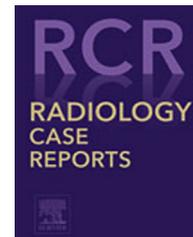


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## Case Report

# Histological assessment of the efficacy of drug-eluting beads in portal tumor thrombosis of hepatocellular carcinoma

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## ABSTRACT

A 58-year-old man was diagnosed with advanced hepatocellular carcinoma with portal vein tumor thrombosis (PVTT). The tumors were multiple and existed in both lobes. Drug-eluting beads transcatheter arterial chemoembolization (DEB-TACE) was performed for the tumors in the left lobe. Embosphere and Hepasphere were selected for embolization of the arteriportal shunt, followed by loaded epirubicin infusion into the left hepatic artery. Computed tomography showed reduction of PVTT. However, liver failure progressed, and the patient died 67 days after DEB-TACE. Autopsy showed that the beads reached the tumor thrombosis in the portal vein. The prognosis of hepatocellular carcinoma with PVTT is poor. Although there are no established treatments for unresectable PVTT, DEB-TACE might be a useful option for such cases.

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## Introduction

Portal vein tumor thrombosis (PVTT) often occurs in cases of advanced hepatocellular carcinoma (HCC). The prognosis of HCC with PVTT is poor because of metastasis and portal

hypertension associated with arteriportal shunting [1,2]. Unresectable cases with PVTT are treated with radiation therapy, continuous hepatic arterial infusion chemotherapy, or transcatheter arterial chemoembolization (TACE). However, the response to treatment, particularly to conventional

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Ethical standard: All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from the patient.

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TACE (cTACE), remains poor [3]. Various drug-eluting beads (DEB) have been developed as new embolus materials for TACE; these include Hepasphere (BioSphere Medical, Roissy-en-France, France); Embosphere (BioSphere Medical, Roissy-en-France, France); and DC beads (Biocompatibles UK, Ltd, London, United Kingdom). DEBs have several features that vary from cTACE, which uses ethiodized oil and gelatin sponge. DEB can carry and slowly release anticancer agents. Furthermore, compared with cTACE, DEB-TACE can embolize vessels that are more peripheral because the DEBs are highly deformable and vary in diameter [4]. These features may be more effective for PVTT cases and can improve the response to TACE. We conducted an autopsy on a patient with advanced HCC with PVTT and severe arterioportal shunt and who had undergone treatment with DEB-TACE to evaluate the efficacy of DEB for such cases.

### Case report

A 58-year-old man was diagnosed with hepatitis B virus infection at the age of 30 years but was lost to follow-up. He visited another hospital due to abdominal pain, and contrast-enhanced computed tomography (CT) was performed. He was diagnosed with liver cirrhosis due to hepatitis B virus and multiple HCC. He was referred to our hospital for treatment.

At the time of hospital admission, ascites was seen on ultrasonography, and blood test showed prolonged prothrombin time. Therefore, we assessed his hepatic functional reserve as Child-Pugh class B. Tumor marker levels were notably increased, the protein induced by vitamin K absence or antagonists (PIVKA-II) level was 5750 mAU/mL, the  $\alpha$ -feto-protein (AFP) level was 3614 ng/mL, and the AFP-L3 measurement was 16.15% (Table 1).

Angiography was performed on the day after hospital admission. CT during arteriography showed that the left lobe was replaced with heterogeneously enhancing tumors with indistinct boundaries and that multifocal HCCs were present in the right lobe. The CT during arterial portography showed tumor thrombosis in the main portal vein and left portal vein

(Fig. 1). The posterior branch of the right portal vein was intact, but the anterior branch was invaded by tumor. Angiography showed that blood flow in the hepatic artery was superior to that in the portal vein because of portal thrombosis. Poorly marginated stains mixed with tumors and liver parenchyma, as well as enhanced thorough arterioportal shunts, were seen in the left and right lobes (Fig. 2). The risk of HCC rupture was thought to be high because the patient complained of abdominal pain.

