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CASE REPORT | LIVER

Lung Metastasis Postradioembolization of Hepatocellular Carcinoma With Tumor in Vein

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ABSTRACT

Transarterial radioembolization (TARE) is one of the few treatment options available for infiltrative hepatocellular carcinoma with tumor in vein. This is backed by the published data showing marginally favorable toxicity profile compared with other locoregional and systemic therapies. Although lung shunt fraction studies are performed to prevent radiation injury to the lungs, TARE-induced embolization/metastasis to the lungs has not been reported before. We report an intriguing case of new lung metastases within 1 month after TARE for infiltrative hepatocellular carcinoma with a tumor in the vein, with only a slightly elevated but acceptable lung shunt fraction. This report brings to light the possibility of such a complication and argues for improved preprocedural assessment of a tumor in vein burden and embolization potential.

INTRODUCTION

Infiltrative hepatocellular carcinoma (IHCC) is a subtype of advanced HCC that carries a very poor prognosis, especially when associated with tumor in vein (TIV). In these patients, treatment options are limited.[1] Locoregional therapies such as transarterial radioembolization (TARE) with or without chemotherapy are performed in the liver-limited disease to downstage. TARE delivers hepatic-selective brachytherapy, relying on the preferential arterial perfusion of the tumor. TARE has been shown to offer some survival benefit but more importantly a milder toxicity profile compared with other therapies for IHCC-TIV.[2,3] We present an intriguing case of new lung metastases within 1 month after radioembolization of an IHCC-TIV.

CASE REPORT

A 56-year-old man with hepatitis C-related cirrhosis presented with new right upper abdominal pain. Other comorbidities included hypertension, coronary artery disease status post bypass grafting, and epilepsy. He denied gastroenterology follow-up after the diagnosis of cirrhosis 5 years ago. History of present illness revealed unintentional weight loss of 50 pounds and dark colored urine worsening over the past year. Mild icterus and right upper quadrant tenderness were elicited on physical examination. Laboratory workup revealed an hemoglobin of 13.5 g/dL, platelets of 205 k/uL, creatinine of 0.6 mg/dL, aspartate aminotransferase of 198 U/L, alanine aminotransferase of 41 U/L, alkaline phosphatase level of 119 IU/L, international normalized ratio of 1.2, serum sodium of 127 mmol/L, bilirubin of 2.1 mg/dL, and alpha-feto-protein (AFP) level of 354,260 ng/mL. Specific disease scores were calculated to be Child-Pugh Class B and Model for End-Stage Liver Disease—Sodium of 21. Imaging showed an infiltrative necrotic 12 × 10-cm mass within posterior segments of the right liver (VI and VIII) along with the thrombosis of the right posterior portal vein, reported as Liver Imaging Reporting and Data System—TIV (Figure 1). A complete diagnosis of unresectable Stage IV-B (T3bN1M0) hepatocellular carcinoma was made after tumor board review. Interventional radiology was consulted for TARE. Review of pre-procedural imaging revealed unremarkable arterial anatomy. Three weeks later, the patient underwent arterial mapping with Technetium-99m macroaggregated albumin (Tc-99m MAA; 4.15 mCi) via standard right femoral artery access and right hepatic superselection. Postmapping liver imaging with single-photon emission computed tomography (SPECT-CT) revealed the expected tracer distribution and an acceptable but borderline high-lung shunt fraction (LSF) of 11% (Figure 2). After another 5-week interval, 133.5mCi dose of Y-90 TheraSphere (MDS Nordion, Ottawa, ON, Canada) was administered to targeted segments.

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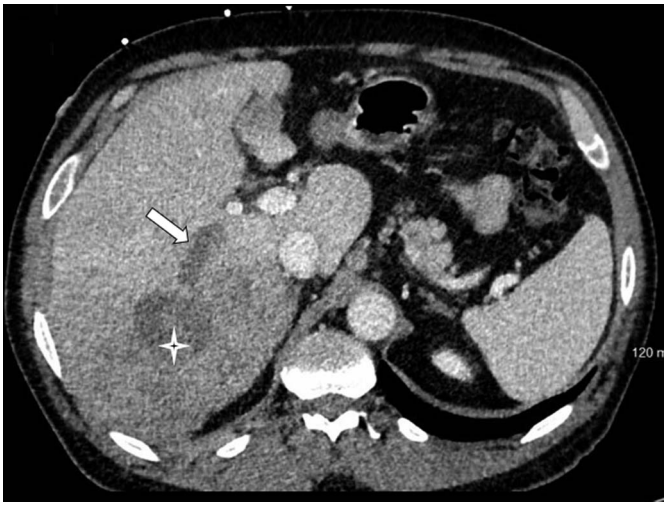

Figure 1. Axial contrast-enhanced computed tomography images before transarterial radioembolization showing a necrotic mass (white star) and tumor in the vein within the right posterior portal vein branch (white arrow).

