

# Excretion of Necrotic Hepatocellular Carcinoma Tissues into Hepatic Lymphatic Vessels after Conventional Transarterial Chemoembolization

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## Abstract

We report a case of necrotic hepatocellular carcinoma tissue excretion into the hepatic lymphatic system after conventional transarterial chemoembolization (cTACE) in an 80-year-old man with liver cirrhosis. A tumor measuring 19 mm in diameter in segment 5 was successfully treated with superselective cTACE. Hepatic lymphatic vessels were not opacified with iodized oil during the procedure. Computed tomography (CT) performed 1 week after cTACE showed dense accumulation of iodized oil in the tumor and in the surrounding liver without opacification of the hepatic lymphatics. Excretion of necrotic tumor tissues containing iodized oil into the lymphatic system was initially observed on CT 9 months after cTACE and the amount of excreted tumor tissues had increased 2 years and 2 months after cTACE without tumor recurrence or any clinical symptoms.

**Key words:** Hepatocellular carcinoma, transarterial chemoembolization, iodized oil, hepatic lymphatic vessel

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## Introduction

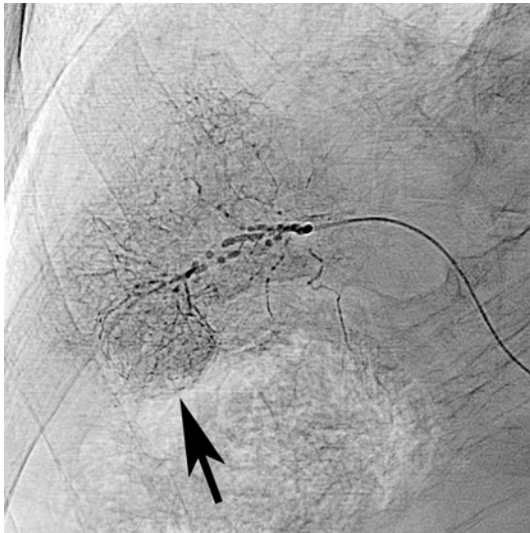
Conventional transarterial chemoembolization (cTACE) using iodized oil and gelatin sponge particles can achieve complete necrosis of hepatocellular carcinoma (HCC) and peritumoral necrosis by blocking the arterial and portal blood supply to tumors [1]. Hence, iodized oil is densely retained in the necrotic areas of HCC for a long time. Necrotic tumor tissues are slowly absorbed and eliminated, and the tumor gradually decreases in size [2]. Occasionally, necrotic tumor tissues adjacent to a large bile duct are excreted into the biliary system and are visualized as high-density materials in the bile duct on computed tomography (CT) [3].

Although the aforementioned clinical course is typical of

HCC lesions treated with cTACE, we encountered a patient in whom cTACE-necrotized HCC tissues were excreted into the hepatic lymphatic vessels. To the best of our knowledge, there have been no reports describing such a phenomenon. Here, we report the clinical course of a necrotic HCC nodule after cTACE in a patient.

## Case Report

An HCC nodule measuring 19 mm in diameter was observed in segment 5 on screening CT in an 80-year-old man with liver cirrhosis associated with hepatitis C. His liver function was Child-Pugh score 6. The levels of serum tumor markers, such as alpha-fetoprotein (3.9 ng/mL) and protein induced by the absence of vitamin K or antagonist II (14 mAU/mL), were not elevated. The patient had previously



