolization, and vascular categories.

Liver Parenchyma Complications

Given the patient population likely to undergo RE, attributing progressive decline in liver function to RE treatment complication as opposed to progression of underlying liver disease or other treatments such as chemotherapy remains difficult. Still, RE has the potential to negatively impact liver function, and proper patient selection remains essential in maximizing the benefits of RE and limiting its potential complications. Among the liver parenchyma complications, RE may result in post-RE syndrome (PRS), radioembolization-induced liver disease (REILD), and biliary injury.

Post-RE Syndrome

PRS is characterized by fever, fatigue, nausea, vomiting, and anorexia. The incidence of PRS has been described as significantly less than the postembolization syndrome encountered following transarterial chemoembolization, but in some series, the incidence of PRS has been reported in as many as 70% of patients.[2] PRS is a self-limited condition and rarely requires hospitalization although symptomatic management may be necessary in some patients. Many centers prescribe steroid courses and antiemetic regimens to minimize the symptoms of PRS. In our institution, a single dose of steroids is given preprocedure and patients are sent home on antiemetic medication as well as narcotics for potential pain.

Radioembolization-Induced Liver Disease (REILD)

REILD is a syndrome characterized by jaundice, ascites, and elevated bilirubin levels developing typically 1-2 months after RE treatment occurring in as many as 5.4% of patients.[3] The process behind the development of REILD is sinusoidal

Abbreviations: HCC, hepatocellular carcinoma; LSF, lung shunt fraction; MAA, macroaggregated albumin; PPI, proton pump inhibitors; RE, radioembolization; REILD, radioembolization-induced liver disease; TIPS, transjugular intrahepatic portosystemic shunt

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obstruction syndrome involving the obliteration of the hepatic venules.[4]

REILD most often occurs in specific patient populations: those with advanced liver disease at the time of RE treatment and patients treated with chemotherapy who undergo whole liver RE therapy.[3] Patient selection and careful treatment planning can limit the incidence of REILD. Recent recommendations have suggested that patients with bilirubin greater than 2 mg/dL or those with nontumoral ascites should not be considered candidates for RE.[5]

The differential for a patient presenting with jaundice or ascites within 3 months of RE treatment should include REILD, and the work-up for such a patient should include laboratory evaluation and imaging of the liver to evaluate for the possibility of biliary obstruction or portal vein thrombosis. Initial treatment involves diuretic administration. More severe cases might require intravenous administration of defibrotide, steroids, or even transjugular intrahepatic portosystemic shunt placement.

Biliary Complications

In a large study of biliary complications, approximately 10% of patients undergoing RE developed biliary sequelae with just under 2% of patients in the study requiring additional interventions on account of biliary pathology. The most common biliary adverse outcomes included biliary necrosis and biliary stricture formation. The patients who required further interventions required drainage of bilomas and abscesses as well as cholecystectomy for radiation