Tracer localization was limited to tumor-containing hepatic segments on postprocedure bremsstrahlung SPECT-CT. Unfortunately, the patient presented back to the emergency department 3 weeks post-TARE with severe abdominal pain. Abdominal, thoracic, and pelvic contrast-enhanced CT demonstrated necrosis within the index tumor (Figure 3) but with new findings of multiple lung metastases which were not present on the thoracic CT performed 53 days before Y-90 embolization (Figure 4). Laboratory test results revealed only a modest drop in AFP. Prominent arterioportal shunting was evident on a retrospective review of intraprocedural images (Figure 5). The patient did not tolerate sorafenib therapy and ultimately opted for home hospice.

DISCUSSION

We present a case of metastatic disease to the lungs within one month after radioembolization of an infiltrative HCC with branch portal vein thrombus. A significant limitation to this report is the possibility of metastatic progression in the near 2-month gap period between preoperative imaging and embolization, especially considering the aggressive tumor profile. However, it would be irrational to dismiss the alternative possibility of iatrogenic metastatic facilitation.

Embolization with beta-emitter Y-90 is indicated in unresectable HCC when (i) HCC is liver limited, (ii) expected survival of at least 12 weeks with the Eastern Cooperative Oncology Group (ECOG) performance status of < 2, and (iii) acceptable hepatic functional status (lack of ascites, total bilirubin <2 mg/dL, and albumin >3 mg/dL).[4] Absolute contraindications to the procedure include a LSF $>$ 20% or a predicted single session lung dose estimation of $>$ 30 Gy on postmapping SPECT.[4] Complications include procedure-related vascular injury, postembolization syndrome, and most importantly complications arising from nontarget embolization.

Radiation pneumonitis can be a serious complication with hepatopulmonary shunting being quite common in patients with cirrhosis. In fact, patients who develop HCC and especially those with IHCC-TIV are more strongly associated with such shunting.[5] This very disease attribute makes it mandatory to perform preprocedure mapping to estimate LSF. In addition to being a good predictor for complications such as radiation pneumonitis, LSF has also been shown to be an independent predictor of metastatic risk in HCC, with 2 times higher LSFs in those with extrahepatic metastases.[6] LSF is currently

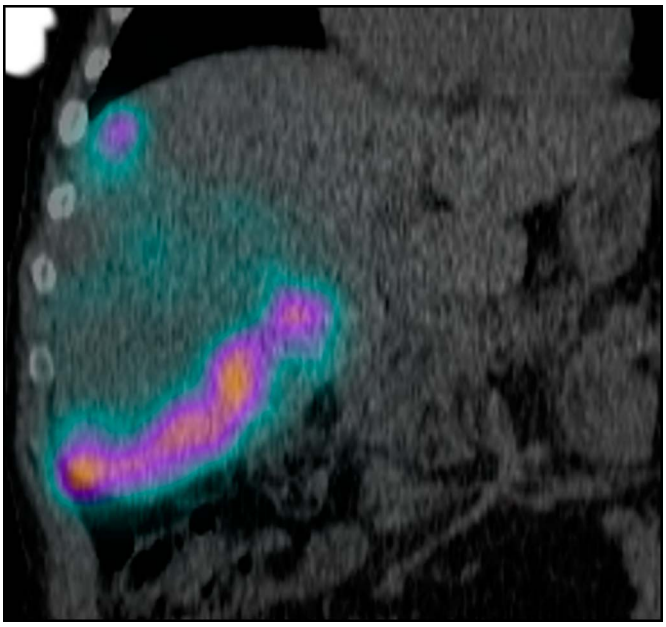

Figure 2. Single-photon emission computed tomography imaging after initial arterial mapping procedure.

