Multiple Ischemic Strokes after Transcatheter Arterial Chemoembolization for Hepatocellular Carcinoma with a Radiographic and Pathological Correlate

Victor Zach, MD,* Beth Rapaport, MD,* Ji Yeoun Yoo, MD,* Lara Goldfeder, MD,+ and Jesse Weinberger, MD*

Introduction: Transcatheter arterial chemoembolization (TACE) is a widely used form of therapy in advanced hepatocellular carcinoma. We report the first pathological data from an autopsy case of multiple cerebral emboli occurring during TACE.

Methods: A Medline search for previous cases of cerebral embolism and TACE revealed 11 other cases. Findings: Multiple microscopic subacute infarcts were found in the cerebrum, midbrain, and cerebellum of our patient on autopsy, but no embolic material was seen. Embolic material was noted in dilated vessels throughout the fibrotic right diaphragm and in the upper lobe of the right lung. Combining the literature search with our patient, the mortality of cerebral embolism after TACE is 25% (n = 12). Intracardiac shunts were seen in 20% of the cases (n = 10). Hyperdense lesions were seen on head CT in 80% of the patients evaluated (n = 10). Chest imaging revealed infiltrate or consolidation in 60% of the cases (n = 5). Pulmonary emboli were reported in 100% of the cases (n = 8). Conclusions: Cerebral embolism after TACE is devastating. Brain pathology supports embolization of ethiodized oil rather than DC beads as the mechanism of cerebral injury. Further pathological studies are needed to better understand the pathophysiology of this condition. Lung pathology confirmed the presence of embolic material in the distal lung, suggestive of a hepatopulmonary shunt undetectable by current modalities. Evaluation for such shunts with emerging modalities such as TCD with emboli detection may be an area of future research. Key Words: Pathology—pathophysiology—mechanism—cerebrovascular accident—embolism—interventional radiology—lipiodol.

© 2012 by National Stroke Association

Transcatheter arterial chemoembolization (TACE) is a form of therapy in advanced hepatocellular carcinoma (HCC). In this procedure, an iodized oil contrast medium, ethiodized oil (lipiodol or ethiodol), is mixed with an anticancer drug and injected into a feeding artery of the tumor. The anticancer drug is transported via a DC beads drug delivery embolization system. As described in the instructions for use, DC beads are biocompatible, hydrophilic, nonresorbable hydrogel microspheres (100-900 μm diameter) produced from polyvinyl alcohol (PVA). Some cases of cerebral embolism occurring after this procedure have been reported recently. This is the first report of autopsy findings in a man with HCC who suffered multiple ischemic strokes during TACE. Based on the pathology, we suggest a possible mechanism for this complication.

Case Report

A 66-year-old, neurologically intact man with a history of alcohol abuse and cirrhosis was diagnosed with HCC 8 months before the procedure. The HCC was resected. On follow-up, however, computed tomography (CT) of the abdomen revealed recurrence with multiple liver masses (largest diameter, 11.5 cm). A diagnostic catheter angiogram via the hepatic artery revealed no contrast leak...
into the systemic circulation. A mixture of 60 mg of adriamycin, 4 cc of ethiodized oil (ethiodol), 4 vials of 100- to 300-μm DC beads, and one vial of 700- to 900-μm DC beads was injected into the right hepatic artery. Eighty-five minutes after skin puncture, the patient suddenly became less arousable, which was initially attributed to sedation with fentanyl (Fig 1). Five minutes later the patient became completely nonverbal, opened his eyes to voice, but was unable to follow commands and was treated with naloxone without improvement. Brain stem reflexes were intact. A right facial droop was present. His arms localized to noxious stimuli, while triple flexion response was seen in his legs. Diffusely brisk reflexes with bilateral ankle clonus were noted. Plantars were extensor bilaterally. Upper extremity digits were cold and cyanotic bilaterally. The patient rapidly progressed to coma and was intubated.

Abdominal CT scan revealed no retroperitoneal hemorrhage and bibasilar atelectasis with consolidation at the right lung base (Fig 1). Noncontrast head CT revealed multiple cortical punctate hyperdensities. Magnetic resonance imaging (MRI) of the brain showed innumerable punctate areas of restricted diffusion throughout both cerebral hemispheres and the cerebellum (Fig 2). Transeosophageal echocardiography (TEE) showed no intracardiac shunt or thrombus, but revealed a mildly reduced ejection fraction. Transcranial Doppler ultrasonography (TCD) with intravenous injection of agitated saline solution for emboli detection was negative. The cerebrospinal fluid was clear, without pleocytosis, but with a protein level of 53 mg/dL. Acute-phase reactants were elevated (fibrinogen, 700 mg%; D-dimer, 6.98 μg/mL). No neurologic improvement occurred after 6 weeks. The family withdrew care.

On autopsy, multiple microscopic subacute infarcts were found in the cerebrum, midbrain, and cerebellum, but no foreign material was seen in the brain. The infarcts were composed of necrosis, macrophages, vascular proliferation, and gliosis. Embolic foreign material was noted in dilated vessels throughout the fibrotic right diaphragm, on the upper surface of the diaphragm in direct continuity with the pleural surface of the right lung, and a microscopic focus was seen in the upper lobe of the right lung. The right liver was predominantly replaced by necrotic tumor, which extended through the capsular surface with tumor adhering to the undersurface of the diaphragm. Histologically, the diaphragm was replaced by fibrous tissue with inflammation. The remainder of the liver was studded with HCC nodules (Fig 3).