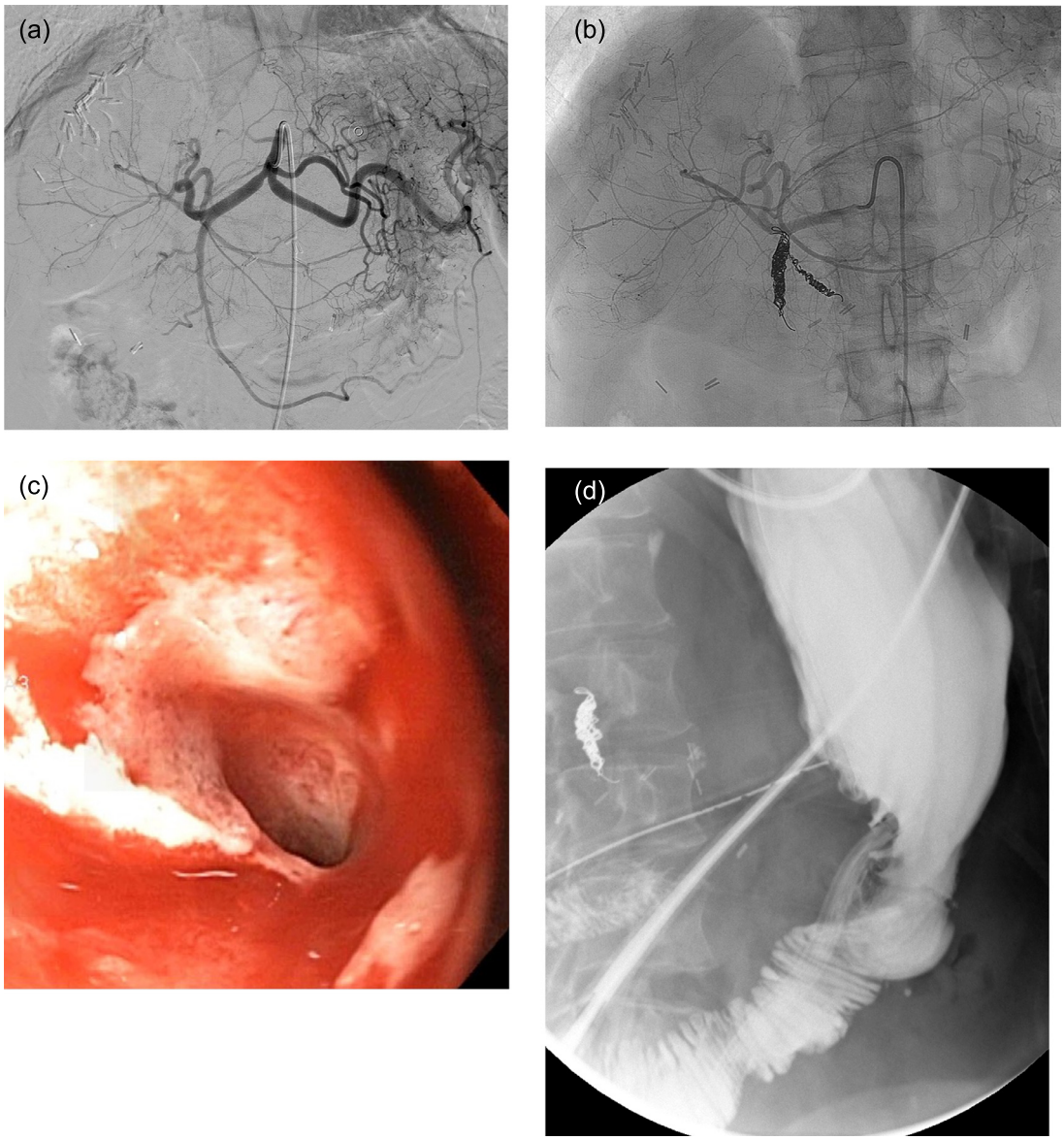

Figure 1 Radiation gastritis. The macroaggregated albumin mapping study celiac axis angiogram (a) demonstrates prominent vessels supplying the stomach and duodenum. The celiac angiogram performed at the time of radioembolization (b) shows packed coils in the right gastric artery and the gastroduodenal artery. The subsequent bremsstrahlung study (not shown) demonstrated mild gastric uptake of yttrium-90 particles. The patient subsequent developed antral gastritis and duodenal ulceration (c) refractory to medical therapies. The patient required a Billroth procedure to treat her duodenal ulcer with postoperative anatomy shown on the postoperative upper gastrointestinal study (d).

cholecystitis. The authors described difficulty in ascribing the incidence of biloma to radiation injury compared with biliary dilatation secondary to tumor compression, and they noted that many patients with biliary dilatation prior to RE demonstrated resolution of such dilatation on post-treatment imaging. Interestingly, biliary necrosis was more common in patients with metastatic liver tumors vs patients with primary HCC with the difference being attributed to peribiliary plexus hypertrophy in the setting of cirrhosis and the chemotherapy history in patients with metastatic liver disease.[6]

If biloma is encountered in the postprocedure course following RE, it can be expectantly managed in an asymptomatic patient as there is potential for it to resolve spontaneously (Fig. 1). Patients with signs of biloma superinfection or those whose biloma is problematic on account of mass effect or obstruction will require percutaneous drainage and antibiotic coverage.

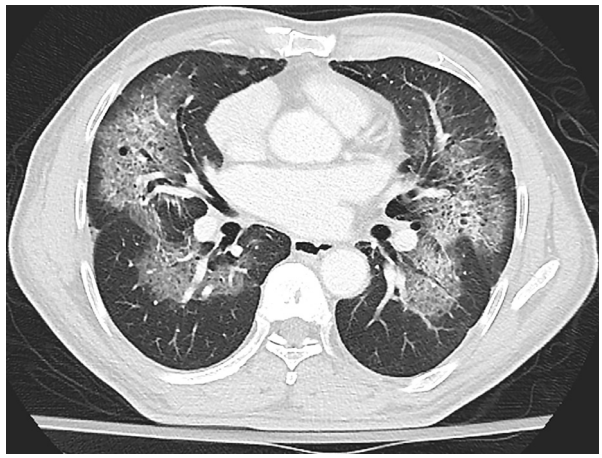

Figure 2 Radiation-induced lung disease. Noncontrast CT in a patient who received y90 2 months prior and developed shortness of breath and decreased exercise tolerance demonstrating classic findings of radiation-induced lung disease: ground glass opacities with peripheral and hilar sparing.

