An Early-stage, Non-hypervascular HCC Successfully Treated by Superselective, Bland Transarterial Embolization Using 40-μm Microspheres

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Abstract. *Transcatheter embolization is considered to be less effective for early-stage hepatocellular carcinomas (HCCs) without a hypervascular arterial supply. In the present case report, a 65-year-old male with hepatitis type C and non-hypervascular HCC located in the hepatic hilum was successfully treated by bland transarterial embolization (TAE). After the temporary protective embolization of normal liver tissue using large gelatin particles, diluted 40-μm microspheres were injected via the tumor-feeding artery. The tumor shrank, and the patient has survived for 25 months without recurrence.*

Superselective transarterial chemoembolization (TACE) and transarterial embolization (TAE) are effective local treatments for hepatocellular carcinoma (HCC). Theoretically, TACE and TAE are useful for hypervascular tumors. HCC frequently involves multi-step sequential development. During the multi-step process of hepatocarcinogenesis, the source of the vascular supply switches from the portal vein to the hepatic artery (1). In early-stage HCC, tumors have no hypervascular arterial supply, only fine-feeding arteries. Therefore, TACE and TAE are generally considered less effective for early-stage HCC (2).

For non-hypervascular, early-stage HCC, tumor ablation, including radiofrequency ablation (RFA) and percutaneous ethanol injection (PEI), are frequently-used treatments. However, ablation therapies are occasionally contraindicated due to tumor location or ascites. Therefore, the development of an effective intra-arterial treatment for non-hypervascular, early-stage HCC is necessary.

Previously, Miyayama *et al*. reported the usefulness of superselective lipiodol-TACE for hypovascular HCC. Their report demonstrated that lipiodol could be distributed into the hypovascular tumor portion. In their series, approximately 60% of tumors, which did not have hypervascular arterial supply with decreased the portal blood flow, obtained the dense lipiodol retention (3).

Currently, precisely-calibrated, small-size microspheres are available in Europe and the United States. We considered that embolization using small-size microspheres could occlude fine tumor feeding arteries, as well as lipiodol, and be effective for non-hypervascular, early-stage HCC. Thus, a case of non-hypervascular, early-stage HCC successfully treated by superselective bland TAE using 40-μm microspheres is reported. To the best of our knowledge, there have been no reports to date regarding bland TAE using microspheres for non-hypervascular HCC.

Case Report

A 65-year-old male with hepatitis type C was found to have a liver nodule, 2.4 cm in diameter, on gadolinium ethoxybenzyl diethylene-triamine-pentaacetic-acid (Gd-EOB-DTPA)-enhanced MRI during a routine follow-up examination. In the arterial phase of Gd-EOB-DTPA-enhanced MRI, a slightly hypo-intense nodule, containing a hyper-intense spot, was seen (Figure 1a). In the hepatobiliary phase, the nodule was depicted as a hypointense area (Figure 1b). From these findings, the nodule was diagnosed as non-hypervascular, early-stage HCC containing hypervascular foci. For the treatment of this tumor, surgical resection and radiofrequency ablation (RFA) were considered. However, firstly, the patient refused surgery, and secondly, ultrasonography did not depict the tumor. In addition, due to the location of the tumor in the right hepatic hilum adjacent

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Key Words: Transcatheter arterial embolization, hepatocellular carcinoma, microspheres, Bland-TAE.