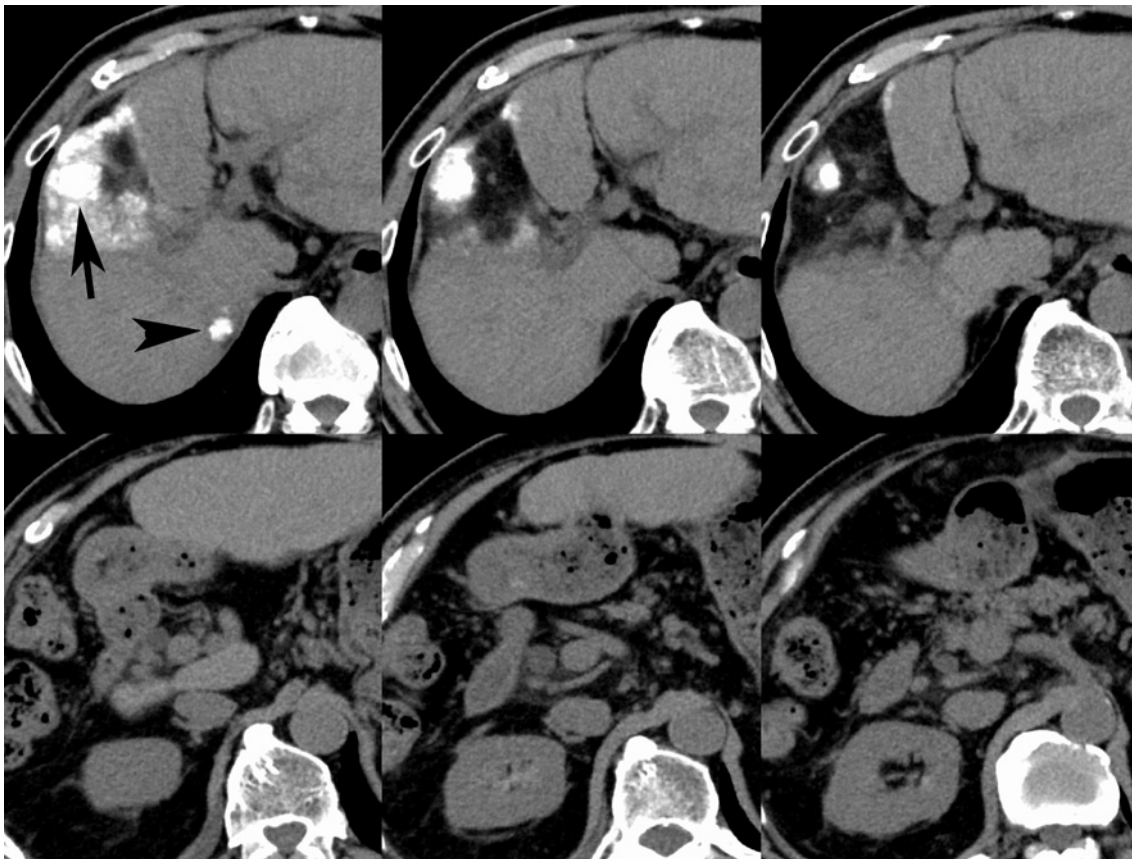
**Figure 1. Spot radiograph during third conventional transarterial chemoembolization (cTACE)**

A branch of the anterior-inferior subsegmental artery of the right hepatic artery was selectively embolized. Hepatic lymphatic vessels are not observed during cTACE. The arrow indicates the tumor.

undergone cTACE for a tumor 7 years ago and cTACE with radiofrequency ablation (RFA) for two newly developed tumors 2 years ago. We also performed cTACE for the treatment of a newly developed HCC nodule. Written informed consent was obtained before the procedure.

