Case Report

Pulmonary Lipiodol Embolism after Transcatheter Arterial Chemoembolization for Hepatocellular Carcinoma: A Case Report and Literature Review

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Acute pulmonary lipiodol embolism is a rare but possibly fatal complication of transcatheter arterial chemoembolization (TACE). The authors report a 63-years-old woman with unresectable large (7.4 x 7.9 cm) hepatocellular carcinoma (HCC) who had been diagnosed pulmonary lipiodol embolism after the first TACE. Intraoperative angiography did not show the communication between pulmonary circulation and tumor feeding artery. After lipiodol injection, she developed oxyhemoglobin desaturation immediately and chest computed tomography (CT) angiography showed lipiodol embolism at basal segments of both lower lobes. She also developed fever after TACE without any evidence of infection. Oxyhemoglobin desaturation had improved to baseline spontaneously within 7 days. Fever persisted for 16 days. Two weeks after TACE, follow-up CT of liver revealed the absence of almost lipiodol granule in lungs. The patient did not receive TACE again because of pulmonary metastasis. In this article we reviewed the cases of pulmonary lipiodol embolism that had been reported in the literature including clinical risk factors, possible mechanisms and the pathophysiology of this complication.

Keywords: *Hepatocellular carcinoma, Chemoembolization, Pulmonary lipiodol embolism*

J Med Assoc Thai 2013; 96 (Suppl. 2): S270-S275
Full text. e-Journal: *http://jmat.mat.or.th*

Transcatheter arterial chemoembolization (TACE) is a standard treatment and widely used in the Child-Pugh A and B patients with large/multifocal, intermediate-stage hepatocellular carcinoma (HCC) in which the randomized controlled study showed a survival benefit[1]. The procedure is minimally invasive, widely indicated and relatively safe. The common complication of TACE is post embolization syndrome which is usually not severe. However the uncommon, potentially serious complication may occur unexpectedly possibly leading to death. The study of Xia et al[2] hasshown that the incidence of severe or rare complications after TACE is 2.68% (54/2012). The uncommon complications included spontaneous rupture of tumor, perforation of duodenum, liver abscess, pulmonary embolization, spasm of hepatic artery, hepatic artery occlusion, bile duct complication, femoral nerve injury and acute renal failure[2].

The incidence of symptomatic pulmonary lipiodol embolism was reviewed in the literature ranging from 0.05-1.8%[2-5]. However, Kita et al has demonstrated that 23% (3 out of 13 patients) of the patients' perfusion lung scans after TACE showed perfusion defects, but these patients were asymptomatic and their perfusion defects had disappeared by 4 weeks later[6].

In this article the authors report a case with pulmonary lipiodol embolism after TACE. In addition, the authors review the cases of pulmonary lipiodol embolism that had been reported in the literature including clinical risk factors, possible mechanisms and the pathophysiology of this complication.

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Case Report

A 63-year-old woman without a history of preexisting liver disease came to Siriraj Hospital in August 2011 with progressive right upper quadrant pain for 2-3 months. Physical examination was unremarkable. Ultrasonography of abdomen showed an 8-cm liver mass. Magnetic resonance (MR) imaging of abdomen revealed two matted liver masses at segment 8 and 5 measuring about 7.4 x 7.9 cm and 5.8 x 5.0 cm in size respectively with typical enhancement of HCC. Tumors invaded anterior branch of right portal vein, middle and right hepatic vein and probably the proximal hepatic inferior vena cava (IVC). She was newly diagnosed of HCV infection. Her serum alpha-

fetoprotein (AFP) level was 46,850 IU/ml and hepatic function was classified as A according to Child-Pugh classification. This HCC is inoperable because of portal and hepatic vein invasion so TACE was offered to the patient.

She was admitted for first TACE one week later. The chest x-ray before TACE showed neither definite pulmonary infiltration nor pulmonary nodule (Fig. 1). Her oxyhemoglobin saturation, measured by pulse oxymeter, at room air was 98%. She had no fever on admission.

