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Treatment of Hepatocellular Carcinoma with Transcatheter Chemo-embolization Using Iodized Oil

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ABSTRACT. Four patients with hepatocellular carcinoma (HCC) were given either an intraarterial injection of iodized poppyseed oil (Lipiodol) alone, an emulsion of iodized oil and doxorubicin hydrochloride (Adriamycin), or the emulsion plus gelatin sponge (Spongel) particles. Hepatic resection was subsequently performed. The frequencies of necrosis in the tumors were evaluated in the cut surface of resected specimens. The emulsion plus gelatin sponge demonstrated the best therapeutic effects. Although the emulsion led to partial necrosis of the tumor, iodized oil alone had practically no therapeutic effect.

Key words : hepatocellular carcinoma — lipiodol — chemo-embolization — comparison of necrotic effects

Transcatheter arterial embolization (TAE) for hepatocellular carcinoma (HCC) has proved to be an effective method in Japan. This procedure has been effective in reducing excess vascularity of tumors as well as tumor bulk by intraarterial infusion of gelatin sponge (Spongel). Intraarterial injection and chemo-embolization using an ethyl ester of poppyseed oil fatty acids containing 38% iodine by weight (Lipiodol; Andre-Gelbe Laboratories, France) has also been developed. These techniques seem to give better results than other forms of treatment for HCC.[1-4] In this report, the therapeutic effects of Lipiodol were evaluated histopathologically with resected specimens.

MATERIALS AND METHODS

Four patients with HCC were the subjects of this study. Detection of the hepatic mass was followed by US, CT and selective hepatic angiography. All patients underwent surgery after embolization. Embolization was performed by infusion of Lipiodol alone in one case, this mixture of Lipiodol and Adriamycin in one case and gelatin powder plus this mixture in two cases. The iodized oil/adriamycin mixture (emulsion) was prepared by mixing 4 ml of Lipiodol and 10-30 mg of Adriamycin in 2 ml of 48% diatrizoate sodium meglumine (Urographin) in a mixer for five minutes.

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Arterial Lipiodol injection chemotherapy and chemo-embolization were slowly performed in 5-10 minutes under fluoroscopic monitoring. For chemo-embolization, gelatin sponge particles were injected through the catheter immediately after injection of the emulsion of iodized oil and the anticancer drug. To evaluate the therapeutic effect on the tumor, the degree of necrosis was estimated by microscopic examination.

RESULTS

The therapeutic effects of the three methods are shown in Table 1. Resected specimens were examined histopathologically. Treatment with iodized oil alone (case 1) had no therapeutic effect ; i. e., there was no necrosis. Slow injection of iodized oil and doxorubicin (case 2) resulted in partial necrosis. Treatment with the emulsion plus gelatin sponge (cases 3,4) lead to complete necrosis.

TABLE 1. Necrosis rate for different embolization methods.

Case	Materials	Interval between therapy and surgery	tumor size (mm)	necrotic area (%)	AFP (ng/ml) Before/After
1. MU 20 M	Lipiodol 5 ml	20 days	33×33×29	0	5400/5200
2. TO 51 M	Lipiodol 5 ml ADM 30 mg	360 days	20×18	30	501/ 257
3. TS 51 M	Lipiodol 6 ml ADM 30 mg Spongel	36 days	33×35	100	414/ 50
4. YN 57 M	Lipiodol 4 ml ADM 10 mg Spongel	33 days	26×22	100	193/ 131

CASE REPORTS

Case 1 : A small liver tumor was detected by ultrasound (US) in a 20-year-old man who had received hemodialysis because of renal failure. He was referred to our hospital in September, 1987. On admission laboratory data showed him to be positive for hepatitis B (HB) antigen and his serum alfa-fetoprotein (AFP) was 5400 ng/ml. On October 7, celiac angiography was performed and a hypervascular tumor of 3.5 cm in diameter was found.