DEB-TACE was performed after obtaining the patient's consent. Treatment of the tumors in the left lobe was prioritized because those were the main lesions. Treatment of the right lobe was postponed to a later date to maintain hepatic reserve. To embolize arterioportal shunts, 10 mL of Embosphere (500–700  $\mu$ m), which was diluted two times with the contrast medium, was infused from the left hepatic artery before chemoembolization. After infusing Embosphere, the enhancement of arterioportal shunts decreased (Fig. 3A). Following embolization by Embosphere, Hepasphere was infused from the same branch. The volume of Hepasphere (50–100  $\mu$ M) was increased 4 times (200–400  $\mu$ m) by addition of 25 mg of epirubicin dissolved in the contrast medium, resulting to 8–10 mL of mixed Hepasphere for infusion. After infusing Hepasphere, tumor staining decreased and the enhancement of the arterioportal shunts nearly disappeared (Fig. 3B). After the treatment, the hepatic functional reserve of the patient was maintained as Child-Pugh class B (9 points). Systemic chemotherapy was not administered after DEB-TACE.

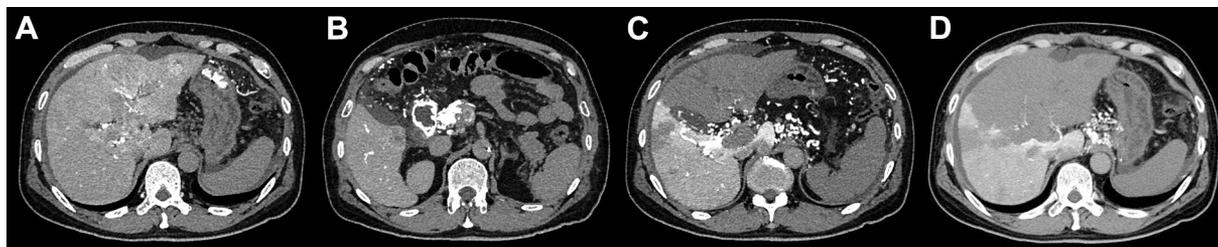
Six days after, contrast-enhanced CT was performed to assess the effect of the treatment. Enhancement of the lateral segment disappeared because of tumor necrosis by DEB-TACE. However, enhancement of the medial segment remained. Invasion of the tumor to the inferior vena cava was shown and suggested rapid progression of the tumor.

The patient was discharged 37 days after treatment but was readmitted at 47 days after treatment because of fatigue and abdominal fullness. Ascites had increased markedly, and jaundice was noted. The level of hepatic functional reserve was Child-Pugh class C (10 points). Tumor markers were

**Table 1 – Laboratory data on admission.**

Blood cells		Biochemistry		Coagulation factor	
RBC	4.15 × 10 <sup>6</sup> / $\mu$ L	AST	163 U/L	PT	61.6%
Hemoglobin	13.7 g/dL	ALT	122 U/L	PT (INR)	1.25
Hematocrit	39.7%	ALP	779 U/L	<b>Virus markers</b>	
WBC	4.3 × 10 <sup>3</sup> / $\mu$ L	$\gamma$ -GTP	448 U/L	HBs-Ag	175 IU/mL
Neutrophils	67.4%	LDH	264 U/L	HBe-Ag	(–)
Lymphocytes	19.2%	Cholinesterase	138 U/L	Anti HBe-Ab	(–)
Monocytes	7.5%	T-Bil	1.5 mg/dL	HBV-DNA	6.0 Log copies/mL
Eosinophils	4.5%	D-Bil	0.5 mg/dL	<b>Tumor markers</b>	
Basophils	1.4%	BUN	12 mg/dL	DCP	5750 mAU/mL
Platelets	11.5 × 10 <sup>4</sup> / $\mu$ L	Creatinine	0.7 mg/dL	AFP	3614 ng/mL
		Total protein	7.2 g/dL	AFP-L3	16.1%
		Albumin	3.3 g/dL		
		NH <sub>3</sub>	48 $\mu$ g/dL		
		CRP	2.53 mg/dL		

RBC, red blood cell; WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkali phosphatase;  $\gamma$ -GTP,  $\gamma$ -glutamyl transpeptidase; LDH, lactate dehydrogenase; Bil, bilirubin; BUN, blood urea nitrogen; PT, prothrombin time; INR, internationalized normalized ratio; DCP, des- $\gamma$ -carboxy prothrombin; AFP,  $\alpha$ -fetoprotein; CRP, C-reactive protein; HBV-DNA, hepatitis B virus-DNA.