Nontarget Delivery Complications of RE

Nontarget delivery of yttrium-90 is a rare event with very significant potential consequences. Given the nature of the therapeutic beta-emitter, irreversible damage to nontarget tissue can have devastating consequences. Nontarget RE administration may cause injury to uninvolved liver parenchyma, the lungs, the gastrointestinal tract, and the gallbladder.

Radiation-Induced Lung Disease

There are limited reports of radiation-induced lung disease following RE, but the cases described in the literature describe a potentially fatal disease characterized pathologically by acute and subacute interstitial pneumonitis and clinically by gradual onset dyspnea and restrictive lung disease 1-6 months following RE therapy.[7] Administered RE may reach the lung parenchyma on account of arteriovenous shunting that is most commonly seen in the setting of HCC.[8]

Technetium-99m macroaggregated albumin (MAA) provides interventional radiologists a means of minimizing the risk of radiation-induced lung disease. Radiation dose reduction is recommended when the dose to the lungs exceeds 30 Gray during a single administration and 50 Gray lifetime.

For a patient presenting with shortness of breath following RE, it is important to exclude infectious and cardiac causes of dyspnea. Chest computed tomography of a patient with radiation-induced lung disease would reveal confluent ground glass opacities with peripheral and hilar sparring[9] (Fig. 2). Treatment of radiation-induced lung disease does not have broad evidentiary support but typically consists of oxygen supplementation and intravenous steroid administration.

Radiation-Associated Gastrointestinal Ulceration

Similar to radiation-induced lung disease, radiation-induced gastrointestinal ulceration is a rare but consequential complication of RE. The incidence of gastrointestinal (GI) ulceration following RE has been reported in approximately 2% of patients treated with RE.[10] Clinical manifestations of radiation-induced gastrointestinal ulceration include abdominal pain, anorexia, nausea, and vomiting developing 5 weeks after treatment on average.[11] While most patients will recovery completely, the duration of symptoms can last for as long as 1 year, may require surgical intervention, and can be deadly (Fig. 3).[12]

Prevention of radiation-associated gastrointestinal ulceration is largely dependent upon careful review of the patient's vascular anatomy, inspection of the pretreatment MAA study with SPECT correlation, and coil embolization when appropriate; many centers, including ours, also prescribe postprocedure proton pump inhibitors.

Esophagogastroduodenoscopy should be obtained for a patient treated with RE who presents with abdominal pain for several weeks duration. At endoscopy, diffusely friable mucosa as well as discreet ulcers are often found within the stomach and occasionally within the duodenum.[11] Once identified, radiation-induced gastrointestinal ulcers may be addressed with proton pump inhibitors medication and avoidance of medications that might irritate the gastric mucosa, such as nonsteroidal anti-inflammatory drugs. Refractory cases might require bowel rest in the form of total parenteral nutrition or jejunostomy placement or even surgical intervention.

Radiation Cholecystitis

Acute cholecystitis secondary to RE is also rare with a limited number of cases reported in the literature. The mechanisms behind radiation cholecystitis following RE are not completely understood but could include direct mucosal injury secondary to radiation and ischemia related to microsphere embolization. Patients who develop radiation cholecystitis will present within several weeks to months with the signs and symptoms of acute cholecystitis including right