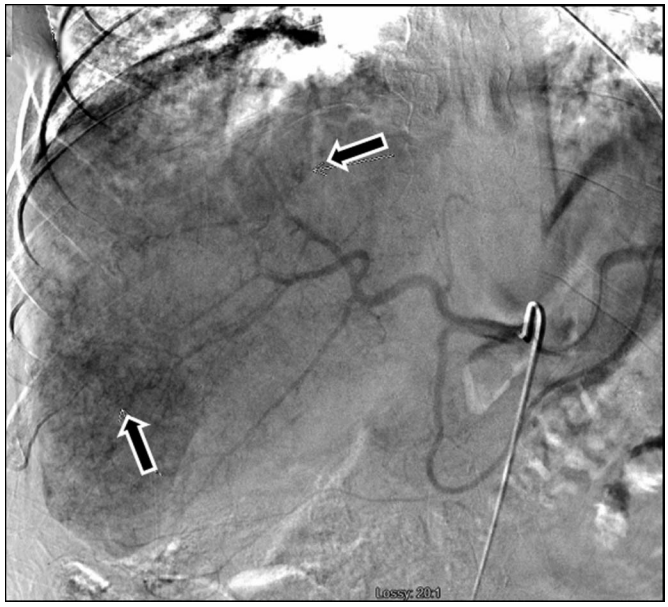

Figure 3. Retrospective review of intraprocedural digital subtraction angiographic acquisition showing prominent arterioportal shunting.

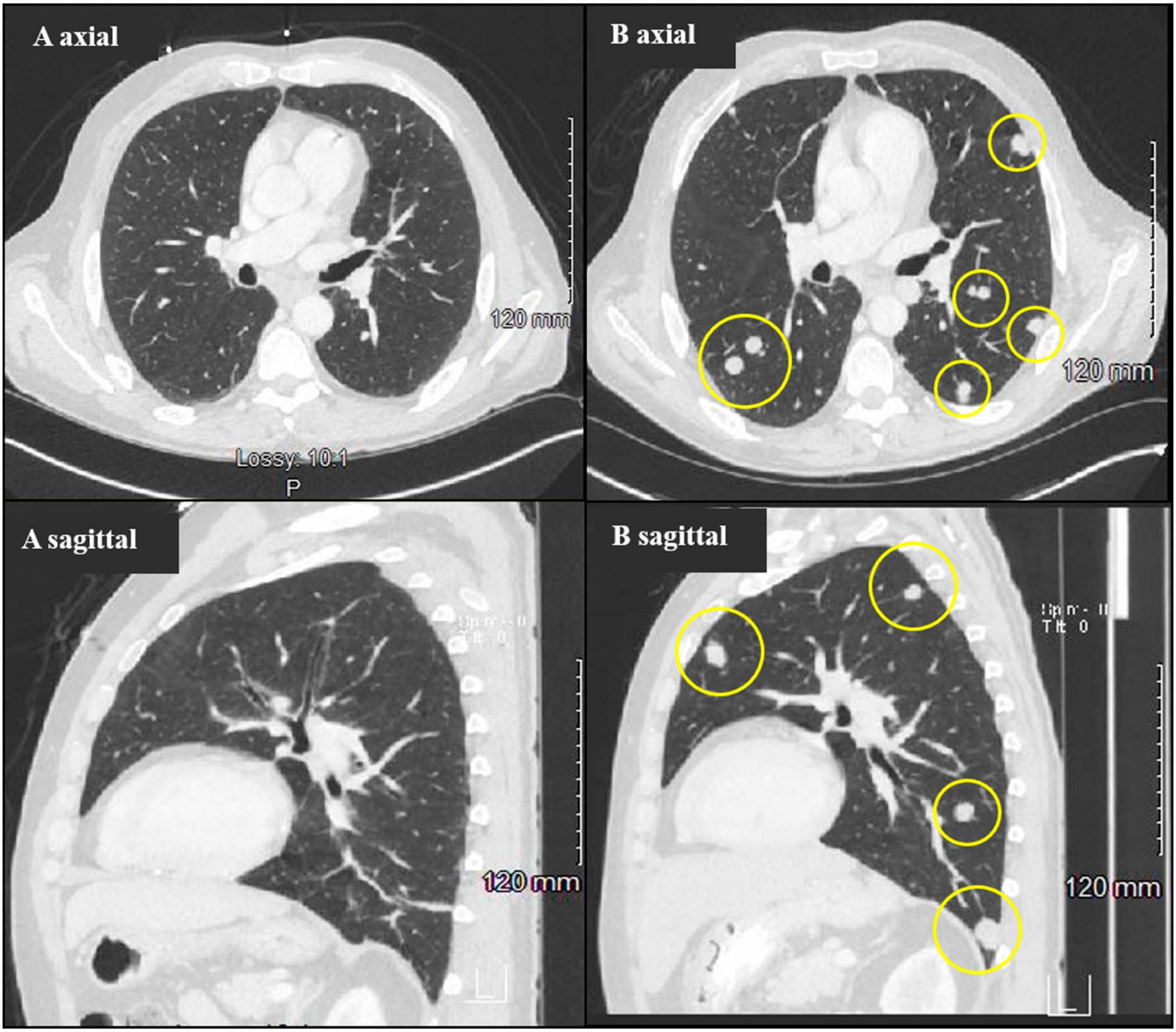

Figure 4. Representative lung window computed tomography images at comparable axial and sagittal planes, (A) before and (B) after transarterial radioembolization showing the development of new multifocal rounded pulmonary metastasis (yellow circles).

