

# BILOMA FOLLOWING TRANSCATHETER ARTERIAL CHEMOEMBOLIZATION WITH MICROSPHERES: A CASE REPORT

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We report a case of intrahepatic biloma following transcatheter arterial chemoembolization (TACE) with microspheres in a 44-year-old male patient. He was diagnosed with hepatocellular carcinoma with satellite nodules and intrahepatic duct invasion in August 2004. TACE was performed with a mixture of lipiodol, epirubicin hydrochloride, and mitomycin followed by microspheres as devascularizing material. Local external irradiation was performed on the area of intrahepatic duct invasion after the first TACE. Owing to local tumor progression and growth of new tumor nodules, a series of TACEs were performed. However, fever and diarrhea developed 2 weeks after the third TACE. Biloma with infection was diagnosed and was then treated successfully with percutaneous drainage and antibiotics. Embolization using microspheres at the proximal right hepatic artery was considered to have been the jeopardizing etiologic factor of biloma formation.

**Key Words:** biloma, hepatocellular carcinoma, microspheres, transcatheter arterial chemoembolization

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Biloma is an encapsulated bile collection outside the biliary tree due to bile leakage [1]. It has been reported to occur as a result of all kinds of biliary injury owing to procedures such as biliary surgery [2], cholecystectomy [3,4], percutaneous biliary drainage, endoscopic retrograde cholangiopancreatography (ERCP), transcatheter arterial chemoembolization (TACE), percutaneous ethanol injection, and radiofrequency ablation [5]. The development of biloma after TACE is closely related to chemoembolic agents [6]. TACE-related

biloma using microspheres has not been previously reported. Herein, we report a 44-year-old man with hepatocellular carcinoma who developed an intrahepatic biloma post embolization with microspheres as a devascularizing agent.

## CASE PRESENTATION

A 44-year-old man, a carrier of chronic hepatitis B, was found to have a 12-cm tumor with satellite nodules in the anterior superior segment (S8) of the right hepatic lobe with local intrahepatic duct invasion in August 2004. Hepatocellular carcinoma was validated by pathologic examination. Surgical resection was not preferred. He received TACE for major tumor in August 2004. Another 5,000 Gy dosage of irradiation was given for bile duct invasion 10 days later.