Angiography revealed a huge tumor mass located in the right hepatic lobes with neovascularization and hypervascularization which was supplied by right hepatic artery (RHA) without arteriovenous (AV) shunting. TACE was performed via the RHA using a non-ionic dye (omnipaque 350 100 ml). Mixture of mitomycin-C (20 mg plus lipiodol 5 ml), 5-FU (500 mg plus lipiodol 5 ml), extradose of lipiodol (8 ml) and gel foam embolization were done. Her angiography is shown in Fig. 2.

Fifteen minutes after the lipiodol injection, the patient developed oxyhemoglobin desaturation, her oxygen saturation at room air was dropped from 98% to 90% but she had no shortness of breath, cough, hemoptysis and her hemodynamic status was competent. Her oxyhemoglobin desaturation had been improved with oxygen cannula (3 liters per minute) to 95%. The chest radiograph after TACE showed plate-liked atelectasis at the basal lungs, minimal right pleural effusion and elevated right dome of diaphragm with lipiodol staining (Fig. 3). She developed fever of 39 degrees Celsius without source of infection which then was diagnosed as post embolization syndrome and non-steroidal anti-inflammatory drug (NSAIDs) was prescribed.

The CT angiography post TACE for 4 days (Fig. 4) showed high density material deposition at right basal lung and posterior basal segment of left lung