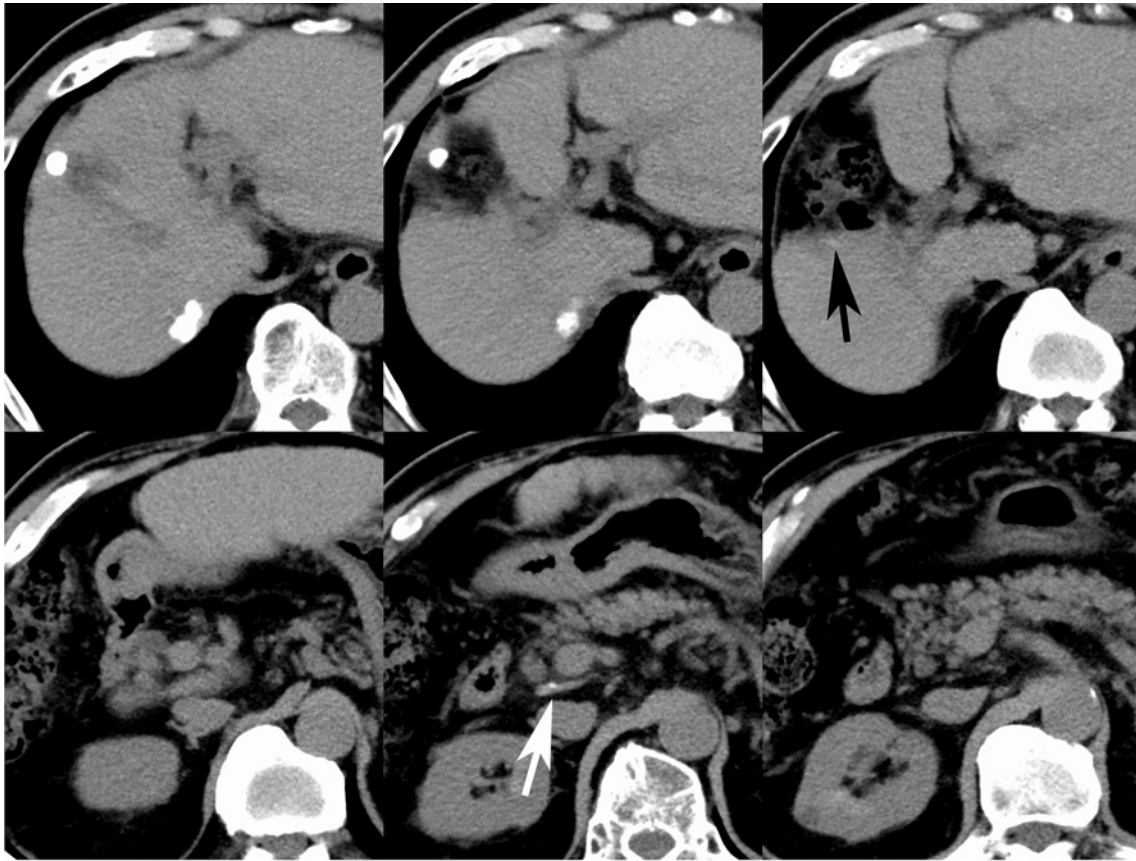
Third superselective cTACE was performed at a branch of the anterior-inferior subsegmental artery of the right hepatic artery using 2 mL of iodized oil (Lipiodol 480; Guerbet Japan, Tokyo, Japan), 10 mg of epirubicin (Farmorbicin®; Pfizer, Tokyo, Japan), and 2 mg of mitomycin C (Mitomycin; Kyowa Hakko Kirin, Tokyo, Japan), followed by a gelatin sponge slurry of approximately 0.2-0.5 mm diameter that was produced from gelatin sponge particles measuring 1 mm (Gelpart, Nippon Kayaku, Tokyo, Japan) using a pumping method. Hepatic lymphatic vessels were not opacified with iodized oil during cTACE (Fig. 1).

Unenhanced CT performed 1 week after third cTACE showed dense accumulation of iodized oil in a limited area including the tumor. Inflow of iodized oil into the lymphatic vessels was not observed (Fig. 2). Subsequently, dynamic CT and magnetic resonance imaging (MRI) were performed every 3-6 months after cTACE to evaluate tumor recurrence. At 6 months after third cTACE, no tumor recurrence was observed. Moreover, iodized oil was not observed in the



**Figure 2. Unenhanced computed tomography performed 1 week after third conventional transarterial chemoembolization (cTACE)**

Iodized oil is densely accumulated in a limited area including the tumor (arrow). However, it is not retained in the lymphatic system. The arrowhead indicates a previously embolized tumor by second cTACE.



**Figure 3.** Unenhanced computed tomography performed 9 months after third conventional trans-arterial chemoembolization (cTACE)

Iodized oil is densely accumulated in the tumor and a small amount of high-density material is observed at the liver surface (black arrow) and in the lymphatic system within the hepatoduodenal ligament (white arrow).