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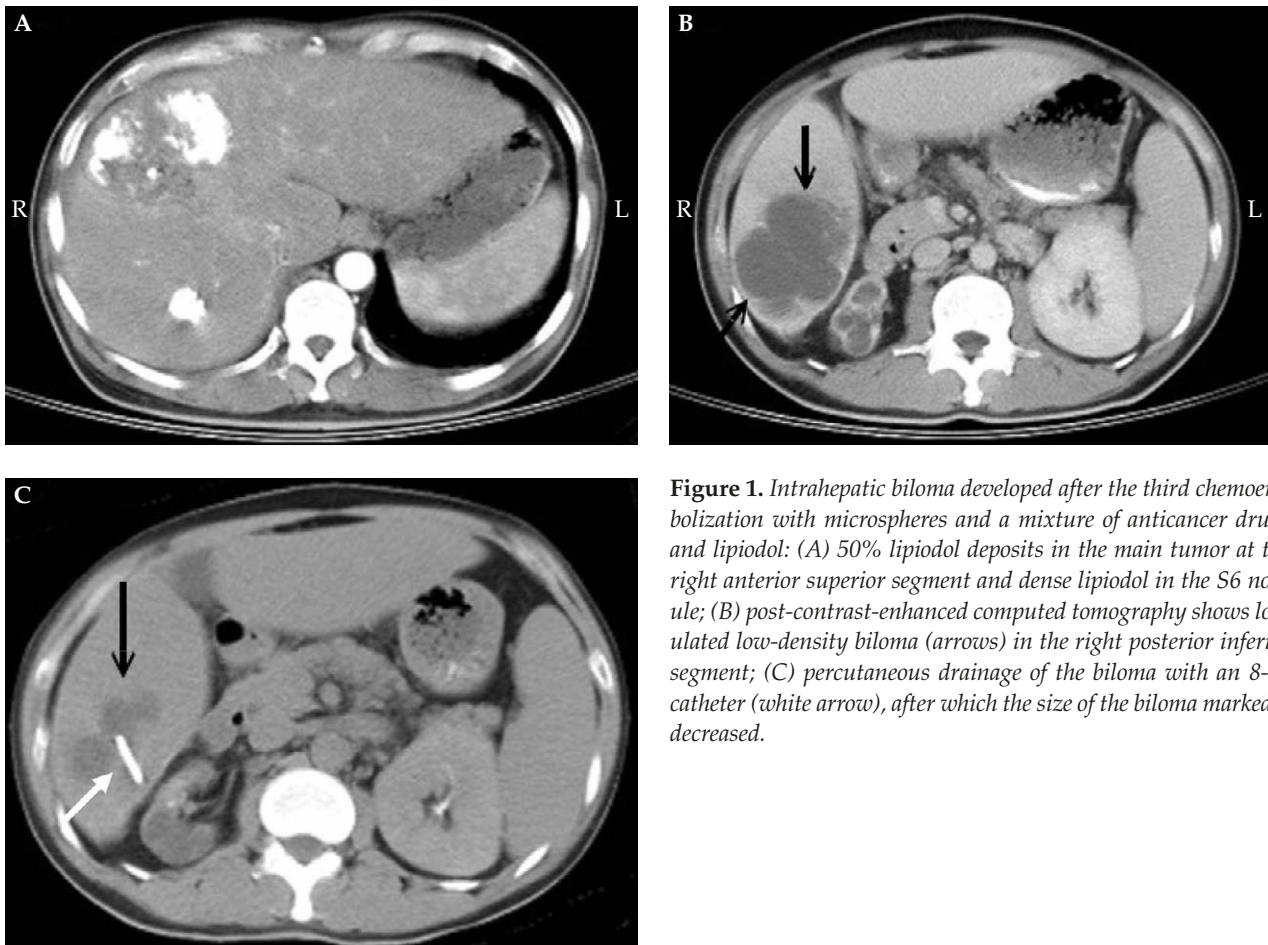
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The embolization agents used in the first TACE session were a mixture of 14 mL lipiodol (Andre Guebet, Aulany-sous-Bois, France), 8 mg mitomycin (Kyowa, Tokyo, Japan) and 40 mg epirubicin hydrochloride (Pfizer, Milan, Italy), followed by microspheres (BioSphere Medical, Roissy CDG Cedex, France) ranging in size between 100 and 300  $\mu\text{m}$  ( $n=4$  mL) as well as 300 and 500  $\mu\text{m}$  ( $n=1$  mL) via the right anterior hepatic artery. No further invasion of the intrahepatic duct was found after the above treatment was given. The main tumor remained the same size with 50% lipiodol deposits at post-embolization computed tomography (CT) evaluation, which revealed a partial embolization result. Another angiography was performed in November 2004, which showed only minor residual tumor. TACE was again performed, with a mixture of 3 mL lipiodol, 3 mg mitomycin and 20 mg epirubicin hydrochloride followed by microspheres ranging in size between 40 and 120  $\mu\text{m}$  ( $n=1.4$  mL) via the right anterior superior hepatic artery. Six months later, CT revealed one new nodule at the

superior portion of the posterior segment of the right hepatic lobe (S7) with suspicious viable tumor part. A third TACE was performed via the right hepatic artery, with a mixture of 4 mL lipiodol, 20 mg epirubicin hydrochloride, and 4 mg mitomycin followed by microspheres ranging in size between 100 and 300  $\mu\text{m}$  ( $n=1$  mL).