**Fig. 1 – Angiogram computed tomography (CT).** CT during arteriography (CT-A) shows that the left lobe is replaced with heterogeneously enhancing tumors with indistinct boundaries (A) and that multiple tumors are present in the right lobe (B). CT during arterial portography (CT-AP) shows tumor thrombosis in the main and left portal veins. The left lobe is not enhanced (C, D).

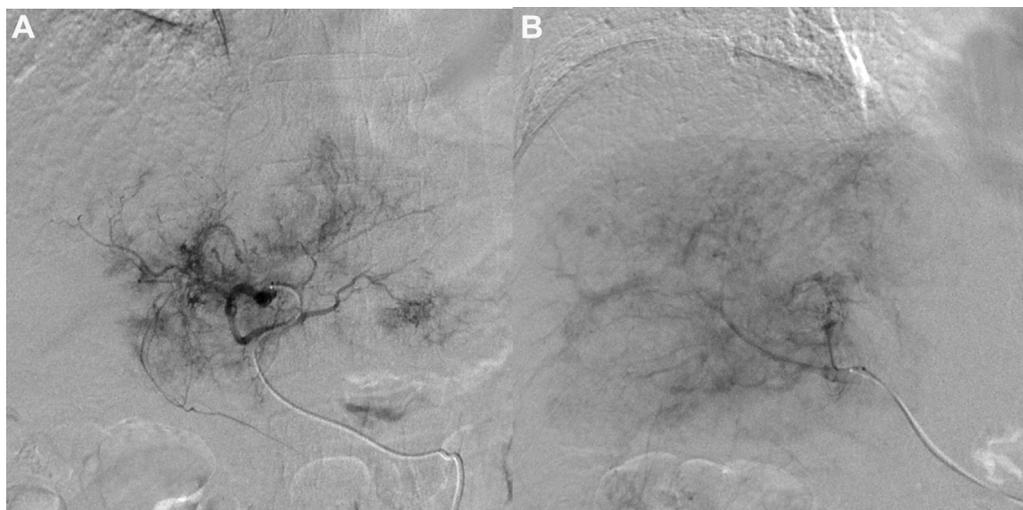
markedly increased; des- $\gamma$ -carboxy prothrombin was 38,227 mAU/mL, AFP was 6615 ng/mL, and the AFP-L3 was 13.1% at that time. Contrast-enhanced CT showed that the PVTT was reduced, but the other tumors had progressed (Fig. 4). Palliative care was initiated, but the HCC tumor in the right lobe ruptured. The patient died 67 days after the DEB-TACE treatment.

An autopsy was performed after obtaining consent from the patient's family. Two types of emboli (deep acidophilic embolus and weak acidophilic embolus) were seen in the portal veins. The average boundary length of the deep acidophilic embolus was  $1113 \pm 579 \mu\text{m}$  and that of the weak acidophilic embolus was  $644 \pm 579 \mu\text{m}$ . This indicated that the deep acidophilic embolus was treated by Embosphere and that the weak acidophilic embolus was treated by Hepasphere. Hepasphere was present in the hepatic artery, portal vein, and tumor. Embosphere was present more proximally in the hepatic artery. Both Embosphere and Hepasphere were seen in the PVTT. The cutout area was 42 cm<sup>2</sup>, and about 80% was occupied with tumors. The area of necrosis induced by DEB-TACE in the tumor was approximately 8.5 cm<sup>2</sup>, whereas that in a normal hepatic parenchyma was approximately 0.3 cm<sup>2</sup>. DEBs were not seen in the other organs (Fig. 5).

## Discussion

Outcomes for patients with unresectable PVTT are poor, even after TACE [3]. In addition, it was reported that there was no difference in efficiency between DEB-TACE and cTACE for PVTT [5]. The reasons for the poor response of PVTT to TACE include the presence of arterioportal shunts and a narrow feeder artery in PVTT. Delivery of anticancer drugs by embolization is difficult with PVTT. Arterioportal shunt was noted in 28.8% to 63.2% of HCC cases [6]. In the presence of arterioportal shunt, the oil emulsion used in cTACE can enter the portal vein through the shunt and result in hepatic infarction. Gelatin sponge, metallic coils, and ethanol have been used to embolize arterioportal shunts [7–10], but the treatment response is poor when PVTT is present. TACE, including DEB-TACE, was able to provide equal or improved survival, compared with the outcomes with sorafenib [11]. DEB-TACE was reported to be efficient for PVTT treatment, but the mechanism of this response has not been shown by previous each papers. In this case, we evaluated the possible mechanism of DEB in treating PVTT by autopsy and histologic examination.