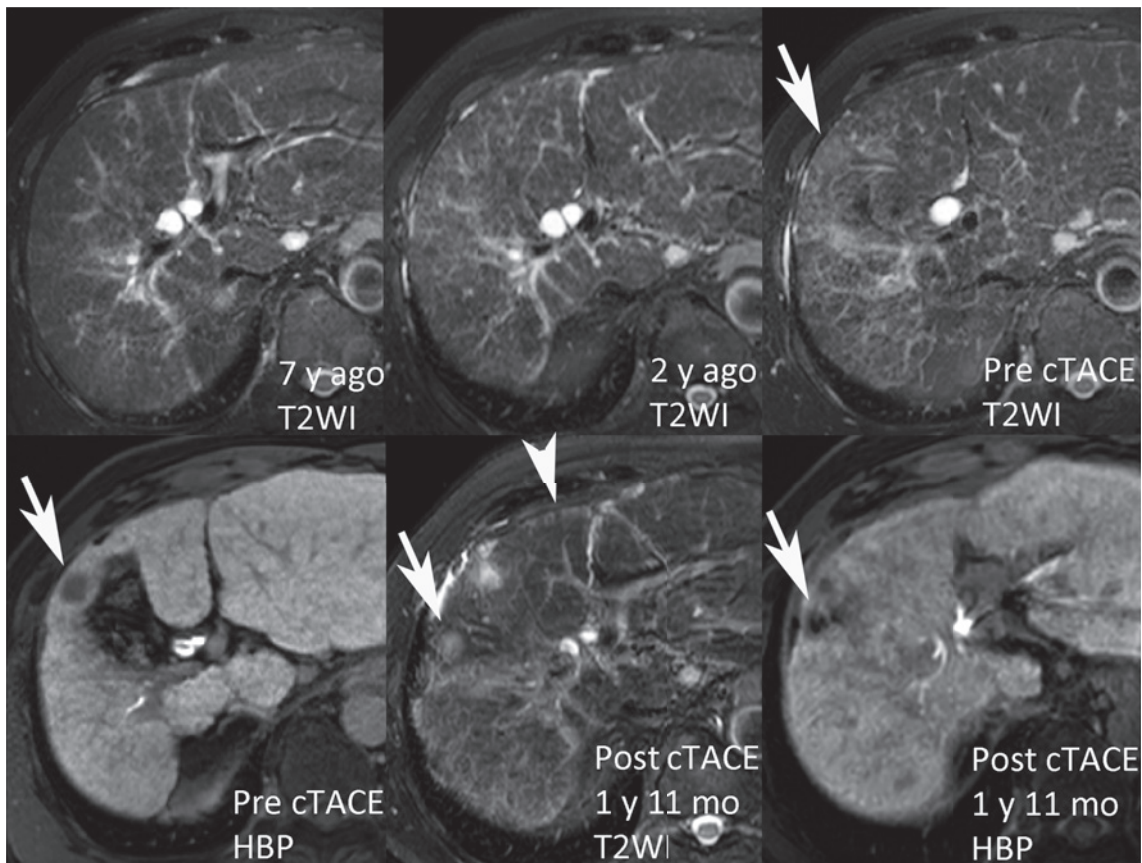
lymphatic vessels. However, CT third performed 9 months after third cTACE showed a small amount of high-density material, considered to be necrotic tumor tissues containing iodized oil, at the liver surface and in the lymphatic systems within the hepatoduodenal ligament (**Fig. 3**). During the follow-up period, the patient exhibited no clinical symptoms such as fever or abdominal pain. Subsequently, the tumor decreased in size and the amount of necrotic tumor tissues in the lymphatic system gradually increased on serial follow-up CT examinations. MRI performed 1 year and 11 months after third cTACE showed the elevation of signal intensity of the embolized tumor on T2-weighted images compared to that in the pre-treatment image, suggesting liquefied tumor necrosis. Hepatic necrosis was not observed around the tumor on the hepatobiliary phase. Additionally, reticular hyperintensity along the portal tracts and the liver surface was observed mainly in the right hepatic lobe on T2-weighted images. It was also observed on MRI performed 7 years before third cTACE, immediately before the first HCC treatment, and gradually became prominent during the follow-up (**Fig. 4**). CT performed 2 years and 2 months after third cTACE revealed that the tumor had shrunk without recurrence and the necrotic tumor tissues were markedly excreted into the lymphatic systems within the hepatoduodenal

ligament through the hepatic lymphatic vessels without any clinical symptoms (**Figs. 5 and 6**).