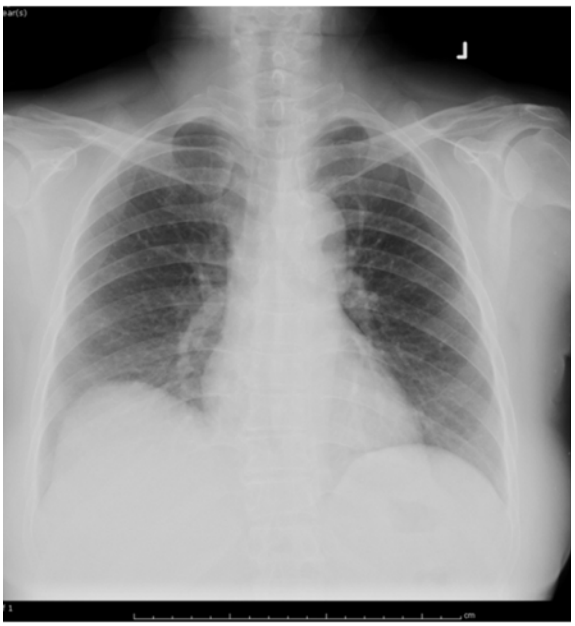

Fig. 1 Chest x-ray before TACE

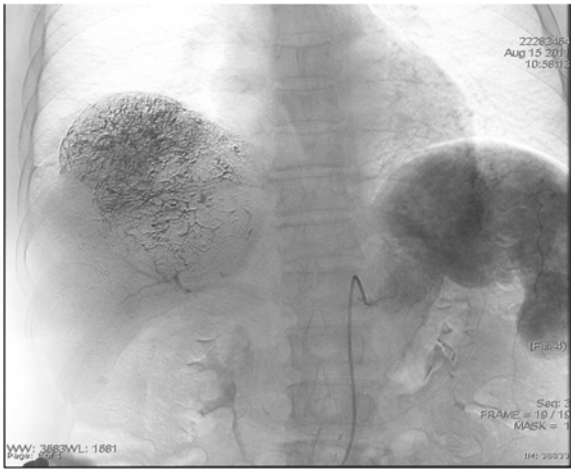

Fig. 2 Angiography shows large tumor at right hepatic lobe without AV shunt

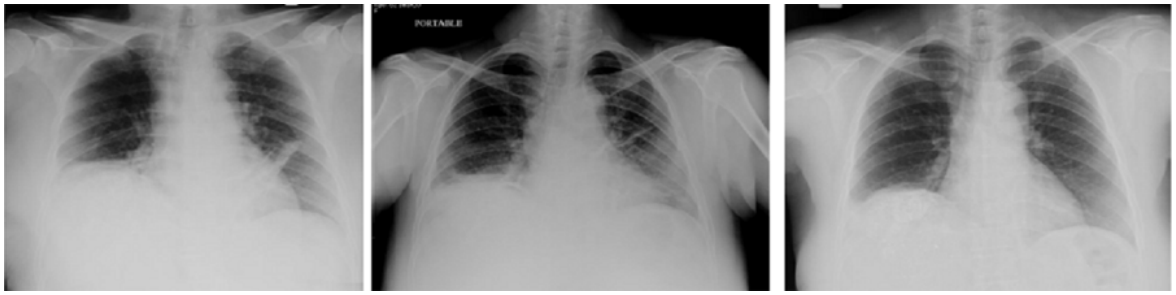

Fig. 3 CXR showed immediate post TACE (Left), post TACE day 3 (middle), and 1 week after TACE (right)

with surrounding atelectasis compatible with pulmonary lipiodol embolism.

The main treatment is supportive care including oxygen therapy, pulmonary rehabilitation and using incentive spirometry to correct atelectasis. The patient did not develop respiratory failure or acute respiratory distress syndrome. Oxyhemoglobin saturation by pulse oxymeter was improved to baseline in 7 days whereas fever persisted for 16 days.

After discharge from the hospital for 2 weeks, the follow-up 3-phase CT of liver showed the residual viable HCC at right hepatic lobe and the absence of almost lipiodol granules at the basal lungs (Fig. 5). The patient did not receive TACE again because of pulmonary metastasis.

Discussion

Pulmonary lipiodol embolism, first reported

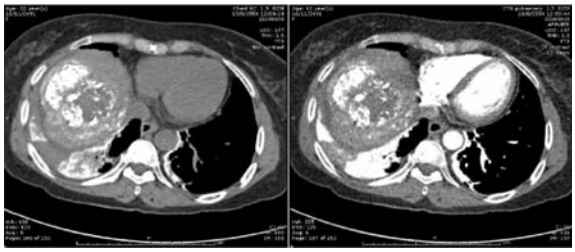

Fig. 4 CT with (right) and without (left) contrast showed lipiodol deposition at bilateral lower lung fields

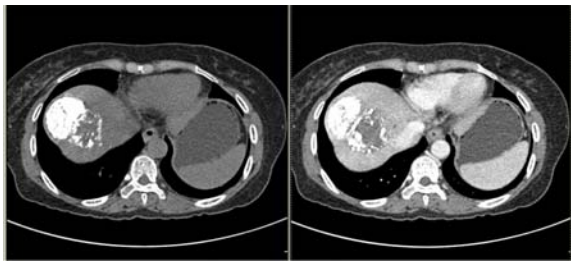

Fig. 5 CT scan after TACE for 2 weeks showed absence of lipiodol granule in bilateral basal lung fields

Table 1. A summary of case reports published in the literature. (ND = no data, No = No chemotherapy used, TACE = transcatheter arterial chemoembolization, D = Dead, S = Survival, M = Male, F = Female, HCC = Hepatocellular carcinoma, PLC = Primary liver cancer, LO = Lipiodol, C/T = Chemotherapy)