Subsequently, 5 ml of iodized oil alone was injected into the proper hepatic artery. A plain X ray film disclosed the presence of Lipiodol within the tumor (Fig. 1a). On October 27, a right hepatic lobectomy was performed. Histological examination of the resected specimen revealed no necrosis of the tumor and Lipiodol droplets and dilatation of the sinusoidal space were noted (Fig. 1b). His serum AFP level remained unchanged after Lipiodol infusion.

Case 2 : This 51-year-old man underwent a CT scan because of general fatigue and liver dysfunction. Since a hepatic tumor was detected by the CT, he was referred to our hospital on August 7, 1987. Hepatic angiography was performed, followed by embolization with an emulsion composed of 5 ml of Lipiodol and 30 mg Adriamycin. His AFP fell from 567 ng/ml to 257 ng/ml and he was discharged on October 9. During follow-up as an outpatient his

AFP increased again one year later and he was admitted on September 6, 1988. Fig. 2a shows incomplete Lipiodol retention within the liver tumor. A right posterior segmentectomy was performed on September 14. Partial necrosis of the tumor was noted, and Lipiodol had accumulated at the periphery of the necrotic area (Fig. 2b).

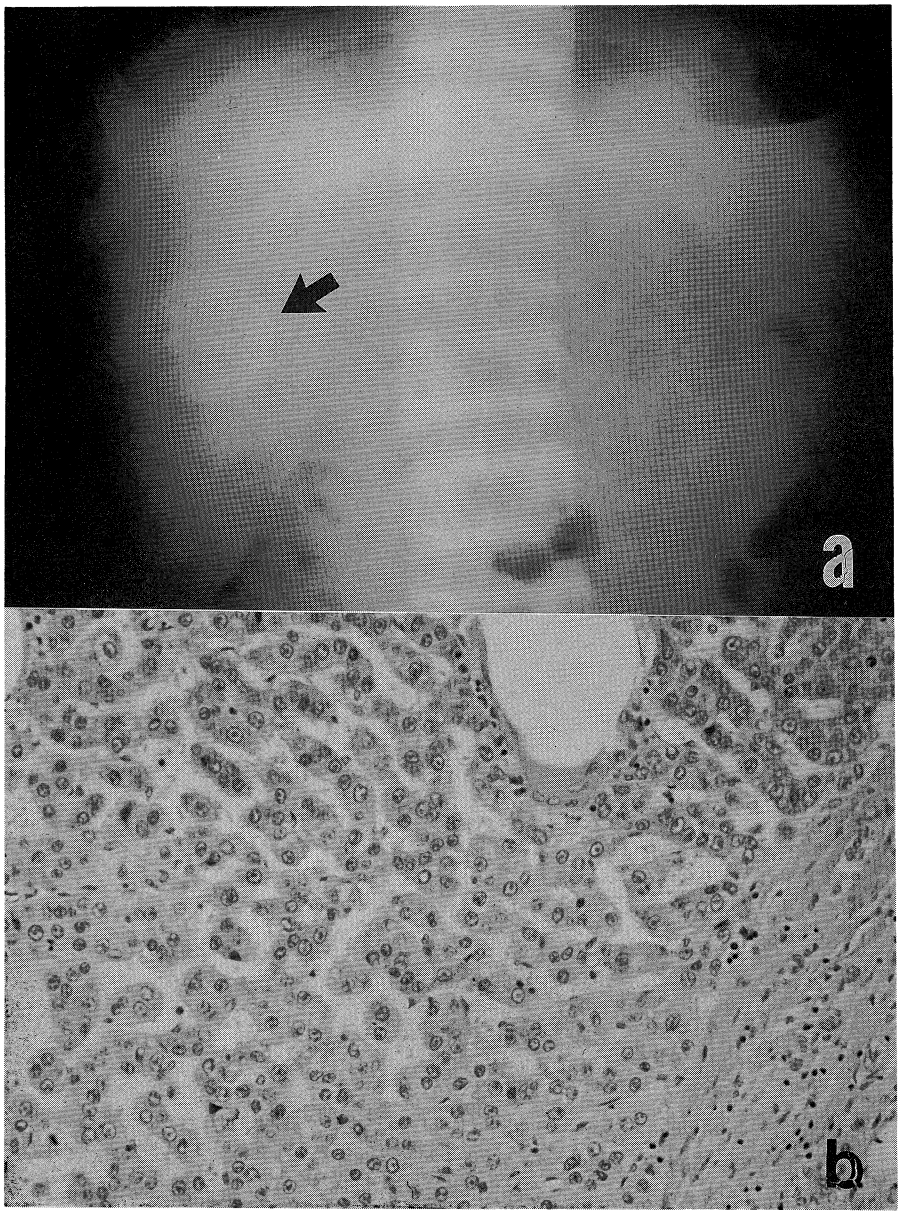

Fig. 1. a. An abdominal radiograph demonstrates accumulation of Lipiodol (arrow) within the tumor (case 1).
b. A histological picture of the resected tumor. Lipiodol droplets and dilatation of the sinusoidal space are noted. No necrosis of tumor cells demonstrated. (HE ×200)

Case 3 : A 51-year-old man who suffered from liver disease was found to have an elevated AFP (325 ng/ml) in December, 1987. Subsequent US and CT examinations demonstrated a 3.5 cm mass in the left lobe of the liver. The patient underwent arterial embolization with 6 ml of Lipiodol and 30 mg of Adriamycin, and gelatin sponge was injected into the proper hepatic artery. A CT scan obtained 14 days later demonstrated uniform high density Lipiodol

