Hepatic Radioembolization Complicated by Gastrointestinal Ulceration

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ABSTRACT

Gastric ulceration is a relatively uncommon but well-described complication of yttrium 90 (Y90) radioembolization therapy in the locoregional treatment of hepatic tumors. Meticulous attention to vascular anatomy, an assessment of antegrade hepatic arterial flow, and knowledge of the dynamic embolic effect of the chosen Y90 particulate at treatment are requirements to reduce the risk of nontarget embolization to gastrointestinal structures. Radiation-associated gastrointestinal ulceration is difficult to treat, and may be associated with gastrointestinal bleeding, bowel obstruction, and perforation. Surgical excision of the involved segment with bypass may be necessary. The increased use of coil embolization of at-risk vessels combined with administration of Y90 particulates with minimal embolic effect has reduced the incidence of radioembolization associated gastrointestinal ulceration.

KEYWORDS: Radioembolization, ulceration, complication

CASE REPORT

An elderly woman with past medical history notable for hypercholesterolemia and hypertension presented to her primary care physician with abdominal pain. Imaging demonstrated hypoattenuating enhancing lesions in segments 2 and 7 (Fig. 1). Percutaneous biopsy of the left hepatic lesion demonstrated adenocarcinoma and the patient underwent left hepatic lobectomy with a wedge excision of the right posterior segment; cholecystectomy was performed at the same time. Surgical pathology was consistent with multifocal cholangiocarcinoma. The patient's immediate postoperative course was uncomplicated. However, 6-month follow-up imaging demonstrated numerous lesions throughout the remaining right lobe suspicious for disease recurrence (Fig. 2). The patient was referred to the interventional radiology service to discuss locoregional treatment options for palliation.

Review of imaging demonstrated patency of the portal vein, surgical changes from left hepatic lobectomy and wedge excision of the right lobe posterior segment, and apparent conventional hepatic arterial anatomy. The patient was considered a candidate for right lobe radioembolization and transarterial chemoembolization. Given that the patient had undergone left hepatic lobectomy and whole-liver therapy was considered, radioembolization was the preferred treatment strategy.

The patient underwent a planning study with technetium 99m macroaggregated albumin (MAA) injection to further define the hepatic arterial anatomy, confirm portal vein patency, and quantify the degree of intrahepatic shunting (Fig. 3). Angiography confirmed conventional hepatic arterial anatomy with patency of the portal vein with surgical changes from left hepatic lobectomy. A microcatheter and glidewire system was used to select the common hepatic artery, demonstrating

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Figure 1 Presenting computed tomography (CT) scan. Arterial phase acquisition from triphasic liver CT scan demonstrating hypervascular lesions in (A) segment VII and (B) segment II. Biopsy of the segment II lesion confirmed adenocarcinoma.

a gastroduodenal artery supplying the right gastroepiploic artery, duodenal, and pancreatic branches. Selective proper hepatic arteriography demonstrated a small caliber vessel arising distally consistent with a right gastric artery, (Fig. 3E). The microcatheter was positioned beyond the origin of the right gastric artery and 4.2 mCi of Tc99m MAA administered. The intrahepatic shunt fraction was calculated at 2.7% and the patient was determined to be a candidate for radioembolization therapy. One week later, the patient underwent Y90 therapy with a 15 Gbq vial of glass microspheres. The patient's immediate postprocedure course was uncomplicated.

One month follow-up imaging demonstrated treatment effect with overall decreased enhancement of the dominant treated lesions (Fig. 4). However, enhancement within both lesions persisted and numerous smaller enhancing foci were now evident, thought to represent treatment of micrometastases. The patient was

scheduled for a second radioembolization treatment to the right lobe. Limited pretreatment mapping was performed for this second therapy session; the previously identified right gastric artery was not clearly identified during pretreatment planning. Proper hepatic arteriography demonstrated good antegrade flow; the first branch at the apex of the proper hepatic artery turn supplied tumor (Fig. 5A). The catheter was positioned just beyond the gastroduodenal artery origin and radioembolization performed using 8.5 Gbq of glass microspheres. Figure 5 highlights differences in microcatheter positioning between the first and second radioembolization treatments. Postradioembolization angiography demonstrated no significant embolic effect.

The patient's second postradioembolization course was complicated by self-limited abdominal pain occurring within 24 hours of treatment. One week later the patient presented with coffee-ground emesis and underwent endoscopy. At endoscopy a large antral prepyloric ulcer was noted with a black eschar as well as a second ulcer in the pyloric channel; no active bleeding was appreciated. Biopsies were not performed secondary to concerns regarding perforation. The patient was started on an intravenous proton pump inhibitor and maintained on a clear liquid diet. A computed tomography (CT) scan was performed to query findings concerning for microperforation. Imaging demonstrated significant wall thickening involving the pyloric channel and first portion of the duodenum without evidence for perforation (Fig. 6 – CT postendoscopy). In the days following, the patient developed nausea followed by intermittent bloody emesis; repeat endoscopy demonstrated progressive narrowing of the pylorus with extension of ulceration to involve the anterior wall of the duodenal bulb. Although a 9 mm scope was successfully passed into the duodenum, the patient was diagnosed with partial gastric outlet obstruction. Placement of a gastrojejun tube was considered; however, the patient was placed on total parenteral nutrition instead due to the suspected high risk of perforation of the pylorus and proximal duodenum.