Two weeks after the third TACE session, the patient's condition became complicated with fever, epigastric pain, and watery diarrhea. Initial laboratory findings showed elevated total bilirubin and C-reactive protein. The white blood cell count had also increased to 32,360/ $\mu\text{L}$ . Abdominal CT disclosed the same findings as the previous TACE of lipiodol deposition at S8 main tumor and a dense lipiodol deposit at S6 new nodule (Figure 1A). However, a newly lobulated low-density mass was also noted over the right posterior segment (S6) of the liver just below the dense lipiodol deposit (Figure 1B). Echo-guided percutaneous drainage was performed and bilious fluid (120 mL) along with debris was extracted. CT scan



**Figure 1.** Intrahepatic biloma developed after the third chemoembolization with microspheres and a mixture of anticancer drugs and lipiodol: (A) 50% lipiodol deposits in the main tumor at the right anterior superior segment and dense lipiodol in the S6 nodule; (B) post-contrast-enhanced computed tomography shows lobulated low-density biloma (arrows) in the right posterior inferior segment; (C) percutaneous drainage of the biloma with an 8-Fr catheter (white arrow), after which the size of the biloma markedly decreased.

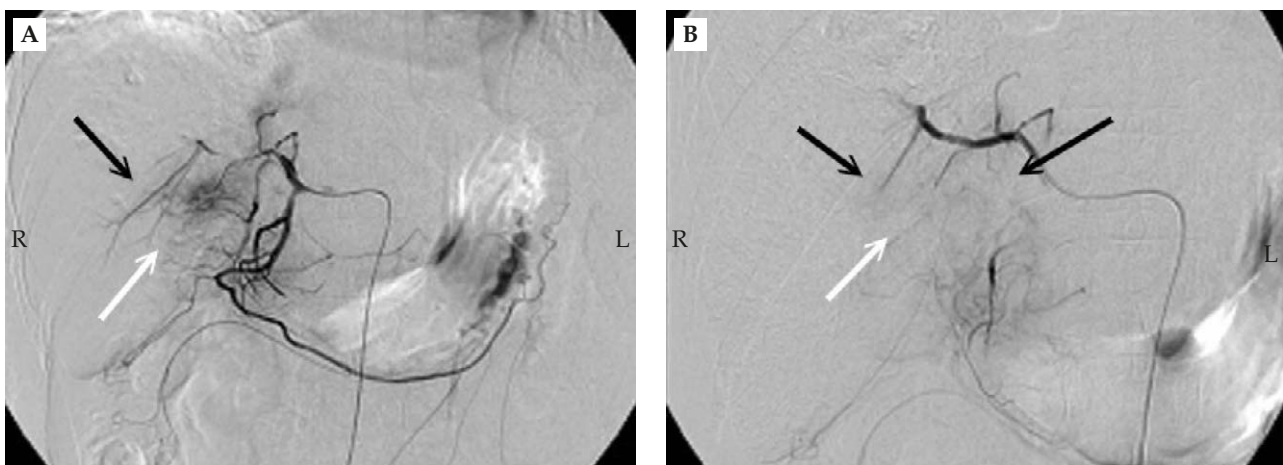
immediately after the drainage procedure revealed collapse of the cystic mass (Figure 1C). Culture of the drained fluid revealed *Klebsiella pneumoniae*. Biloma with infection was diagnosed. He was then treated with intravenous cefmetazole sodium (Sankyo, Tokyo, Japan) 1 g every 6 hours for 6 weeks, and subsequent oral cefaclor (TBC, Taoyuan, Taiwan) 500 mg three times daily for another 2 weeks. During the hospitalization period, his fever fluctuated for 3 weeks and gradually returned to normal. His white blood cell count slowly declined from a peak of 32,360/ $\mu$ L to 8,140/ $\mu$ L over 2 weeks. His C-reactive protein levels on admission and 2 weeks later were 218.2 and 74.5  $\mu$ g/mL, respectively. Total bilirubin levels were 3.7 and 1.81 mg/dL, respectively. Bile was drained with a daily amount > 100 mL for 20 days, and then this decreased. Shrinkage of the biloma was achieved 2 months later and the catheter was eventually removed.

## DISCUSSION

TACE is widely used in the treatment of hepatic tumors. The complications of TACE include acute hepatic failure, liver infarction or abscess, intrahepatic biloma, multiple intrahepatic aneurysms, cholecystitis, splenic infarction, gastrointestinal mucosal lesions, pulmonary embolism or infarction, tumor rupture, variceal bleeding, and iatrogenic dissection or perforation of the celiac artery and its branches [7].