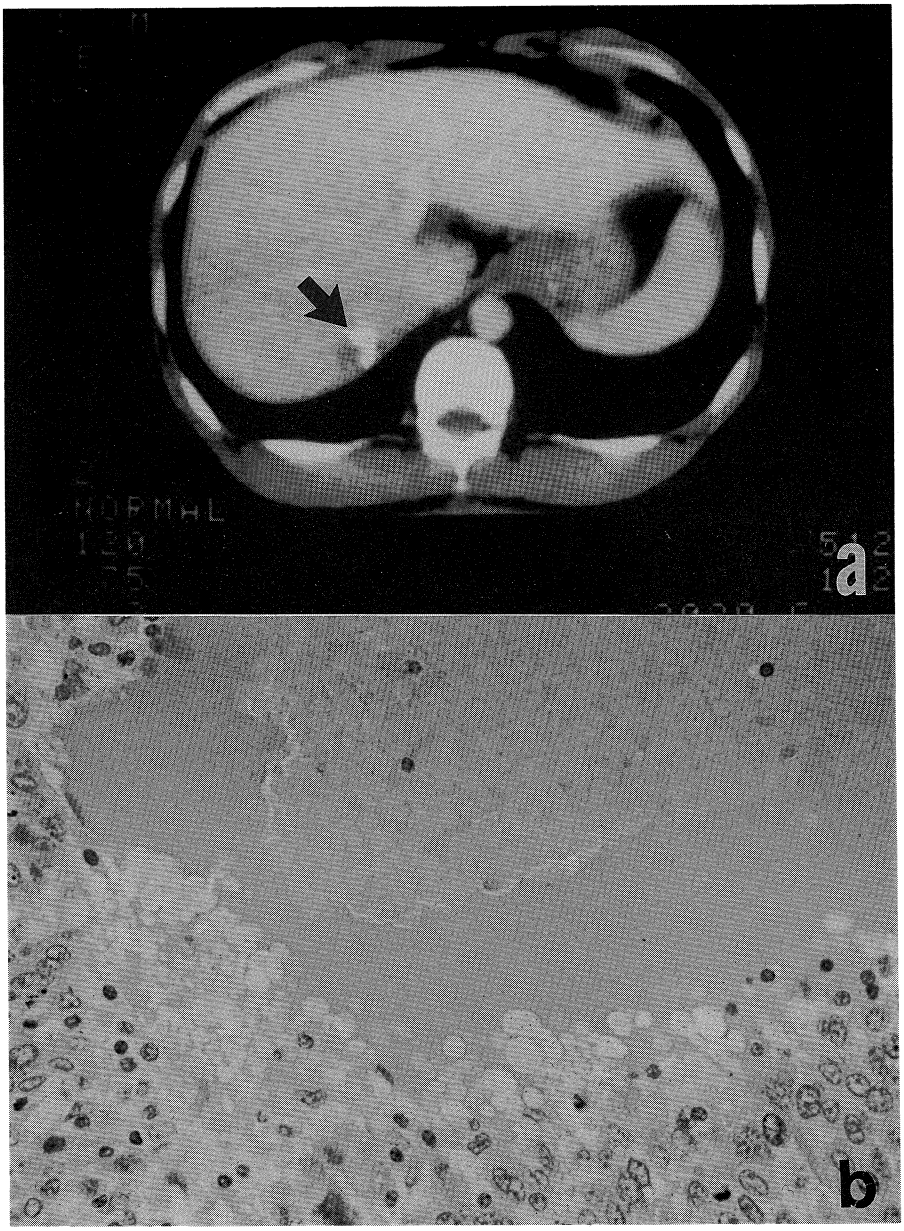

Fig. 2. a. A CT scan one year after embolization shows the remnant of Lipiodol (arrow) within the tumor (case 2).
b. A photomicrograph of the resected tumor shows partial necrosis and accumulation of Lipiodol droplets at the periphery of the necrotic area. (HE ×200)

deposition within the tumor (Fig. 3a). His AFP also decreased from 414 ng/ml to 50 ng/ml. A left lateral segmentectomy was done in March, 1988. The resected specimen had an encapsulated, well-differentiated 3.5×3.3 cm in size, which was completely necrotic. Histologically, the cancer cells were all necrotic and Lipiodol droplets were noted among necrotic tumor cells (Fig. 3b).

