Hepatic Radioembolization Complicated by Fulminant Hepatic Failure

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ABSTRACT

A 68-year-old man with a history of metastatic colorectal carcinoma underwent left hepatic lobectomy and right hepatic wedge resection as initial treatment of his metastatic disease. He subsequently underwent right lobar radioembolization for treatment of a segment 8 lesion. At 6 weeks postembolization, he developed hepatic dysfunction which rapidly progressed to fulminant liver failure. A liver biopsy revealed hepatic venous obstruction and fibrosis. The patient died 14 weeks after radioembolization.

KEYWORDS: Hepatic failure, liver failure, fibrosis, radiation induced liver disease, transarterial embolization, radioembolization, yttrium-90, metastatic disease, colorectal carcinoma

CASE REPORT

A 68-year-old man with no significant past medical history was diagnosed with colorectal carcinoma, American Joint Committee on Cancer (AJCC) TMN stage I. He underwent right hemicolectomy with no adjuvant therapy. His initial postoperative course was unremarkable.

On surveillance abdominal computed tomographic (CT) imaging 15 months after his initial surgery, he was noted to have multiple metastatic lesions to his left hepatic lobe. He underwent left hepatic lobectomy as well as adjuvant chemotherapy consisting of five cycles of folinic acid, fluorouracil, oxaliplatin (FOLFOX) and bevacizumab. Sixteen months later, an additional right hepatic lobe lesion adjacent to the gallbladder was identified on surveillance CT imaging. He subsequently underwent right hepatic wedge resection and cholecystectomy one month later. At this time, no further chemotherapy was given. Shortly thereafter, the patient's disease progressed and multiple metastatic lesions, in-

cluding a 2.7 cm lesion in segment 8, were noted on CT imaging (Fig. 1).

The patient was referred to the interventional oncology service for evaluation and possible treatment. Radiofrequency (RF) ablation, radioembolization, and chemoembolization were all considered. Given the segment 8 lesion's proximity to the diaphragm, lung base, and heart, radiofrequency ablation was felt to be high risk. Laparoscopic treatment was essentially precluded by the patient's history of multiple prior abdominal surgeries. Radioembolization was elected given its efficacy and favorable toxicity profile.

The patient underwent initial abdominal visceral arteriography to assess for anatomic variants of the visceral blood supply as well for administration of technetium 99m-labeled macroaggregate albumin (99m Tc-MAA) for shunt calculation. Arteriography demonstrated a right gastric artery that arose from the mid portion of a very short segment of proper hepatic artery. Additionally, the gastroduodenal artery was noted to be

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Complications in Interventional Oncology; Guest Editor, Robert

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Semin Intervent Radiol 2011;28:246-251. Copyright © 2011 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel: +1(212) 584-4662.

DOI: <http://dx.doi.org/10.1055/s-0031-1280674>.

ISSN 0739-9529.

Right Hepatic Segment VIII Met- Pre Y90

Figure 1 Right hepatic lesion, pre-yttrium-90: (A) Coronal and (B) axial computed tomography (CT) scans in the arterial phase demonstrate a 2.7 cm, subdiaphragmatic lesion. Note the proximity to the left heart and pleural surface. (C) Axial fludeoxyglucose positron emission tomography (FDG-PET) scan demonstrating increased uptake in this lesion consistent with metastasis.

very close to the origin of the right hepatic artery. These were both coil embolized to prevent reflux of particles and non-targeted embolization. Selective right hepatic arteriography demonstrated mild focal hypervascularity in segment 8, compatible with the patient's known metastatic lesion. No other focal hypervascular lesions were identified.

Radioembolization of the right hepatic artery with 10 GBq of yttrium-90 (y-90) glass microspheres was estimated to deliver between 114 Gy and 146 Gy to the treatment volume. The shunt fraction from the liver to the lungs was calculated at 2.3%, resulting in a maximum radiation dose to the lungs of 3.2 Gy. The patient subsequently underwent uneventful Y-90 radioembolization 3 weeks after his initial planning arteriography.

In the immediate postradioembolization phase, the patient experienced fairly substantial nausea, very mild weight loss, and occasional vomiting as well as some fatigue, grade 2 based on the common toxicity criteria (CTC version 4.0). His symptoms improved during the course of the initial 6 weeks postradioembo-

lization. Otherwise, he had no major complications. His initial postembolization CT revealed essentially stable disease in the liver. His carcinoembryonic antigen (CEA) was 43.8 ng/mL prior to embolization and 44.1 ng/mL at his 6-week follow-up. His initial liver function tests (LFTs) were normal, with a bilirubin of 0.9 mg/dL and alkaline phosphatase of 54 u/L.