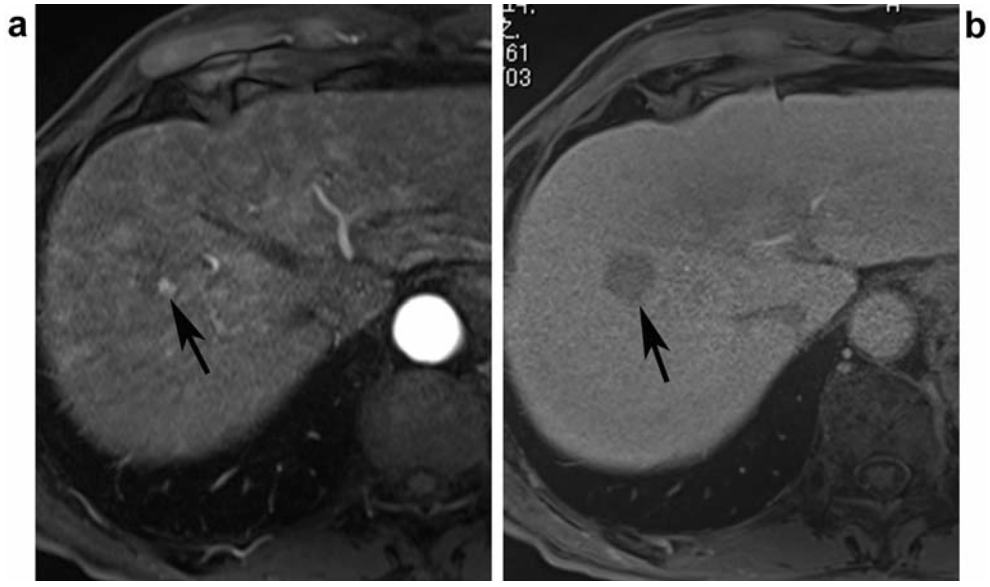

Figure 1. *a. The arterial phase of Gd-EOB-DTPA-enhanced MRI before bland TAE shows a slightly hypointense nodule containing a hyperintense spot, which is a hypervascular foci (arrow). b. The hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI before bland TAE shows a markedly hypointense nodule (arrow).*

to the bile duct and portal vein, RFA could be considered to cause bile duct injury and a heat sink effect could lead to incomplete ablation. Therefore, transarterial embolization became the treatment of choice for this tumor. To precisely observe the blood flow into the tumor, CT during angiography was conducted using a hybrid CT/angio system (Aqullion 16/ Infinix Celeve, Toshiba, Tokyo, Japan). The CT during arterial portography (CTAP) showed that the tumor had no portal vein supply (Figure 2a). CT during hepatic arteriography (CTHA) showed that the tumor had a similar or smaller arterial supply compared to normal hepatic parenchyma, except for the hypervascular foci (Figure 2b). On digital subtraction arteriography (DSA), tumor stain was not depicted (Figure 2c). The patient had good liver function (Child-Pugh A). Although superselective lipiodol-TACE could be considered to be effective for this tumor from Miyayama's report (3), we determined to use recent small microspheres.

The treatment strategy was as follows: (i) tumor-feeding arteries were confirmed using selective CT during arteriography because the DSA could not depict the tumor stain; (ii) the "temporary protective embolization" technique was used to avoid complications caused by embolization with small microspheres in a large liver area because of the tumor location in the hepatic hilum (4); and (iii) small microspheres, calibrated to be 40-μm in size, were used because the non-hypervascular tumor could have fine tumor vessels.

Firstly, a 2.0-Fr microcatheter (Estream; Toray Medical, Tokyo, Japan) was inserted into the anterior branch of the right hepatic artery. The selective CTHA showed that the tumor was located within the enhanced area, and a large hepatic volume was supplied from this artery (Figure 3a). Secondly, the microcatheter was inserted into the distal hepatic branches (A5 and A8), and gelatin particles, 1 mm in size, (Gelpart; Nippon Kayaku, Tokyo, Japan) were injected at the distal sites of the tumor feeding arteries to block the distal branches. Thirdly, 40-μm microspheres (Embozene; CeloNova BioSciences, Newnan, GA, USA), diluted 60 times with contrast material (iopamidol 150 mgI/mL), were injected slowly *via* the proximal site of the anterior branch of the right hepatic artery with a 1-mL syringe. During the injection, a slight tumor stain was seen on fluoroscopy (Figure 3b). The microsphere injection was stopped when the anterior branch of the right hepatic artery was completely occluded. Non-enhanced CT obtained immediately after TAE showed high density within the tumor, which could indicate that microspheres were present within the tumor.

The liver enzymes and C-reactive protein levels before and after TAE showed no remarkable changes (Table I). CT obtained one week after TAE showed that the area inside the tumor had a slightly higher density on non-enhanced CT, and a remarkably lower density area inside tumor was seen on contrast-enhanced CT. Perfusion CT demonstrated decreased arterial vascularity of the tumor (Figure 4). Shrinkage of the tumor was seen on the follow-up CTs obtained 1 and 3 months after TAE (Figure 5). Currently, this patient has no local recurrence 25 months after TAE.