## Discussion

The liver is the largest lymph-producing organ, accounting for 25%-50% of the lymph passing through the thoracic duct [4]. Especially in a cirrhotic liver, an increase in the formation of new lymphatic vessels due to an increase in lymph production up to 30-fold [5]. The hepatic lymphatic system helps remove the waste products, immune cells derived from the sinusoidal microcirculation, hepatocytes, and non-parenchymal cells in the form of lymph by transporting it through the lymphatic vessels to the draining lymph nodes [4].

In a previous report, hepatic lymphatic vessels were opacified with iodized oil in 3.1% of tumors during ultraselective cTACE (defined as cTACE performed at the most distal portion of the tumor-feeding subsegmental hepatic artery) without any clinical symptoms [6]. Hepatic lymphatic vessels are likely to be opacified when ultraselective cTACE is performed in a highly limited area. It has been suggested that dilation of lymphatic vessels caused by liver cirrhosis and/or pre-existing lymphatic-vessel communica-



**Figure 4.** Serial magnetic resonance imaging examinations before and after third conventional transarterial chemoembolization (cTACE)

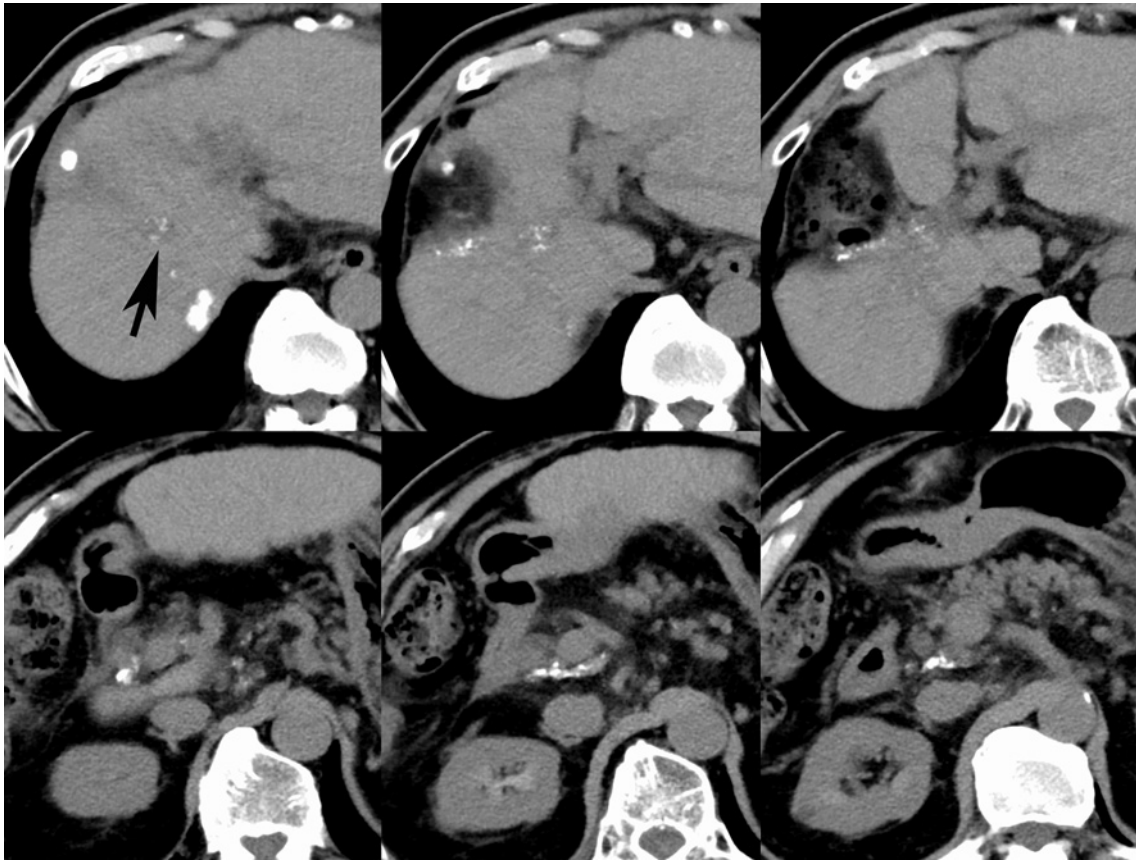
Gadoteric acid-enhanced magnetic resonance imaging (MRI) performed 1 year and 11 months after cTACE shows elevated signal intensity of the embolized tumor, suggesting liquefied tumor necrosis on T2-weighted imaging and no hepatic necrosis around the tumor on the hepatobiliary phase. Additionally, reticular hyperintensity along the portal tracts, mainly in the right hepatic lobe, had been observed on T2-weighted MRI performed 7 years before third cTACE, immediately before the treatment of the first hepatocellular carcinoma, and gradually became prominent during the follow-up. It is also observed at the liver surface (arrowhead) on T2-weighted MRI 1 year and 11 months after third cTACE. Moreover, the right hepatic lobe gradually shrank during the follow-up. Arrows indicate the tumor.