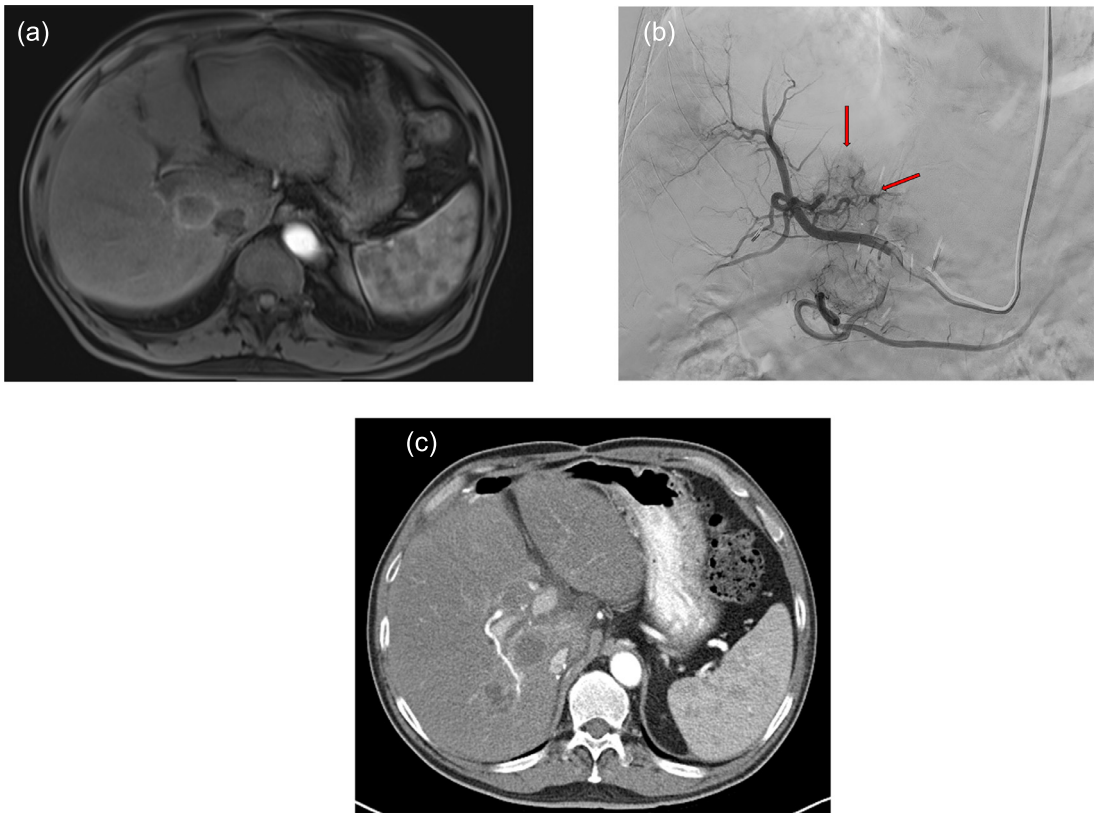

Figure 3 Biloma formation. Contrast-enhanced arterial-phase T1-weighted imaging (a) demonstrates an enhancing mass adjacent to the inferior vena cava in the right hepatic lobe. The patient went on to treatment with radioembolization with the proper hepatic artery angiogram (b) demonstrating tumor blush (red arrows) corresponding to the tumor identified on contrast enhanced MRI. A post-treatment contrast enhanced CT (c) shows no enhancement of the treated tumor with a new hypodense collection seen within the right hepatic lobe. The patient required antibiotic therapy and percutaneous drainage to treat the superinfected bilomas. (Color version of figure is available online.)

upper quadrant abdominal pain, nausea, vomiting, and fever.[13]

A spectrum of preventative steps has been discussed in the literature. Some recommendations—such as positioning of the microcatheter distal to the cystic artery origin when feasible—are noncontroversial and should be followed in all cases. If it is not possible to avoid the cystic artery origin when administering therapy, measures such as temporary embolization with gelfoam or induction of spasm in the cystic artery can be considered.

Upon presentation with signs and symptoms concerning for radiation cholecystitis, relevant laboratory studies and imaging of the abdomen beginning with a right upper quadrant ultrasound and possibly also including a computed tomography scan should be obtained. Given the similar presentation and timeframe to radiation induced gastrointestinal ulceration, esophagogastroduodenoscopy should also be considered. In addition, review of the patient's MAA and RE angiograms and relevant postprocedure nuclear medicine studies should be conducted to determine if there was significant exposure of the gallbladder to administered microspheres. While the diagnosis is being established, patients should generally be started on intravenous hydration and a pain control regimen. Most patients can be managed conservatively with just supportive care (hydration, pain control, and antibiotics). In patients with refractory symptoms cholecystectomy is the definitive therapy although cholecystostomy placement may be considered depending on the patient's comorbid conditions.

Vascular Complications

Performing RE incurs the same risks of arterial access and vascular injury as other intra-arterial therapies. Access site hematomas and pseudoaneurysms as well as arterial dissections have been described in the setting of RE. There is increased concern for vascular injury in patients who are undergoing chemotherapy treatment, especially bevacizumab.[14] In patients on chemotherapy that is high risk for vascular interventions, those drugs should be held for at least 3 weeks prior to any vascular procedure. As in all cases, careful handling of instruments is paramount for patient safety. When vascular injuries are encountered, angioplasty, stenting, and subsequent medical management may be required (Fig. 4). As these complications are not unique to locoregional therapy, they have not been discussed in detail here.

