Hemorrhage Following Drug-Eluting Bead Transarterial Chemoembolization of Hepatocellular Carcinoma

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Case Presentation

We report the case of a 78-year-old woman with hepatocellular carcinoma who underwent drug-eluting bead transarterial chemoembolization (DEB-TACE). On the first routine follow-up CT six-weeks post procedure, the patient was found to have residual enhancing tumor and active intra-tumoral hemorrhage (**Fig 1A**). Follow-up laboratory values demonstrated a decrease in hemoglobin. Subsequent catheter arteriogram confirmed active arterial hemorrhage as well as enhancement along the periphery, suggestive of residual tumor, which was treated with repeat embolization (**Fig. 1B**). Several arteries supplying the residual tumor were embolized using drug eluting bead transcatheter chemoembolization (DEB-TACE). Additionally, the active arterial extravasation was treated with 0.018" coil embolization using platinum microcoils achieving post-embolization hemostasis (**Fig. 1C**). Nine-month follow up imaging demonstrated no residual enhancing tumor or evidence of active extravasation of contrast material (**Fig. 1D**).

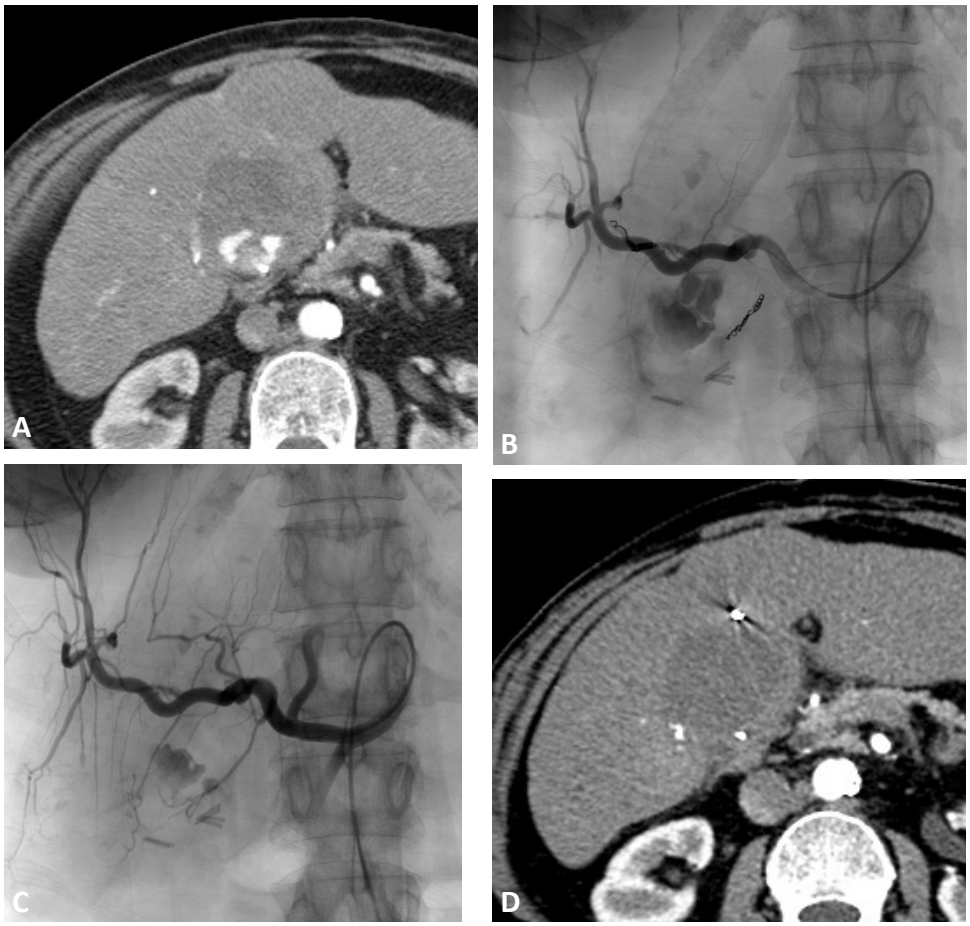

Figure 1. Early (**A**) arterial phase CT imaging demonstrates active arterial intra-tumoral hemorrhage in the segment IVB hepatocellular carcinoma, as well as residual enhancement along the periphery of the treated tumor bed, six weeks following initial DEB-TACE. Digital subtraction angiography (DSA) of the right hepatic artery following repeat DEB-TACE and placement of 3mm .018" VortX microcoils (Boston Scientific, Quincy, MA, USA) into two arteries supplying the segment V hepatocellular carcinoma (**B**) demonstrates no further extravasation of contrast (**C**). 9 month follow up CT (**D**) demonstrates no residual enhancing tumor or extravasation of contrast, compatible with successfully treated hepatocellular carcinoma.