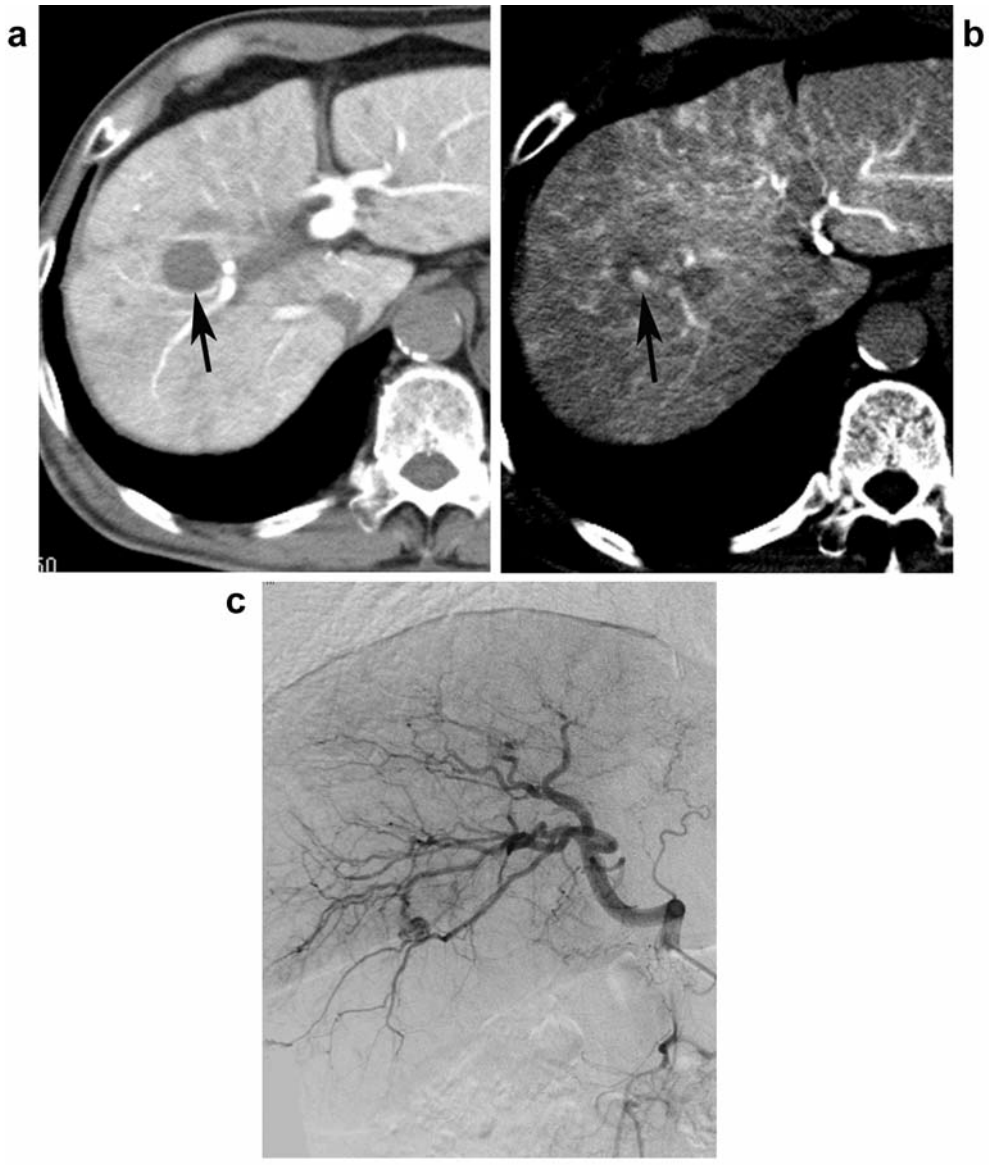

Figure 2. *a. CT during arterioportography (CTAP) shows the hypodense nodule without a portal supply (arrow). b. CT during hepatic arteriography (CTHA) shows the hyperdense spot within the slightly hypodense nodule (arrow). c. Tumor stain is not depicted on the hepatic arteriography.*

Discussion

Early HCC was clearly defined in the international consensus meeting on small nodular lesions in the cirrhotic liver (5). Although indications for treatment of early HCC remain controversial, tumors with hypo-intensity in the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI, decreasing portal blood flow on CTAP, or over 1.5 cm in diameter should be treated (6). The tumor in the present case had all of the above. A tumor biopsy was not performed before treatment due to the risk of causing arterial-portal or arterial-venous shunts after the needle puncture.