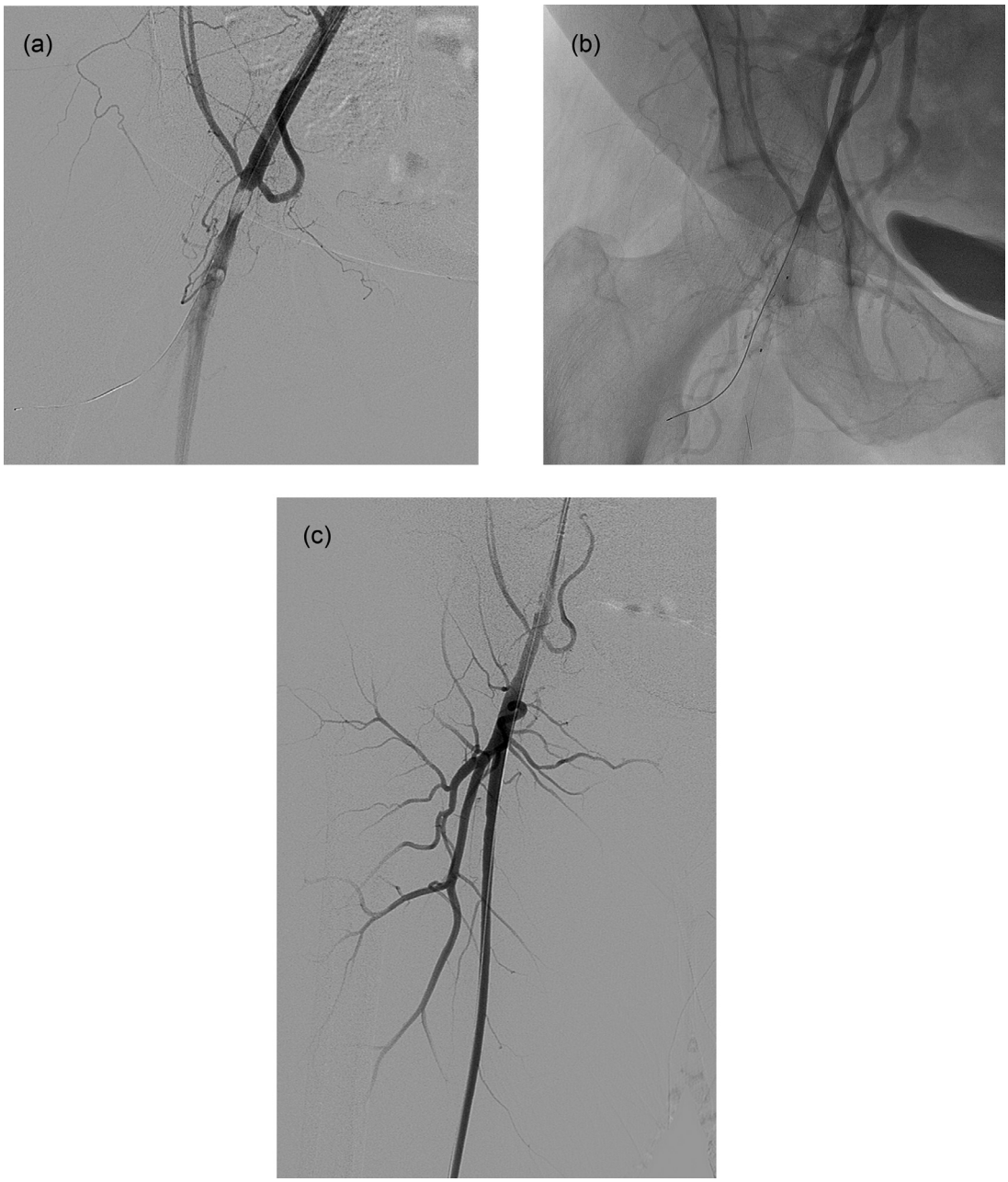

Figure 4 Common femoral artery occlusion. Following macroaggregated albumin mapping performed via right common femoral artery access, the patient developed claudication in the right lower extremity. Subsequent angiogram (a) showed filling defects within the right common femoral artery consistent with the footplate and collagen plug of a malfunctioned closure device. A SpiderFX (Medtronic, Minneapolis, MN) device (b) was deployed distal to the foreign bodies and utilized to sweep them into the sheath. Completion angiogram (c) following retrieval demonstrates a patent right common femoral artery.

Conclusion

RE has become a more common treatment for metastatic disease and HCC. Complications are rare and, in most cases, the best treatment is avoidance with appropriate measures taken before administration of y90 during the mapping procedure. Complications that do occur should be recognized quickly and with appropriate management dire consequences can be avoided.

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