Key Imaging Findings

Active intra-tumoral contrast extravasation

Successful transarterial hemostasis and TACE

Diagnoses

Active intra-tumoral hemorrhage following TACE with subsequent transarterial embolization

Discussion

Background.

Complications of TACE are well described in the literature and include liver failure (2.3%), post-embolization syndrome, tumor lysis syndrome (4.6%), abscess (1-2%), non-target embolization, gastrointestinal bleeding, and arterial access site complications.[1] While arterial hemorrhagic complication in the setting of percutaneous intervention has been well documented, intra-tumoral hemorrhage in the setting of transcatheter intervention is rare and hemorrhagic necrosis in the setting of hepatocellular carcinoma as a complication following TACE has not been commonly described in the literature. We report a case of clinically significant hemorrhage within hepatocellular carcinoma (HCC) after drug eluting bead transcatheter chemoembolization (DEB-TACE).

Clinical Course.

A 78-year-old woman with significant medical history, including congestive heart failure, anemia, chronic obstructive pulmonary disease, and coronary artery disease (recently treated with drug eluting coronary artery stents mandating long-term systemic anticoagulation) was diagnosed with a solitary 5.1 cm HCC in segment IVb of the liver on multiphasic dynamic contrast-enhanced (DCE) abdominal computed tomography (CT). The patient had no evidence of positive hepatitis B or C serology or excessive alcohol intake but had insulin dependent diabetes mellitus, morbid obesity, and hypercholesterolemia, consistent with metabolic syndrome and non-alcoholic steatohepatitis. Due to multiple co-morbidities and poor functional status, the patient was deemed a poor surgical candidate for curative resection. Pre-procedure hemoglobin and hematocrit values were 12.2 g/dL and 35.9%, respectively. Her warfarin was held prior to the procedure and her pre-procedure INR was 1.2. The patient subsequently underwent uneventful drug-eluting bead transarterial chemoembolization of the right hepatic lobe. Two vials of drug eluting beads (LC Bead™) 100-300 microns, (Biocompatibles, Inc., Oxford, CT, USA) loaded with 75 milligrams of doxorubicin were diluted with 16 mL of contrast material for a total volume of 20 mL. A total dose of 150 milligrams of doxorubicin was administered to the right hepatic lobe. Chemoembolization was carried to near stasis, and subsequent bland particle embolization was not required. Post-procedure admission was unremarkable, and the patient was discharged home on post-procedure day 1 with minimal pain. Anticoagulation was restarted 5 days following chemoembolization.

Six week follow-up multiphasic DCE-CT demonstrated residual nodular enhancement in the periphery of the treated tumor and extravasation of intravenous contrast material into the central necrotic portion of the tumor in the arterial and subsequent phases (**Fig. 1A**), compatible with residual viable tumor, as well as active intra-tumoral hemorrhage. The patient had poor appetite and increased fatigue following the original TACE procedure and had persistent abdominal tenderness in the midepigastrium on physical examination. Her INR was found to be 2.6 and her hemoglobin was 9.9 g/dL. The patient's warfarin was stopped and her coagulation status was corrected with fresh frozen plasma. Despite correction of her INR to 1.7, her hemoglobin level continued to drop to 8.7 g/dL.

Emergent hepatic arteriogram was performed and active extravasation of contrast from multiple branches of the right hepatic artery supplying the tumor was demonstrated. Multiple small arteries supplying the tumor were subselectively catheterized with a Renegade™ Hi-flo™ microcatheter system (Boston Scientific, Quincy, MA, USA), and a small dose of drug eluting beads loaded with 75 milligrams of doxorubicin was administered into each feeding vessel. In addition, two arteries supplying the tumor that demonstrated active extravasation were then coiled using 3mm - VortX 0.018" platinum microcoils (Boston Scientific, Quincy, MA, USA). Post-

embolization angiogram demonstrated improved angiographic appearance with no further active extravasation of contrast and no further tumoral enhancement (**Fig. 1B and C**).

The patient was observed in the hospital and then discharged on post-embolization day three. The patient's hemoglobin remained stable throughout the hospital stay. At her one month follow-up visit, the patient denied pain and had improved significantly with stable laboratory values. Follow-up multiphasic DCE-CT at nine months demonstrated no residual enhancing tumor or evidence of active extravasation of contrast material.

Topic Review.