Table I. *Laboratory test results before and after bland-TAE.*

	Pre	1 day	3 days	7 days
CRP (mg/dl)	0.0	1.1	0.5	0.5
AST (U/L)	36	38	28	29
ALT (U/L)	35	46	34	29
LDH (U/L)	192	266	265	199
ALP (U/L)	230	273	231	227

CRP: C-reactive protein, AST: aspartate aminotransferase, ALT: alanine aminotransferase. LDH: Lactate dehydrogenase, ALP: alkaline phosphatase.

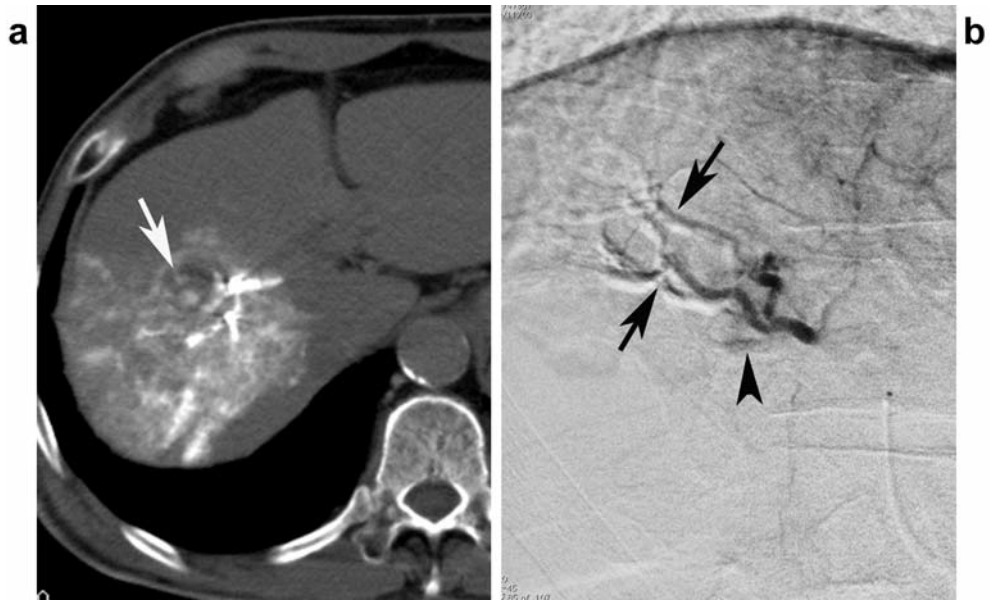

Figure 3. *a. Selective CT during arteriography shows that the tumor is located within the enhanced area (arrow), and a large hepatic volume is supplied from this artery. b. Angiography during the injection; the distal hepatic branches (A5 and A8) were embolized by gelatin particles (arrows). A slight tumor stain can be seen on fluoroscopy (arrowhead).*

Treatment of early HCC by TACE/TAE is a major challenge because the response to arterial embolization depends primarily on the development of tumor vessels. However, Miyayama's report showed that tumors with a hypovascular portion could be successfully treated by superselctive lipiodol TACE in many cases (3). When we use microspheres in such cases, the selection of the size of microspheres could be a key issue. In general, non-hypervascular tumors have fine tumor feeding vessels. Therefore, small-size microspheres could be effective for early-stage HCC. In the present case, 40-μm microspheres, the smallest size commercially available, were chosen. However, further studies to investigate the optimal size of microspheres are necessary. Highly-diluted microspheres were injected to avoid proximal occlusion of the hepatic artery.

Regarding the necessity of chemo-agents, Osuga *et al.* previously reported that bland TAE using microspheres was effective for hypervascular HCC (7). To date, there is no consensus regarding the efficacy of chemo-drugs in the embolization of HCC. However, TACE using newly-developed, small-size, drug-eluting microspheres, *i.e.* 40-μm Embozene TANDEM (CeloNova BioSciences) and 75-150-μm DC Bead^{M1} (Biocompatible, Farnham, UK), should be promising, with a stronger effect than bland TAE (8).