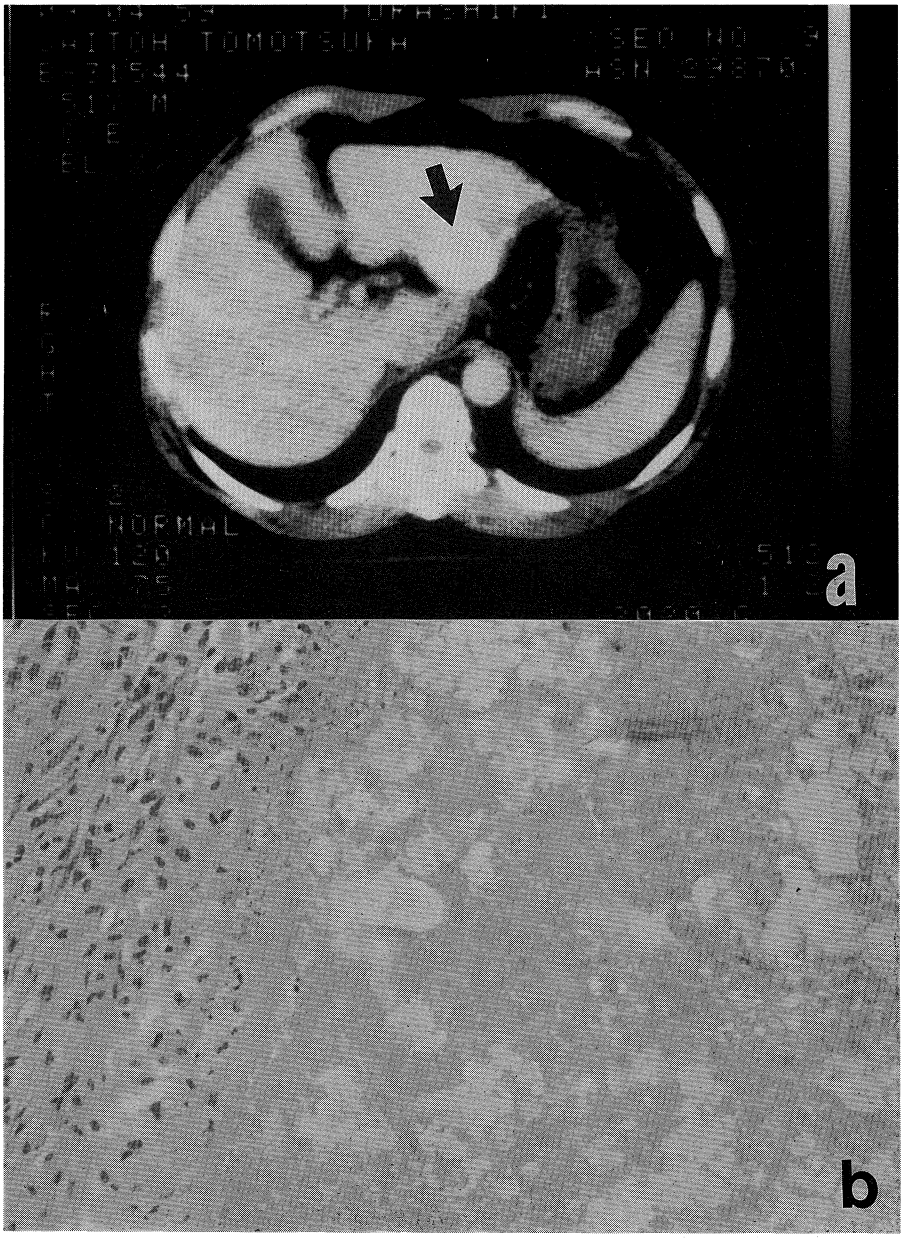

Fig. 3. a. A CT scan demonstrates a high density lesion (arrow) in the left lobe of the liver (case 3).
b. The tumor cells are almost completely necrotic and no viable tumor cells remain subcapsularly. (HE ×200)

DISCUSSION

TAE using gelatin sponge with anti-cancer drugs such as mitomycin C and doxorubicin has raised the one year survival in unresectable HCC patients in a large series in Japan[5] was 33.3%. However, histopathological studies of the resected specimens after TAE demonstrated that viable cells often remain in the intracapsular and/or extracapsular area.[6,7] In this study, resected specimens were examined and compared after intraarterial treatment with three different modalities. Iodized oil alone had almost no therapeutic effect. Injection of iodized oil and doxorubicin in emulsion caused partial necrosis of the tumor. Treatment with the emulsion plus gelatin sponge induced complete necrosis of the tumor. The same kind of trial was previously performed by Takayasu *et al.*,[8] emulsion plus gelatin sponge causing complete necrosis of the main lesion in 83% of case, daughter tumors in 53%, tumor thrombin 17%, and the foci of intracapsular invasion in 67%. The reason why gelatin sponge plus the emulsion induced complete necrosis can be explained in the following manner: Smaller particles of iodized oil embolized peripheral arterial branches, arterial branches, while gelatin sponge obliterated more proximal feeding arteries. The combined use of these materials also prevented early release of the chemotherapeutic agent from the iodized oil that was lodged in the tumor vessels.