Reference	Patient No.	Sex	Age (years)	Cancer type	Max. tumor size (cm)	TACE method		Symptom onset	Recovery period (days)	Outcome (days)
						LO(ml)	C/T(mg)			
2	1	ND	ND	PLC	ND	25	ND	0.25	-	D
7	2	M	75	HCC	ND	8	40	0.04	12	S
3	3	M	44	HCC	17	40	60	4	28	S
3	4	M	56	HCC	18	30	50	5	14	S
3	5	F	31	HCC	20	30	50	2	21	S
3	6	M	61	HCC	18	26	50	4	-	D
3	7	M	57	HCC	20	25	55	2	14	S
3	8	M	55	HCC	14	22	50	2	10	S
12	9	ND	7	Hepato blastoma	ND	14	50	0^	7	S
8	10	M	27	HCC	10	10	8	4	-	D*
8	11	M	63	HCC	15	17	13	1	14	S
14	12	F	81	HCC	14	15	ND	4	14	S
9	13	F	7	HCC	11	10	ND	0.04	-	D
4	14	M	76	HCC	14.5	40	40	0^	21	S
10	15	F	62	HCC	15	30	50	0^	ND	S
11	16	F	49	HCC	10	ND	ND	1	9	S
5	17	M	80	HCC	10.4	50	No	0.04	ND	S
5	18	F	83	HCC	12.8	20	No	4	ND	S
5	19	M	37	HCC	5	30	50	3	-	D
5	20	F	76	HCC	17	20	60	3	-	D
13	21	M	36	HCC	ND	40	40	ND	ND	S
	Our case	F	63	HCC	8	18	20 + 500#	0.01	14	S

*Pulmonary tumor emboli were found postmortem. ; #MMC + 5-FU; ^ = immediate

by Samejima et al[7] in 1990, is one of the most severe complications after TACE because it may be a life-threatening condition. A summary of the case reports published in the literature is shown in Table 1.

Chung et al reported six patients with symptomatic pulmonary oil embolism having respiratory symptoms of cough, hemoptysis, and dyspnea which developed 2-5 days after transcatheter oily chemoembolization (TOCE)[3]; it could progress to non-cardiogenic pulmonary edema[4] or acute respiratory distress syndrome (ARDS) but this scenario was extremely rare[5].

The mechanism of pulmonary lipiodol embolism is now not well understood. The possible mechanisms of this condition that have been described in the literature are as follows.

1. There is a communication between the tumor feeding artery and hepatic vein and a large amount of lipiodol flowing into the pulmonary artery via the arteriovenous shunt[8] causespulmonary lipiodol embolism.

2. The communication between the tumor feeding artery and the branches of the right pulmonary artery is presented since the tumor invaded into the diaphragm and the lipiodol goes into the branches of the right pulmonary artery through this communication[2].

3. There is a chance of leakage of the agent into the hepatic vein and then into the pulmonary circulation, thus causing pulmonary oil embolization[8]. Risk factors for pulmonary lipiodol embolism after TACE include the dose of iodized oil injected, the presence of AV shunt and trans-inferior phrenic artery embolization. The most important factor is the amount of iodized oil injected, especially if more than 20 ml[4]. There is a significant correlation between the amount of lipiodol and clinical severity of pulmonary injury[4]. Lipiodol can cause the injury of lung through the free fatty acid component, when microemboli obstruct microvascular vessel; unbound free fatty acid is capable of activating the inflammatory cascade and cytokine is released then resulting in pulmonary capillary leakage and non-cardiogenic pulmonary edema[4]. This pathogenesis is similar to fat embolism syndrome induced acute lung injury or ARDS[5].Not only can the free fatty acid cause lung injury but also acarcinostatic drug such as adriamycin can cause pulmonary toxicity; several cases of doxorubicin induced organizing pneumonia have been described[5].

In the present case, HCC is rather small in size (8 cm in maximal diameter)compared to others shown in the summary of case reports of pulmonary lipiodol embolism, the total amounts of injected lipiodol are 18 ml (less than 20 ml) and angiography before TACE did not show AV shunt, but MRI revealed tumors invasion into anterior branch of right portal vein, middle and right hepatic vein and suspected proximal hepatic IVC invasion. Hence the pulmonary lipiodol embolism might develop due to the leakage of lipiodol through the hepatic vein and IVC.

