# Acute Respiratory Distress Syndrome After Transcatheter Arterial Chemoembolization of Hepatocellular Carcinomas

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**Abstract:** *Background:* Acute respiratory distress syndrome (ARDS) associated with pulmonary lipiodol embolism is a rare complication of transcatheter arterial chemoembolization (TACE). We performed a survey of ARDS associated with pulmonary lipiodol embolism after TACE. *Methods:* A retrospective analysis of the cases of all patients with hepatic tumors who received transcatheter arterial embolization or TACE between January 2006 and December 2006 was performed. The diagnosis of pulmonary lipiodol embolism was confirmed by chest computed tomography (CT). *Results:* The diagnosis of ARDS associated with pulmonary lipiodol embolism was confirmed in 4 patients. All had large (≥5 cm) and hypervascular tumors. There was no evidence of hepatocellular carcinoma arteriovenous shunting in any of our patients as determined by angiography and multidetector CT. The volumes of lipiodol infused in the 4 patients were 50, 20, 30, and 20 mL. Only 2 patients received injections of carcinostatic agents. The onset of respiratory symptoms occurred between 1 hour and 4 days after TACE. Respiratory symptoms consisted of dyspnea and tachypnea. Chest CT scans revealed linear high-density shadows, suggestive of lipiodol retention in both lungs of all patients. *Conclusion:* Pulmonary lipiodol embolism after TACE can occur within a short time frame. Whether or not there is intrahepatic arteriovenous shunting detected by multidetector CT and angiography, clinicians should avoid high doses of iodized oil and carcinostatic agents. We suggest that CT should be used for the diagnosis of pulmonary lipiodol embolism.

**Key Indexing Terms:** Acute respiratory distress syndrome; Computed tomography; Hepatocellular carcinoma; Pulmonary lipiodol embolism; Transcatheter arterial chemoembolization. **[Am J Med Sci 2009;338(5):357–360.]**

Transcatheter arterial chemoembolization (TACE) is used for the treatment of hepatic tumors. However, complications after this procedure have been reported, including acute hepatic failure, liver abscess, intrahepatic biloma formation, liver infarction, multiple intrahepatic aneurysms, gallbladder infarction, severe cholecystitis, splenic infarction, gastrointestinal mucosal lesions, pulmonary embolism, tumor rupture, and variceal bleeding.[1] Pulmonary oil embolism is an infrequent serious complication after TACE.[1,2] The complication rate of pulmonary oil embolism after TACE as reported by Sakamoto et al[1] was 0.17%.

Acute respiratory distress syndrome (ARDS) associated with pulmonary lipiodol embolism after TACE is an extremely rare pulmonary complication that has been attributed to hepatocellular carcinoma (HCC) arteriovenous shunting.[3,4] To further understand and prevent this rare complication, we performed a retrospective analysis of cases of documented ARDS associated with pulmonary lipiodol embolism among patients diagnosed with hepatic tumors who received transcatheter arterial embolization (TAE) or TACE. We also describe the characteristic computed tomography (CT) features of pulmonary lipiodol embolism.

## METHODS

The medical records of 89 patients diagnosed with hepatic tumors who underwent TAE or TACE between January 2006 and December 2006 at our hospital were retrospectively reviewed.

The diagnosis of hepatic tumor was based on elevated levels of serum $\alpha$-fetoprotein, the presence of chronic liver disease associated with chronic liver hepatitis B or C, and angiography and abdominal multidetector CT (MDCT) findings. Chest radiographic, abdominal MDCT, and laboratory test findings, including complete blood count, blood biochemistry, and $\alpha$-fetoprotein were obtained for all patients.

TAE was initiated with the infusion of iodized oil (lipiodol; Guerbet, Aulnay-sous-Bois, France) through the proper hepatic artery, left hepatic artery, or right hepatic artery. For TACE, iodized oil and doxorubicin hydrochloride (Adriamycin; Pfizer Italia S.R.L., Milano, Italy) were infused. After infusion, gelatin sponge particle (Spongostan standard; Johnson & Johnson Medical Pty., Gauteng, South Africa) was injected until flow in the hepatic artery was sluggish. The doses of iodized oil and doxorubicin hydrochloride ranged from 4 to 50 mL and 6 to 60 mg. These were dependent on tumor size and vascularity.

The diagnosis of pulmonary lipiodol embolism was confirmed by chest CT, which revealed linear high-density shadows in both lower lungs. The diagnosis of ARDS was made with reference to the American European Consensus Conference Criteria, including the acute onset of illness, bilateral chest radiographic infiltrates consistent with pulmonary edema, pulmonary artery occlusion pressure ≤18 mm Hg (or absence of clinical evidence of left atrial hypertension), and hypoxemia as measured by the ratio of the arterial partial pressure of oxygen ($PaO_2$) to the fraction of oxygen inspired ($FiO_2$) ≤200.

## RESULTS

We identified 4 patients who developed ARDS associated with pulmonary lipiodol embolism. The characteristics of these patients are summarized in Table 1.