In the present case, a patient with HCC and PVTT was treated with DEB-TACE. DEBs have several features that are



**Fig. 2 – Angiography.** Tumor stains and stains of liver parenchyma enhanced through arterioportal shunts are shown on angiograms of the left (A) and right (B) hepatic arteries.

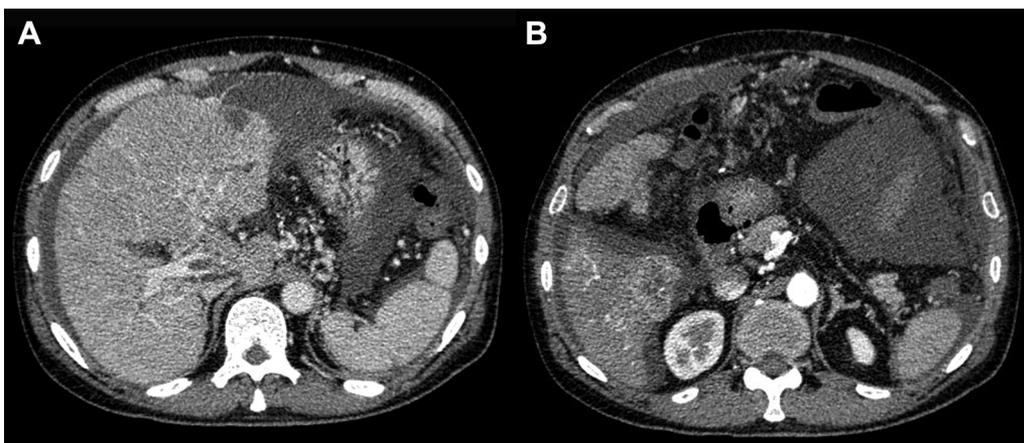


**Fig. 3 – Drug-eluting beads—transcatheter arterial chemoembolization (DEB-TACE). Enhancement of arterioportal shunts on angiogram decreased after infusing Embosphere (A). Arterioportal shunts and tumor stains are not detected on angiogram after infusing Hepasphere (B).**