Regarding the prevention of pulmonary lipiodol embolism, we should pay attention to the following points[2]:

1. Whether there is an arteriovenous fistula during the procedure.

2. Notice whether the patient develops cough during procedure.

3. The dose of iodize oil should not exceed 20 ml.

4. Postoperative evaluation of the symptoms of pulmonary embolism, CXR and arterial blood gas analysis should be done to rule out the possibility of pulmonary embolism.

5. Calculate the degree of intrahepatic arteriovenous shunting with technetium Tc99m-labeled macroaggregated albumin (99mTcMAA)[8].

6. Reducing the degree of AV shunt by temporary balloon occlusion of hepatic vein branch with AV shunts in HCC patient with marked AV shunting[4].

There is no therapy that has been shown to be effective for pulmonary lipiodol embolism. Treatment may be symptomatic treatment with respiratory support. High-dose methylprednisolone/corticosteroid can limit local accumulation of free fatty acids, inhibit complement-mediated leukocyte aggregation and block further cytokine storm[4]. Heparin is beneficial in counteracting blood cell aggregation to prevent further arterial occlusion[4]. However, treatment with corticosteroid and heparin has not been shown to reduce the morbidity and mortality associated with this condition[5].

Potential conflicts of interest

None.

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ภาวะสารประกอบไขมันอุดตันหลอดเลือดแดงในปอดภายหลังการฉีดยาเคมีอุดตันหลอดเลือดแดงที่เลี้ยงมะเร็งตับ: รายงานผู้ป่วยหนึ่งราย และบททบทวน

ธรรมพร เนาว์รุ่งโรจน์, ธีรวัฒน์ นาคสงวน, ยิ่งยง ชินธรรมมิตร์

ภาวะสารประกอบไขมันอุดตันหลอดเลือดแดงในปอดภายหลังการฉีดยาเคมีอุดตันหลอดเลือดแดงที่เลี้ยงมะเร็งตับเป็นผลข้างเคียงที่พบน้อยแต่อาจถึงแก่ชีวิต คณะผู้นิพนธ์ได้รายงานผู้ป่วยหญิงอายุ 63 ปี เป็นโรคมะเร็งตับขนาดใหญ่ 7.4x7.9 เซนติเมตร ซึ่งไม่สามารถผ่าตัดออกได้ เกิดภาวะสารประกอบไขมันอุดตันหลอดเลือดแดงในปอดภายหลังการฉีดยาเคมีอุดตันหลอดเลือดแดงที่เลี้ยงมะเร็งตับครั้งแรก การฉีดสีดูหลอดเลือดระหว่างการทำหัตถการไม่พบจุดเชื่อมระหว่างหลอดเลือดแดงในปอดและหลอดเลือดที่เลี้ยงก้อนเนื้องอก ภายหลังการฉีดสารประกอบไขมันผู้ป่วยมีระดับความเข้มข้นออกซิเจนในเลือดลดลงทันที ผลตรวจเอกซเรย์คอมพิวเตอร์ดูหลอดเลือดในปอดพบส่วนประกอบไขมันอุดตันหลอดเลือดแดงที่ปอดส่วนล่างทั้งสองข้าง ผู้ป่วยมีอาการไข้ร่วมด้วยโดยไม่มีหลักฐานการติดเชื้อ ระดับความเข้มข้นออกซิเจนในเลือดต่ำดีขึ้นเองใน 7 วัน ไข้อยู่นาน 16 วัน ผลตรวจเอกซเรย์คอมพิวเตอร์สองสัปดาห์หลังหัตถการพบว่าส่วนประกอบไขมันในปอดหายไปเกือบทั้งหมด ผู้ป่วยไม่ได้รับการทำหัตถการอีกเนื่องจากมะเร็งกระจายไปที่ปอด ในบทความนี้คณะผู้นิพนธ์ได้ทบทวนรายงานผู้ป่วย รวมทั้งปัจจัยเสี่ยง กลไก และพยาธิกำเนิดที่เป็นไปได้