tions in individual patients may influence the visualization of lymphatic vessels, in addition to the magnitude of cTACE [6]. However, the present case is different from the previously reported cases as opacification of the hepatic lymphatic vessels with iodized oil was not observed during cTACE or on CT performed 1 week after cTACE.

In HCC tissues treated with cTACE, iodized oil is retained in the lumen of the tumor microvasculature and in the extracapillary space [2]. The mechanism of iodized oil accumulation in the microvasculature is believed to be related to the viscosity and the surface tension of iodized oil emulsions. The reason for iodized oil retention in the extracapillary space is believed to be slow decomposition and absorption of iodized oil due to the lack of a reticuloendothelial or lymphatic system in the HCC tissue [7]. In contrast, a study on the biodistribution of radiolabeled lipids showed that the bile is the major route by which iodized oil is excreted from the liver parenchyma [7]. Additionally, iodized oil in the

liver parenchyma is recovered via the lymphatic system due to its lipid nature.

It is unclear why necrotic tumor tissues containing iodized oil were suddenly excreted into the lymphatic vessels 9 months after cTACE despite the lack of a lymphatic system in the tumor. To the best of our knowledge, this is the first report demonstrating excretion of necrotic HCC tissues containing iodized oil into the lymphatic system. The hepatic lymphatic vessels can theoretically remove necrotic HCC tissues from the liver; however, this route is unusual as there are no connections between the tumor and the lymphatic system. There is a possibility that hepatic necrosis by cTACE might result in a connection between the tumor and the lymphatic system. However, hepatic necrosis usually develops within a few days after cTACE; therefore, the connection might be created early after cTACE. In the present case, excretion of necrotic tumor tissues into the lymphatic system was initially revealed on CT 9 months after cTACE.



**Figure 5.** Unenhanced computed tomography performed 2 years and 2 months after third conventional transarterial chemoembolization. The tumor with iodized oil accumulation has shrunk without recurrence. Necrotic tumor tissues are markedly excreted into the lymphatic systems within the hepatoduodenal ligament and refluxed into the hepatic lymphatic vessels (arrow).