TACE involves the regional injection of chemotherapeutic agents followed by an embolic agent. TACE is considered the mainstay of therapy for unresectable HCC, achieving a median survival benefit of more than two years in patients when compared to optimal medical management alone.[2] Reported complications of TACE include liver failure (2.3%), post embolization syndrome, tumor lysis syndrome (4.6%), abscess formation (1-2%), non-target embolization, gastrointestinal bleeding, and arterial access site complications.[1]

Drug eluting beads, which can be loaded with doxorubicin or irinotecan are delivered by transcatheter arterial embolization (DEB-TACE). DEB-TACE has been shown to be safe and effective by Varela, et al., and Poon, et al.[3,4] However, patients in each of these studies developed severe complications. Six serious complications occurred in 35 patients treated with DEB-TACE (17.1%) in the Poon study, including hepatic rupture, hepatic failure, spontaneous bacterial peritonitis, bleeding ulcers, and bleeding esophageal varices.[4] The patient who developed hepatic rupture had a 10 centimeter subcapsular HCC. Both studies demonstrated significantly less systemic effects of doxorubicin than in patients treated with intravenous doxorubicin chemotherapy.

DEB-TACE has been shown to be as safe and as effective as conventional TACE for the treatment of HCC lesions which are smaller than 5 cm. Lammer, et al. demonstrated no statistically significant difference in the number of serious adverse events in the Precision V trial.[5] Another small study has demonstrated a significant survival benefit in patients treated with DEB-TACE compared with those treated with conventional TACE. More studies are probably needed to confirm the survival benefit of DEB-TACE over conventional TACE. Regardless of the technique used, it is critical for the interventional radiologist and the treatment team to recognize and appropriately treat these complications. We report an interesting case of active extravasation into a treated lesion presumably from intra-tumoral necrosis.

Close follow-up is vital to detection of complications following TACE. All TACE patients at our institution are admitted for overnight pain management and observation for potential life threatening complications of TACE. Most patients are discharged on post TACE day 1. TACE patients are followed with multiphase CT or MR imaging 6 weeks following their procedure. This patient's intra-tumoral hemorrhage and residual tumor were found at her initial routine 6 week follow-up visit.

Hepatic rupture is a known but not well documented complication in patients who undergo TACE for the treatment of large HCC.[6-8] Hepatic rupture is thought to result from intra-tumoral hemorrhage into treated necrotic HCC. Most cases of hepatic rupture occur within the first few days after TACE, but hepatic rupture has been reported up to 45 days following TACE.[9] Our case of intra-tumoral hemorrhage was detected 46 days after DEB-TACE without hepatic rupture. This case may represent a rare incident of impending hepatic rupture imaged prior to rupture. Hepatic rupture following TACE is most commonly seen in larger tumors. The late presentation in this case may be due to the smaller size and/or the intraparancymal location of the tumor.

Intra-tumoral hemorrhage during TACE has only been reported once by Choi, et al.[10] In the only previously reported case of intra-tumoral hemorrhage, active extravasation of contrast was visualized during the TACE procedure. Choi, et al. speculated the hemorrhage in their case was due to angiitis caused by gelfoam, lipiodol, or mitomycine or while they used careful technique, trauma from manipulation of wires or catheters may have contributed.[10]

The treatment of active intra-tumoral hemorrhage in the setting of recurrent or residual tumor requires thoughtful planning. First and foremost

is the problem of treating the potentially life-threatening hepatic hemorrhage. Hepatic arterial hemorrhage can be treated with temporary embolic agents such as gelfoam pledget or gelfoam slurry or permanent embolic agents such as glue, a covered stent, or platinum coils.[11,12] Second is the problem of treating any residual tumor enhancement and leaving open the option of retreating residual or recurrent tumor in the future.

In this case, we embolized the small arteries supplying the residual tumor with drug eluting beads (LC Bead™ 100-300 microns) loaded with 75 milligrams of doxorubicin to treat the residual tumor. Repeat angiography demonstrated persistent hemorrhage into the necrotic cavity. Because hemorrhage persisted despite embolization with 100 to 300 micron LC Bead™, a permanent embolic agent was required to treat the hemorrhage. Multiple platinum coils were then used to embolize the bleeding arteries. Using coils precludes future chemoembolization of those vessels. At the time, the risks of continued bleeding and potential hepatic rupture outweighed the benefits of future TACE in this patient.

Conclusion

Clinically significant intra-tumoral hemorrhage is a rarely documented complication of DEB-TACE as most patients may present with frank hepatic rupture. The risk for hepatic rupture increases in large HCC and may increase in patients on systemic anticoagulation and systemic chemotherapy. Repeat chemoembolization with subsequent coil embolization may be an effective treatment option in the rare event of hemorrhagic complications of TACE, such as in impending hepatic rupture.

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