[8] Lipiodol was first utilized as carrier of anticancer agents as SMANCS/LIPIODOL by Maeda *et al.*[9] in 1979. SMANCS consisted of SMA (styrene maleic anhydride copolymer)+ NCS (neocarcinostatin). The molecular weight of SMANCS was reported to be 17000. Reabsorption of SMANCS from blood vessels is difficult but it can be absorbed absolutely by lymphatic vessels. Cancer tissues lack lymphatic vessels and SMANCS can remain in the tumor tissue for long time. Konno *et al.*[10] found that hepatic artery infusion of Lipiodol was retained selectively in tumor tissue in 1983. SMANCS and Lipiodol were dissolved together and injected into the feeding artery of the HCC, inducing selective tumor targeting of the anti-cancer agent. Recently, and other anticancer agents, such as Adriamycin (ADM) mitomycin C (MMC) have replaced SMANCS because of easy preparation of the Lipiodol-anticancer drug emulsion. Our results showed that Lipiodol alone has no therapeutic effect, but that a necrotic effect is induced by the retained Adriamycin within the emulsion. However, a question still remains as to whether Lipiodol itself has no embolizing effect or not. If Lipiodol could be accumulated densely within a tumor, it might obliterate tumor vessels and induce cessation of blood supply to the tumor, resulting in tumor necrosis. Further investigations should be carried out to answer this question.

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