The patient continued to have mild fatigue and occasional nausea, grade 1 based on CTC version 4.0. Six weeks after radioembolization, he was noted to have worsening LFTs with a bilirubin of 18 mg/dL and alkaline phosphatase of 263 u/L. He had also developed melena in the interim but continued to be hemodynamically stable. A magnetic resonance imaging scan (MRI) of the abdomen at 10 weeks postembolization demonstrated diffuse, heterogeneous enhancement of the liver parenchyma with areas of hypoenhancement in the right hepatic lobe and compensatory hypertrophy of the caudate lobe (Fig. 2). These findings have been reported in and are generally typical of radiation induced liver disease.¹

MR Liver Post-Y90- RIH

Figure 2 Liver magnetic resonance images (MRIs) 10 weeks after yttrium-90 (Y-90): (A,B) Coronal and (C) axial contrast-enhanced MRI demonstrating diffuse, heterogeneous enhancement of the liver parenchyma with areas of hypoenhancement. There is compensatory hypertrophy of the caudate lobe. Note patency of the portal and hepatic veins. There is also necrosis of the Y-90 treated segment 8 lesions. Peripheral enhancement of the lesions probably represents residual tumor.

Figure 3 Liver Doppler ultrasound, 11 weeks after yttrium-90: (A) Transverse image through the liver hilum demonstrates patent portal vein with markedly slowed velocities measuring ~ 0.06 m/s. (B) Transverse image through the right hepatic vein shows patency. The main hepatic vein was also patent (not shown).

Figure 4 Core liver biopsy, transjugular: Demonstrates centrilobular necrosis, hepatic parenchymal atrophy, and venous congestion. These findings are consistent with radiation induced liver disease.

His overall clinical picture, laboratory values, and imaging were consistent with rapidly progressive liver dysfunction. The hepatic dysfunction was almost certainly due to his radioembolization, especially given the time course of the above findings. Subsequent, transjugular core liver biopsy revealed centrilobular necrosis, hepatic parenchymal atrophy, and venous congestion (Fig. 3). These findings are consistent with radiation-induced liver disease (RILD) and are along the spectrum of findings seen in hepatic venous outflow obstruction diseases (e.g., Budd-Chiari).² The biopsy findings were concordant with subsequent liver Doppler ultrasound (US), which revealed a patent portal vein with markedly slowed velocities (Fig. 4). As such, consideration was given to transjugular intrahepatic portosystemic shunt (TIPS) placement. Ultimately, conservative treatment was elected. The patient was started on subcutaneous enoxaparin injections and discharged home in stable condition.

The patient's liver failure continued to progress with his serum bilirubin rising to a peak of 44 mg/dL. His alkaline phosphatase remained elevated, measuring 250 u/L. The patient was no longer a candidate for any further treatment given progression of his liver failure. He eventually died of liver failure 14 weeks after radioembolization.

DISCUSSION

Colorectal carcinoma (CRC) is the third most common cancer in both incidence and mortality.³ Hepatic metastases constitute a significant clinical problem and are estimated to occur in up to 50% of patients with CRC.⁴

In the majority of cases, the liver is the initial or only site of metastatic disease. The 5-year prognosis in patients with untreated hepatic metastatic disease continues to be poor, around 1%.⁵ Fortunately, over the past 20 years, a host of new therapeutic options have been developed to extend the median survival time for a subset of these patients by 1–2 years.⁴ Furthermore, ~10–25% of patients with liver disease will have lesions that are amenable to a combination of local resection and systemic therapy. However, the majority of these patients will still go on to develop progressive, chemorefractory disease.^{4,6} These patients continue to represent a therapeutic dilemma, as a multitude of treatment options are available. No standard of care, however, has been established for this particular subset of patients.

Our patient fit into this typical pattern of treatment: colectomy after diagnosis of CRC, isolated, solitary metastatic disease to the liver treated with surgery and chemotherapy, and subsequent metastases to the liver treated again with surgery. After his disease continued to progress despite therapy, he was referred to the interventional oncology service for liver directed therapy. As briefly discussed above, his overall treatment options for his segment 8 lesion at the time he presented to our service were laparoscopic resection, RF ablation, and embolization, either chemo- or radioembolic. Transarterial embolization, in this case radioembolization with Y-90, was chosen given his prior abdominal surgeries and the proximity of the lesion to the diaphragm and heart.

Radioembolization has been shown to produce significant control of tumor growth, including in metastatic tumors from colorectal cancer.⁷ In a series by Sato et al involving 137 patients, radioembolization for hepatic metastases was found to be clinically well tolerated. The most common toxicity in their series was postembolization syndrome, which includes fever, nausea, and nonspecific malaise. Major complications in their series were rare and only included radiation cholecystitis and gastric ulceration.⁶

Potential major clinical complications of radioembolization can be categorized as extra- and intrahepatic. The extrahepatic risks are usually related to nontarget embolization or shunts and include gastrointestinal, pancreatic, and pulmonary complications. These are rare and can often be avoided by meticulous technique and preembolization imaging with radiolabeled MAA, as in the case of our patient.^{8,9} Intrahepatic complications are also very rare and include RILD, radiation-induced cholecystitis, and bile duct complications.