Figure 2 Radioembolization referral computed tomography scan. Selected axial cuts from an arterial phase acquisition demonstrates surgical changes from left hepatic lobectomy and numerous hypervascular lesions in the residual right liver lobe.

Figure 3 Radioembolization planning study. Angiographic images of the (A) celiac axis, (B) superior mesenteric artery, (C) portal vein, (D) common hepatic artery, and proper hepatic artery (E) early and (F) late phases demonstrating conventional hepatic arterial anatomy and surgical changes from left hepatic lobectomy and cholecystectomy. A small vessel (arrow, E) is noted to arise from the vertical segment of the proper hepatic artery with a visible branch, consistent with gastrointestinal supply likely presenting a right gastric artery. Multiple hepatic tumors enhance on delayed imaging (F).

The gastrointestinal surgery service was consulted regarding options for surgical bypass or jejunostomy tube placement. Partial gastric outlet obstruction persisted at endoscopy performed 3 months later. The patient was

taken to surgery and underwent an antrectomy and proximal duodenectomy, with roux-en-y gastrojejunostomy. Surgical diversion enabled the patient to tolerate a general diet.

Figure 4 Postradioembolization treatment computed tomography (CT) scan. Selected axial cuts from an arterial phase acquisition at CT demonstrates reduced but persistent enhancement in numerous lesions throughout the residual right liver lobe.

Figure 5 Microcatheter positioning during radioembolization. Microcatheter positioning for the first radioembolization treatment (A) was more proximal than that at the second radioembolization treatment (B). Selective angiography of the branch arising at the apex of the vertical portion of the proper hepatic artery confirmed tumor perfusion (C).

Figure 6 Gastrointestinal ulceration at computed tomography (CT). Axial cut from arterial phase CT scan demonstrates antral ulceration (black arrow) and thickening of the pyloric channel (white arrows).

The patient's postdiversion course was complicated by several episodes of biliary sepsis, managed by intravenous antibiotics. Follow-up imaging performed 9 months after the second radioembolization treatment demonstrated progression of locoregional hepatic disease. Following a goals of care discussion, the patient expressed the desire to have a do not resuscitate order; she expired shortly thereafter from biliary sepsis.

DISCUSSION

Case Summary/Published Incidence

Gastrointestinal ulceration following hepatic radioembolization is a known complication related to nontarget embolization. The published incidence varies widely from 0% to 29%.¹⁻⁵ Differences in pretreatment coil embolization techniques, the radioembolic agent, and the radioembolic dose may account for the discrepancy in incidence. The largest study to date in the United States where a total of 200 patients were treated reported an incidence of 12% for gastrointestinal ulceration.⁶

In experienced centers the incidence of symptomatic gastrointestinal ulceration is below 5%.^{2,4,6,7} There are no studies comparing the available microspheres in terms of GI complication rates. In addition, too few studies are available to definitively ascertain the incremental risk of gastrointestinal ulceration by the administered dose.

Mechanism of Complication

The highly variable nature of the arterial supply to the liver with interconnections to the blood supply of the stomach and duodenum poses challenges to the safe arterial delivery of radioactive particles in the treatment of locoregional liver tumors. Nontarget embolization

through any combination of mechanisms is the underlying etiology of gastrointestinal ulceration related to radioembolization therapy. Hence, an important component of the planning study is careful assessment for the origins of the right gastric artery, gastroduodenal artery, left gastric artery, and retroduodenal artery relative to the planned catheter treatment position. It is also critical to assess antegrade arterial flow to judge the likelihood of reflux during radioembolization. Operators also need to anticipate dynamic changes from the embolic effect of the radioembolic spheres, as slowed antegrade flow increases the risk of particle reflux. In addition, prior or concomitant chemotherapy, particularly with vascular endothelial growth factor receptor agents reduces antegrade arterial flow. In the presence of these agents, the vessels are very susceptible to focal dissection and spasm; care should be taken with microcatheter and guidewire manipulation as this affects antegrade flow.

Prior to radioembolization, operators should coil embolize vessels thought to be at risk for causing nontarget embolization. Ideally performed prior to the assessment of hepatic and tumor shunting with macroaggregated albumin, this can also be performed immediately prior to radioembolization without repeating a shunt assessment. Differences between catheter positioning during MAA infusion and radioembolization may inadvertently result in nontarget embolization.

Unlike dyspeptic ulcers, radioembolization ulcers originate on the serosal surface of the viscera. This theoretically reduces the ability of acid reducing medications to facilitate healing. Serosal ulcerations also predisposes to adhesions, increasing the complexity of surgical intervention.