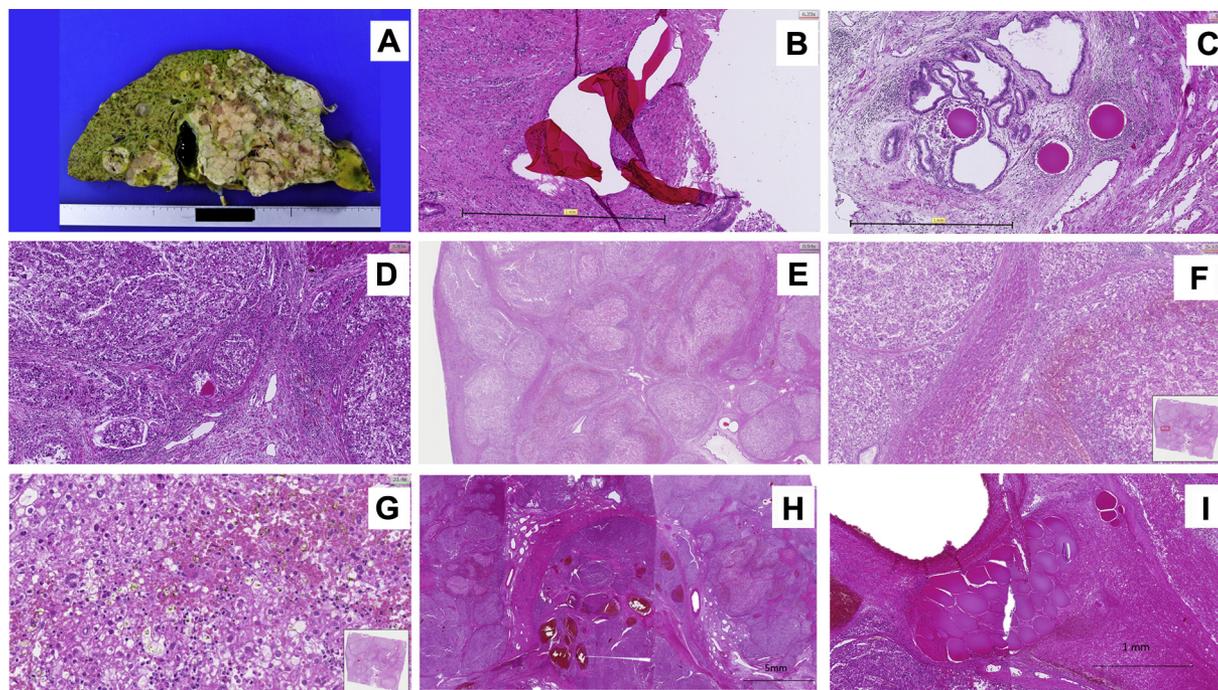
suitable for treatment of PVTT; these include uniform sizes and availability of products with various diameters [4]. Moreover, DEBs are highly deformable and can fit into the intravascular lumen. These features make it possible to choose an optimal particle size for target vessels and to embolize more peripheral vessels. Thus, DEB can travel into the PVTT through narrow feeder vessels. When embolizing arterioportal shunts, a large embolus can lodge in proximal vessels, whereas an overly small embolus can pass the shunt and embolize into the portal vein. DEBs can embolize the shunt vessels if the size is larger than that of the intravascular lumen because DEB can deform and embolize the vessel. In this case, the CT examination showed that the PVTT was reduced (Fig. 4), and we histologically confirmed that the Embosphere and Hepasphere reached the vein with tumor thrombosis (Fig. 5). Furthermore, slow release of an anticancer agent from DEBs in a PVTT enables a sustained effect [12,13].

In the present case, the patient died early after treatment. Had he lived longer, the PVTT size might have decreased in response to the slow release of anticancer drug from the DEB (Figs. 5H and I). Several experiments have characterized DEBs in animal models [14–17], but not in the human liver. To the best of our knowledge, this was the first report that histologically demonstrated the efficacy of DEBs in a human subject.

In the present case, multiple arterioportal shunts occurred in response to portal vein thrombosis. Embolizing from a vessel proximal to arterioportal shunts carries a risk of ischemic injury to the normal hepatic parenchyma. For safety, arterioportal shunts were treated with Embosphere (500–700  $\mu\text{m}$ ) before TACE. Histologic examination showed some Hepasphere beads in the portal vein. Although the observed necrotic area measured 8.8  $\text{cm}^2$  and the normal lesion area was 0.3  $\text{cm}^2$  (3.4%), there was minimal damage to the normal



**Fig. 4 – Contrast-enhanced computed tomography (CT). The portal vein tumor thromboses of the main and left veins have been reduced (A). The tumors in the right lobe have progressed (B).**



**Fig. 5 – Histologic findings in the liver. Gross findings of the tumors (A). Embosphere (deep acidophilic embolus, hematoxylin-eosin stain,  $\times 6.23$ ) (B) and Hepasphere (weak acidophilic embolus, hematoxylin-eosin stain,  $\times 5$ ) in the hepatic artery (C). Hepasphere in the tumor alveolar (hematoxylin-eosin stain,  $\times 5.83$ ) (D). The margins of the tumors have necrosed (hematoxylin-eosin stain,  $\times 5.15$ ) (E). Epirubicin released from the beads is shown in the tumors (hematoxylin-eosin stain,  $\times 21.4$ ) (F). Portal vein tumor thrombosis (G). Embosphere and Hepasphere are shown in the PVTT (H, I). PVTT, portal vein tumor thrombosis.**

lesion. Therefore, DEB-TACE can be safely used for PVTT in the context of an arterioportal shunt.

In summary, this report described a case in which advanced HCC with PVTT was treated with DEB-TACE. We confirmed the accumulation of the DEBs for PVTT by autopsy and histologic examination. Accumulation of additional cases is needed to confirm the efficacy and safety of DEBs for the human liver.

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