RILD was first described in the 1960s in patients undergoing external beam radiation to the entire liver and initially referred to as radiation-induced hepatitis (RIH). The term RILD is favored over RIH, as RIH implies inflammation rather than

the underlying sinusoidal congestion, eventual venous occlusion, and fibrosis that serve as the pathologic manifestation of RILD. RILD typically occurs 4–8 weeks after initial treatment. The most common clinical manifestations include nausea, vomiting, abdominal pain, jaundice, and ascites. Many laboratory abnormalities have been reported, the most specific being elevated alkaline phosphatase, one of several elevated LFT parameters our patient had.¹⁰ The response to injury is variable with some patients dying in the acute phase while the majority survive with chronic liver failure.¹¹ As discussed above, our patient initially had mild clinical side effects without any evidence of major clinical complication. However, 6 weeks after Y-90 therapy, he developed hepatic failure which presented as ascites, jaundice, and elevated alkaline phosphatase and serum bilirubin. His hepatic failure rapidly progressed and became fulminant, ultimately leading to his death.

Most studies on RILD have been in the setting of external beam radiation for abdominopelvic malignancies. Little data have been published on the true incidence of RILD from liver-directed therapy with radioembolization with Y-90. Sangro et al studied liver disease induced by radioembolization of liver tumors in 45 patients who underwent the treatment for primary or secondary liver tumors. The patients in this study population had hepatic malignancy without chronic liver disease, could not be treated with other modalities, and had already received the standard of care for their given cancer. Additionally, their study population patients had good functional status. Three patients (6.7%) developed findings consistent with RILD. All 3 of these patients had received prior chemotherapy while none of the patients who had not been given chemotherapy prior to radioembolization developed RILD.¹¹

In a retrospective study by Kennedy et al with a study population of 515 patients using resin microspheres, 28 (4%) patients developed RILD. They analyzed a multitude of factors to determine if any were predictive for RILD. They concluded that 10 factors, none of which included serum laboratory values, had a significant association in predicting RILD postembolization. Of the 10 significant factors, the most clinically relevant appear to be treatment of the right lobe, right lobe volume, and activity delivered to the patient (GBq), and number of prior liver treatments.¹²

Goin et al, in a study analyzing liver toxicities in 88 with hepatocellular carcinoma patients treated with glass microspheres, reported a relationship of tumor volume, pretreatment serum bilirubin level, and delivered dose of radiation with the risk of RILD. Specifically, they reported a trend toward significance of elevated total serum bilirubin with RILD. Doses of greater than 150 Gy and tumor volume of greater than

70% of the right lobe also trended toward with significance in their association with RILD.^{13,14}

As briefly alluded to earlier, the proposed mechanism of injury in RILD is thought to be related sinusoidal congestion, parenchymal atrophy, and subintimal fibrous thickening of the central veins in the early phase and dense fibrous occlusion of the veins in the late phase.⁸ The incidence is increased in patients who have received systemic chemotherapy, as was this case in our patient who received FOLFOX. FOLFOX has hepatic toxicities that are theorized to be secondary sinusoidal endothelial damage and fibrosis, effects which were compounded by prior chemotherapy and hepatectomies.¹⁵ Although our patient's total serum bilirubin was normal prior to radioembolization, the combination of prior chemotherapy with liver toxic medication, left hepatectomy, partial right hepatectomy, and significant tumor burden in the remainder of his liver all served to significantly decrease the patient's hepatic reserve. These factors served to significantly increase his risk of RILD.

In summary, a variety of treatment options is available for liver-directed therapy in patients, including those with metastatic disease from colorectal carcinoma. Radioembolization is an established treatment for chemorefractory metastatic CRC to the liver with increased median survival and mild adverse events.^{6,9} A careful history, with particular attention to prior liver surgeries, prior chemotherapeutic regimens, and history of chronic liver disease should be elicited to avoid major complications. Particular attention should be given to patients who have received prior chemotherapy, especially platinum-based agents such as FOLFOX, as they may have decreased hepatic reserve, even in the presence of normal LFTs. Preoperative imaging to assess for tumoral and nontumoral liver volume should also be obtained, as should liver function tests to establish if there is ongoing liver dysfunction. Although no definitive predictive model for RILD has been established, the above-mentioned parameters appear to help stratify a patient's risk for developing RILD. In this manner, patients can be selected with the goal of maximizing therapy and minimizing potential major complications, including RILD.

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