performed by injecting Tc-99m MAA intra-arterially into the liver as a test run before actual Y-90 administration. In most centers, images are then obtained using a planar gamma camera. The fraction of total counts reaching the lung (LSF) are derived by calculating the geometric mean of counts detected in the manually drawn region of interest over the lung on both anterior and posterior planar views. LSF values are known to become less reliable with time, especially beyond 4 hours because of biologic disintegration of MAA.[7] LSF was calculated with planar imaging at 45 minutes postinjection in our case. Although SPECT-CT is performed at many centers, for visual assessment of extrahepatic deposition, it is not routinely used for LSF calculation. Given its poor anatomic resolution and the inability of performing attenuation correction, planar imaging is prone to overestimation of shunt fraction when compared with SPECT-CT.[8] Ideally, LSF should be less than 10%. Although dose adjustments can be performed in patients with LSF ranging between 10% and 20%, those with LSF exceeding 20% are excluded from treatment.[9] Although our patient only had a borderline high LSF of 11%, multiple other risk factors for metastatic progression were present including a large tumor burden with macrovascular invasion and very high AFP levels. To this point, Fleming et al proposed a judicious way of pre-TARE patient selection by inversely customizing the LSF cutoff based on anatomic tumor bulk and aggressive features.[5]

An abscopal effect of radiation-induced augmentation of antitumor immune response has been described in the literature.[10] On the contrary, this case exhibits a "reverse" abscopal effect.

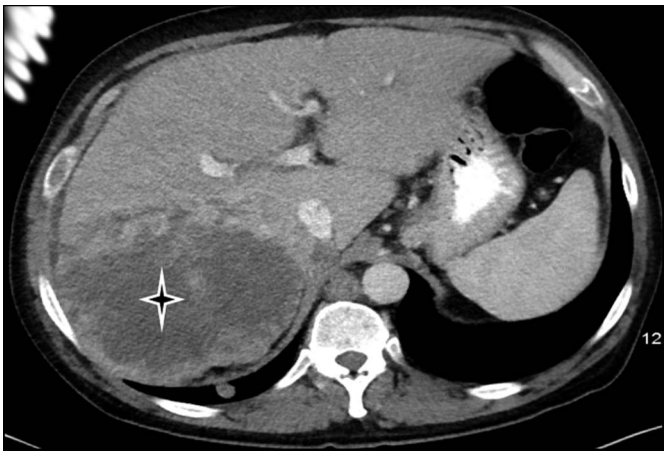

Figure 5. Axial contrast-enhanced computed tomography images taken 53 days after transarterial radioembolization showing the necrosis of the index tumor (black star).

Our literature search for similar cases incidentally revealed a growing body of evidence showing a trend for regional (but not metastatic) tumor potentiation after other locoregional therapies including ablation and transarterial chemoembolization.[11–13] Tumor size, proximity to a sizeable portal vein, infiltrative morphology, and lower age have been linked to higher risk of such an occurrence.[11] Multiple potential mechanisms have been proposed: (i) iatrogenic arterioportal shunt creation, (ii) induction of immune activation (high regional hepatocyte growth factor which in turn can activate downstream c-Met pathway leading to a greater vascular endothelial growth factor synthesis) and, (iii) increased intratumor pressure from associated edema causing rupture of the index lesion and dissemination of viable tumor cells.[11,12,14] In conclusion, this report brings to light the possibility of metastatic potentiation after TARE in patients with IHCC-TIV and argues for improved preprocedural assessment of TIV burden and thoughtful consideration of adjunctive biochemical markers, especially when deciding for TARE candidacy in patients with borderline elevated LSF values.

DISCLOSURES

Author contributions: H. Kapoor and S. Sanampudi wrote the manuscript. J. Owen and D. Raissi revised the manuscript. H. Kapoor is the article guarantor.

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Informed consent was obtained for this case report.

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