Embolization of a large hepatic volume using small-size microspheres could cause liver dysfunction and biliary damage (9). Therefore, a temporary protective embolization technique with 1-mm gelatin particles was used prior to injection of the microspheres. As a result, the present patient had less toxicity. Protection using degradable starch microspheres (DSM) was also possible (4).

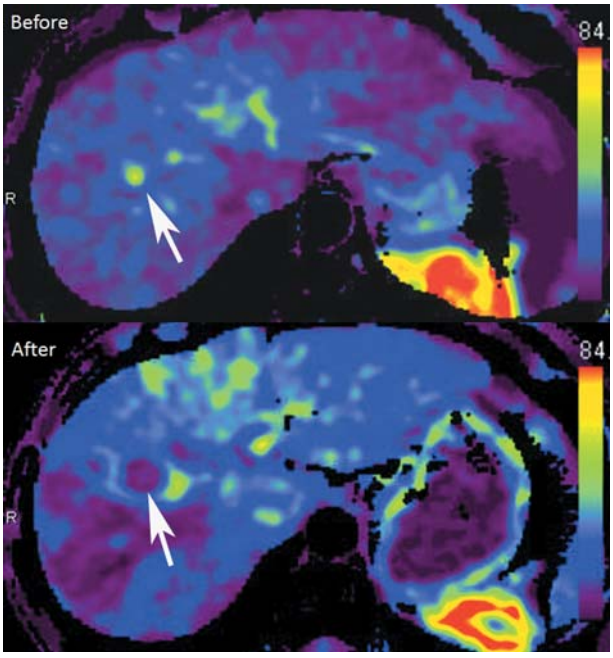

Figure 4. *Perfusion CTs before and 1 week after bland TAE demonstrate the decrease of the arterial vascularity of the tumor after bland-TAE (arrows).*

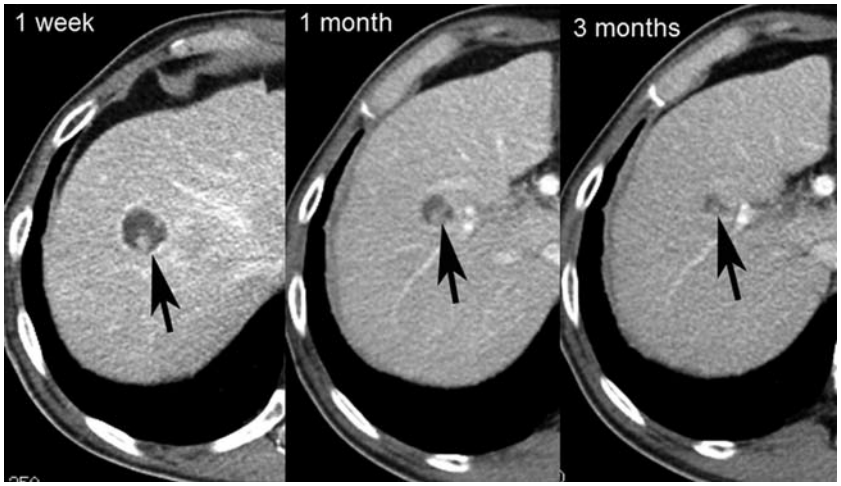

Figure 5. *Follow-up CT 1 week, 1 month, and 3 months after bland TAE show the shrinkage of the tumor (arrows).*

It could be difficult to evaluate the efficacy of treatment after bland TAE for a non-hypervascular tumor because injected microspheres are not visible, and tumor enhancement cannot be seen before or after TAE. CT perfusion images obtained before and after TAE could quantitatively assess the arterial vascularity. In addition, the tumor shrinkage during the follow-up period indicated good tumor control.

In conclusion, superselective bland TAE using 40-μm microspheres could be effective for early-stage HCCs with fine tumor-feeding arteries. This treatment might also be useful for non-hypervascular HCCs refractory to superselctive lipiodol TACE.

Conflicts of Interest

The Authors declare that they do not have any conflicts of interest nor any financial disclosures.

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