Intrahepatic biloma is one of the major complications that can result in severe illness such as abscess or sepsis [5]. Sakamoto et al reported that the incidence of intrahepatic biloma post TACE was 0.87% (20/2,300 patients) [7]. The risk is probably high when TACE is performed by using "small-sized" emboli. Although the pathogenesis of biloma after chemoembolization is not completely understood, the microvascular damage of peribiliary capillary plexus which results in bile duct necrosis and bile leakage is considered the most likely mechanism [8–10]. Microsphere size < 60  $\mu$ m may allow them to enter the peribiliary plexus and cause microscopic injury [11]. Areas of bile duct injuries or biloma should be closed to the area of TACE [8].

In our patient, development of intrahepatic biloma was in the area of smaller recurrence as distinct from the main tumor. During the previous two TACEs, super-selective embolization was performed via the right anterior branches. In contrast, the third TACE was performed via the right hepatic artery in order to cover the newly grown tumors located at the posterior segments (Figure 2A). Owing to a decrease of the main tumor burden, it is possible that a greater amount of embolization agents went into the posterior branch of the right hepatic artery, resulting in biloma developing there. Angiography immediately after the third TACE showed obliteration of most of the distal branch of the right hepatic artery correlated with the development of biloma (Figure 2B). Irradiation might contribute to the development of biloma; however,



**Figure 2.** Arteriography reveals some tumor stains over the right hepatic lobe. The third TACE was performed via the right hepatic artery with a mixture of 4 mL lipiodol, 20 mg epirubicin hydrochloride, and 4 mg mitomycin followed by microspheres ranging in size between 100 and 300  $\mu$ m ( $n=1$  mL). (A) Pre-embolization: the tumor burden (white arrow) and the distal branch of the right hepatic artery (black arrow) were enhanced by contrast media. (B) Post-embolization: angiography shows disappearance of tumor stain (white arrow) and obliteration of the branches of the right hepatic artery (black arrows).

irradiation had been performed 7 months previously and had targeted the right anterior branch of the bile duct, which was not correlated with the position of the biloma. Thus, it was not considered the primary cause of the biloma in this case.

Microspheres are spherical-shaped polyvinyl alcohol embolic devices that provide targeted vascular occlusion or reduction of blood flow within target vessels. The characteristics of microspheres are lack of aggregation, smoothness and possession of a hydrophilic surface, all of which should result in a lower rate of complications [12]. According to general medical opinion, microspheres that range in size between 100 and 300  $\mu\text{m}$  are too large to obstruct the peribiliary plexus artery, and injury to the bile duct should thus not occur. However, in our patient, the development of biloma was closely related to the time of embolization that included use of microspheres. Embolization using microspheres at the proximal right hepatic artery was considered to have been the jeopardizing etiologic factor of biloma formation in this patient.

In conclusion, the development of biloma might occur with current medical procedures and techniques; new agents that have fewer side effects or complications have yet to be developed. This case shows the importance of a delicate approach to avoid this uncommon complication, and the necessity of close observation of any patient receiving embolization using any kind of embolization agent.

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# 經肝動脈化學栓塞使用 *Microspheres* 併發膽汁瘤 — 病例報告

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我們報告一位 44 歲男性肝癌患者，使用 *microspheres* 施行經肝動脈化學栓塞療法後發生膽汁瘤。他是在 2004 年 8 月被診斷出肝癌並且合併肝內膽管侵犯。患者隨即接受經肝動脈化學栓塞治療，使用 *lipiodol* 混合 *epirubicin hydrochloride* 及 *mitomycin* 並以 *microspheres* 作為血管阻斷藥物。在第一次肝動脈栓塞治療之後加上局部放射線治療肝內膽管侵犯部分。由於追蹤發現長出新腫瘤，患者後來又接受一系列肝動脈栓塞治療。在第三次栓塞治療後二星期出現發燒及腹瀉的情形，診斷為膽汁瘤合併感染，隨即以抗生素及引流治療。我們認為使用 *microspheres* 栓塞近端右肝動脈是誘發導致膽汁瘤的危險原因。

**關鍵詞：**膽汁瘤，肝癌，*microspheres*，經肝動脈化學栓塞

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