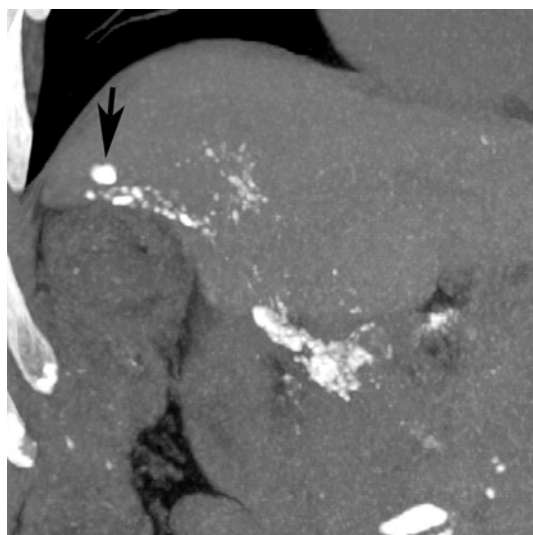
Therefore, we speculate that chronic inflammation caused by cTACE might have created a direct connection between the tumor and the neighboring lymphatic vessels. The fistula between the tumor and the lymphatic vessels might gradually enlarge, consequently leading to the excretion of liquified HCC tissues into the lymphatic vessels.

The tumor location and the degree of development of hepatic lymphatic vessels may also contribute to the occurrence of this rare phenomenon. There are two lymphatic systems in the liver: a superficial system beneath the capsule is connected via lymphatic channels to a deep lymphatic system, which courses along the portal channels [8]. The deep lymphatic system originates in the prelymphatic spaces—the space of Disse and the space of Mall—and runs in the Glisson's sheath. The deep lymphatic plexuses follow the portal vein, bile duct, and hepatic artery to the edge of each lobule of the liver. The two systems join together as larger collecting vessels that exit the liver at the hilus. These vessels enter lymph nodes in the region of the hilus and hepatoduodenal ligament, where they are joined by lymphatic vessels from the extrahepatic biliary tract [8].

Dilatation of lymphatic vessels in the portal tract, edema, ductular proliferation, and inflammatory cell infiltration have been demonstrated as intrahepatic periportal hyperintensities

on T2-weighted MRI [9]. In the present case, T2-weighted MRI demonstrated reticular hyperintensity along the portal tracts and the liver surface, mainly in the right hepatic lobe. These findings might indicate dilated hepatic lymphatic vessels in the Glisson's sheath and the liver capsule. Our patient also had a tumor in the subcapsular area of the liver where dilated lymphatic systems were present. Such specific backgrounds might facilitate the connection between the tumor and the superficial lymphatic system. The patient also had a history of two cTACE sessions for HCC. However, the connection between the tumor and the lymphatic system did not develop after previous treatments, although one of the two tumors developed 2 years ago was also located at the liver surface (Fig. 2) where the lymphatic vessels were already dilated (Fig. 4). For the aforementioned tumor, additional RFA was performed after previous cTACE. Therefore, the lymphatic vessels around the tumor might have been simultaneously ablated by RFA, and hence, the connection between the tumor and the lymphatic system might not have developed.

The clinical significance of this phenomenon is unclear. If viable tumor cells are present in the excreted tumor tissues, lymph node metastasis may develop in the future [10]. However, we postulate that complete tumor necrosis could



**Figure 6. Coronal view of a thick-slab maximum intensity projection image of unenhanced computed tomography performed 2 years and 2 months after third conventional transarterial chemoembolization**

**Iodized oil is clearly visible in the hepatic lymphatic vessels and in the lymphatic systems within the hepatoduodenal ligament. The arrow indicates the tumor with iodized oil accumulation.**

be achieved by superselective cTACE because serial CT images showed that iodized oil was retained densely and uniformly throughout the HCC nodule for a long time. Therefore, the risk of lymph node metastasis may be extremely low. However, further observations are required to determine the clinical importance of this phenomenon.

In summary, we report a case of a patient in whom necrotic HCC tissues containing iodized oil were excreted into the lymphatic system 9 months after cTACE. This phenomenon may be rare; however, we believe that hepatic lymphatic vessels can remove necrotic tumor tissues from the liver when a connection between the tumor and the lymphatic system is created by chronic inflammation due to cTACE.

**Conflict of interest:** The authors declare that they have no conflicts of interest and funding to report.

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