Our patients had a mean age of 69 years (range 37–83 years) and included 2 men and 2 women. The etiologies of hepatic tumors were chronic hepatitis B in 3 patients and chronic hepatitis C in 1 patient. Initial chest radiographic findings were normal in all patients. Angiography and MDCT revealed no evidence of HCC arteriovenous shunting in any of the patients. All patients had large (≥5 cm) and markedly

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TABLE 1. Characteristics of the patients with pulmonary oil embolism after TACE

| | Patient Number | | | |
|---|---|---|---|---|
| **Characteristic** | **1** | **2** | **3** | **4** |
| Age (yr)/sex | 80/M | 83/F | 37/M | 76/F |
| Angiography and MDCT findings | | | | |
| AV shunt | – | – | – | – |
| Tumor size (cm) | 10.4 | 12.8 | 5 | 17 |
| Hypervascularity of tumor | + | + | + | + |
| TACE or TAE method | | | | |
| Site of agent injection | Right HA | Right HA | Right HA | Right HA |
| Lipiodol (mL) | 50 | 20 | 30 | 20 |
| Lipiodol (mL/Kg) | 0.64 | 0.34 | 0.41 | 0.37 |
| DH (mg) | | | 50 | 60 |
| Respiratory symptoms | D, T | D, T | D, T | D, T |
| Onset duration | 1 hr | 4 d | 3 d | 3 d |
| P/F ratio | 53.2 | 99.1 | 107.7 | 131.6 |
| Characteristic of chest CT (linear high-density shadow) | + | + | + | + |
| Other complications | Nil | Nil | Hepatic failure | Hepatic failure |
| Outcome | Recovered | Recovered | Died | Died |

+, present; −, absent; TAE, transcatheter arterial embolization; TACE, transcatheter arterial chemoembolization; AV shunt, arteriovenous shunting in the hepatocellular carcinoma; CT, computed tomography; MDCT, multidetector CT; DH, doxorubicin hydrochloride; D, dyspnea; HA, hepatic artery; P/F, $PaO_2/FiO_2$ ratio; T, tachypnea.

hypervascular tumors. The volumes of lipiodol infused for the 4 patients were 50, 20, 30, and 20 mL. Only patients 3 and 4 were injected with adriamycin.

Respiratory symptoms developed within 1 hour to 4 days after TACE and TAE. Respiratory symptoms consisted of dyspnea and tachypnea. Chest radiography revealed diffuse infiltrations over both lung fields in all patients. Chest CT examinations revealed linear high-density shadows, suggestive of lipiodol retention in both lungs [Figure 1(A)–(D)]. Left ventricle ejection fractions (as determined by echocardiography), blood cultures, urine cultures, and sputum cultures were normal in all patients. The $PaO_2/FiO_2$ ratio was $<200$ in all patients.

These findings were consistent with a diagnosis of ARDS associated with pulmonary lipiodol embolism.

All patients underwent endotracheal tube intubation and were mechanically ventilated to maximize lung protection. Furthermore, patients 1, 2, and 3 received hydrocortisone steroid therapy. After treatment, condition improved in 2 of the 4 patients who were subsequently discharged without sequelae. Overall condition deteriorated in the remaining 2 patients (patients 3 and 4). Both developed oliguria with acute renal failure. Patient 4 received continuous venovenous hemodialysis. Despite intensive treatment, both patients 3 and 4 died subsequent to multiple organ failure.

## DISCUSSION

Similar to lymphangiography, lipiodol-induced pulmonary embolism after TACE can cause severe lung injury, and ARDS associated with a pulmonary lipiodol embolism developing after TACE has been reported.[3–5] We have summarized the reported cases of pulmonary oil embolism associated with TACE in Table 2. The respiratory symptoms reported were nonspecific and included cough, dyspnea, hemoptysis, and tachypnea. Respiratory distress usually occurs several days after lymphangiography.[3] According to Chung et al[2], the onset of respiratory symptoms associated with pulmonary lipiodol embolism after TACE occurred between 2 and 5 days. In our patients and other reported cases, respiratory symptoms were apparent within shorter time frames, ranging from within hours to several days after TACE.[2–4,6,7]

The amount of lipiodol infused and arteriovenous shunting in the tumor are risk factors for developing pulmonary lipiodol embolism.[2–4] There seemed to be a higher rate of lung complication rate after TACE in our patients and other reported cases (Table 2) with larger volumes of infused lipiodol. Chung et al[2] recommended that the maximum safe dose of lipiodol is 15 to 20 mL (approximately 0.25 mL/kg). In the current study, although the volume of lipiodol did not exceed 20 mL in patients 2 and 4, the doses were greater than 0.25 mL/kg. As already noted, arteriovenous shunting in the tumor is another risk factor. The hepatic arteriovenous shunt (HAVS) is the link between the hepatic artery or its branches and the portal hepatic vein. HCC is the most common condition associated with HAVS.[8] In an animal study, Kishi et al[9] demonstrated that lipiodol infusion into the hepatic artery resulted in dose-dependent increases in circulating levels of the agent and embolism of lipiodol droplets (through sinusoids and pulmonary capillaries) in the systemic circulation.

MDCT is an important medical imaging examination technology and can facilitate the diagnosis of HAVS associated with HCC.[8] In the current cohort of patients studied, there were no instances of arteriovenous shunting detected as determined by MDCT and angiography. In most previous reports, arteriovenous shunting has not been detected by means of angiography.[2–4,6,7]

Technetium-99m-macroaggregated albumin has been suggested to be a useful tool for pretherapeutic evaluation of extratumoral shunting in HCC.[10] Ho et al[11] demonstrated that lung shunting correlated with tumor size in the patients with HCC. In patients with HCC, there was an increase in mean lung shunting with increasing tumor sizes up to 15 cm. Thereafter, mean lung shunting remained almost unchanged up to a