Diagnosis

Clinically, the diagnosis should be suspected when patients experience abdominal pain after radioembolization therapy. Endoscopy is required for definitive diagnosis, as radiation-associated cholecystitis or pancreatitis can also present with abdominal pain.^{8,9} Although the abdominal pain is often short lived, as the injury progresses, gastrointestinal bleeding is commonly reported. Endoscopic findings include erythema, mucosal erosions, and ulceration. Definitive diagnosis can be made by endoscopic biopsy, demonstrating the radioembolic microspheres lodged in capillaries. Biopsy is recommended to verify the etiology of gastrointestinal ulceration; nonsteroidal antiinflammatory medication, *Helicobacter pylori*, and stress ulcers can have a similar appearance at endoscopy. Gastrointestinal ulceration from radioembolization is likely underreported secondary to the multifactorial nature of pain in the treatment population. A low threshold for endoscopic referral is necessary to recognize this complication.

Treatment

Gastrointestinal ulceration caused by radioembolization is challenging to treat. Currently, there is no consensus on the most efficacious treatment strategy; therapy is directed toward the patient's symptoms, based on the extent and location of gastrointestinal tract involvement. As mentioned above, a low threshold for endoscopy is a prerequisite for early therapy. The institution of proton pump inhibitors is a mainstay of treatment along with cessation of nonsteroidal antiinflammatory medications. Recurrent gastrointestinal hemorrhage can be managed by direct endoscopic therapy or selective bland targeted arterial embolization.

Edema may result in partial or complete bowel obstruction, requiring either distal enteric feeding or bowel rest with total parenteral nutrition. These patients in particular are at high risk for bowel perforation. In this subset of patients, surgical bypass and excision of the involved segment is the definitive therapy. Although radiation injury increases the risk of poor wound healing and associated complications at surgical anastomoses, excision of the involved segment with uninvolved tissue at the margins mitigates these potential complications.

The prophylactic treatment of all radioembolization patients with gastric acid suppression is an unproven recommendation to reduce the incidence of gastrointestinal ulceration.⁴

Prognosis

Patient prognosis is intimately related to injury severity. Those patients whose symptoms are primarily pain and bleeding have a good prognosis. Nearly all will recover from the injury. Ultimately, patient prognosis is related to the extent of their oncologic disease.¹⁰

Patients who have partial or complete bowel obstruction and are not considered good surgical candidates have the worst prognosis. These patients are at high risk of bowel perforation and gastrointestinal hemorrhage. Patients may decline the therapy to treat the gastrointestinal ulceration considering their overall prognosis and the invasive nature of the recommended treatment. Fortunately, severe injury requiring surgical management is uncommon, accounting for 6% reported patients with gastrointestinal ulceration.⁴

CONCLUSION

Gastrointestinal ulceration is a well-recognized yet uncommon complication of hepatic radioembolization therapy. A low threshold for suspecting gastrointestinal ulceration is a requisite for early diagnosis in this patient population. Although conservative management may be successful, surgical intervention may be necessary when unresponsive to medical therapy.

REFERENCES

1. Blanchard RJ, Morrow IM, Sutherland JB. Treatment of liver tumors with yttrium-90 microspheres alone. *Can Assoc Radiol J* 1989;40(4):206–210
2. Carretero C, Munoz-Navas M, Betes M, et al. Gastro-duodenal injury after radioembolization of hepatic tumors. *Am J Gastroenterol* 2007;102(6):1216–1220
3. South CD, Meyer MM, Meis G, et al. Yttrium-90 microsphere induced gastrointestinal tract ulceration. *World J Surg Oncol* 2008;6:93
4. Murthy R, Brown DB, Salem R, et al. Gastrointestinal complications associated with hepatic arterial Yttrium-90 microsphere therapy. *J Vasc Interv Radiol* 2007;18(4):553–561, quiz 562
5. Riaz A, Lewandowski RJ, Kulik LM, et al. Complications following radioembolization with yttrium-90 microspheres: a comprehensive literature review. *J Vasc Interv Radiol* 2009;20(9):1121–1130, quiz 1131
6. Kennedy AS, Coldwell D, Nutting C, et al. Resin 90Y-microsphere brachytherapy for unresectable colorectal liver metastases: modern USA experience. *Int J Radiat Oncol Biol Phys* 2006;65(2):412–425
7. Szyszko T, Al-Nahhas A, Tait P, et al. Management and prevention of adverse effects related to treatment of liver tumours with 90Y microspheres. *Nucl Med Commun* 2007;28(1):21–24
8. Salem R, Thurston KG. Radioembolization with 90yttrium microspheres: a state-of-the-art brachytherapy treatment for primary and secondary liver malignancies. Part 2: special topics. *J Vasc Interv Radiol* 2006;17(9):1425–1439
9. Carr BI. Hepatic arterial 90Yttrium glass microspheres (Therasphere) for unresectable hepatocellular carcinoma: interim safety and survival data on 65 patients. *Liver Transpl* 2004;10(2, Suppl 1):S107–S110
10. Steel J, Baum A, Carr B. Quality of life in patients diagnosed with primary hepatocellular carcinoma: hepatic arterial infusion of Cisplatin versus 90-Yttrium microspheres (Therasphere). *Psychooncology* 2004;13(2):73–79