**Literature Review**

We performed a Medline literature review, searching for previous cases of cerebral embolism and TACE. We found 11 other cases (Table 1). In these cases, along with our patient (n = 12), there was a 25% mortality of cerebral embolism after TACE. Hyperdense lesions were seen on head CT in 80% of the patients (n = 10). Pulmonary emboli were reported in 100% of cases studied (n = 8), chest imaging revealed infiltrate or consolidation in 60% of cases studied (n = 5), and intracardiac shunts were seen in 20% of cases studied (n = 10).

**Discussion**

The foreign embolic material found in the right upper lobe of the lung suggests an undetected hepatopulmonary shunt presumably caused by invasion of HCC into the lung or the passing of embolization material from the hepatic artery through the HCC into the hepatic vein and subsequently to the right atrium. We hypothesize that after the injection of adriamycin, ethiodized oil, and DC beads into the right hepatic artery, the mixture

---

**Graph 1.** Cushing's reflex appears at 85 minutes and is accompanied by a rapid decline in Level of Arousal.
embolized via one of these two mechanisms into the lung vasculature. Emboli then traveled systemically from the lung.

In normal individuals, pulmonary parenchymal precapillary and capillary blood vessel diameter is 8-15 μm, and pulmonary venule diameter is 20-50 μm. DC beads are visible without staining under direct microscopy. They were not visible in the brain of our patient. DC beads are not resorbable and are too large to pass through the normal pulmonary vasculature.

In contrast, smaller molecules, such as ethiodized oil, can pass through the pulmonary circulation and embolize systemically. The protein was found to pass through the lungs in 3%-6% of normal subjects undergoing perfusion lung scans with 99m-Tc-labeled macroaggregated albumin. Fat globules <7 μm in diameter can pass directly through the pulmonary arteriolar network, enter the systemic circulation, and cause cerebral injury. Previous reports of cerebral embolism after TACE all implicated ethiodized oil as the culprit, based on radiologic findings. Our pathology findings support the theory that ethiodized oil is the cause of the embolism in victims of stroke after TACE.

An absence of ethiodized oil on brain pathology would be expected due to the oil’s relatively short half-life in vivo (5.2-12.6 days). The postmortem examination of our patient’s brain was performed 42 days (3.3-8.0 half-lives) after exposure to the oil.

Our study excludes DC beads as the source of the cerebral emboli. However, there may be a scenario in which this can occur. Hepatopulmonary syndrome can result in the dilatation of pulmonary capillaries up to 15-100 μm. The smallest beads that our patient received were 100 μm in diameter. DC beads are known to undergo a slight decrease in size, up to 20%, when being loaded with chemotherapeutic agents. After mixing with adriamycin, the smallest bead might have been 80 μm in diameter. In patients with hepatopulmonary syndrome, these factors might allow larger DC beads to also embolize systemically. Because DC beads are not resorbable and are larger than ethiodized oil molecules, systemic embolization of this type may be even more devastating.

According to the National Comprehensive Cancer Network Practice Guideline for Hepatobiliary Cancers (v. 1.2010), TACE is contraindicated in patients with main portal vein thrombosis, Child-Pugh C liver dysfunction, and total bilirubin >3 mg/dL. The presence of marked arteriovenous shunting to portal, hepatic, or pulmonary veins should be a contraindication as well. Unfortunately, our patient’s shunt (hepatopulmonary or hepatic artery to hepatic vein) was not detectable by catheter angiography, suggesting insufficient resolution or too-slow flow through the shunt for detection.

Transpulmonary shunting also occurs at a slower rate than shunting via the heart. Echocardiography with agitated saline can be falsely negative in a patient with
a transpulmonary shunt, unless the operator anticipates the visualization of agitated saline in the left atrium after a significant delay.\textsuperscript{11} Our TEE and TCD for emboli detection were performed without a delay, making them less sensitive to the presence of a transpulmonary shunt. Monitoring for emboli during TACE with TCD may ad-
dress this problem. More studies are needed to test this hypothesis.

The role of intracardiac shunts in this disorder remains controversial. In theory, embolization material may pass from the hepatic artery into the hepatic vein via aberrant connections created by HCC invasion. This would allow return of the embolization material to the right atrium via the inferior vena cava. The material would then enter the lung and require a transpulmonary shunt to travel systemically, unless there is a shunt in the heart already granting this access. A recent report described two patients with ischemic stroke after TACE with a patent foramen ovale (PFO). All other reported patients, as well as our patient, demonstrated no evidence of PFO on TEE.\textsuperscript{2,8,14} TCD with emboli detection has a sensitivity of 95\%-97\% and a specificity of 75\% for identifying a right-to-left shunt.\textsuperscript{15,16} TCD detected emboli in 11\% of the patients who had a negative TEE. Transpulmonary shunt detection and ease of incorporating the Valsalva maneuver resulted in the greater rate of detection with TCD.\textsuperscript{15} Thus, intracardiac shunts can contribute, but are not necessary for this condition to occur.

The consolidation at the right lung base seen on CT obscured the tumor margin, limiting the utility of the study. Other modalities, such as TCD with emboli detection before TACE, might be useful in these high-risk patients. Further studies are needed.

Previous case studies reported that noncontrast head CT scans revealed multiple punctate hyperdensities, whereas fluid attenuation inversion recovery (FLAIR) MRI revealed hyperintense lesions in the subacute and chronic disease phases, and diffusion weighted imaging (DWI)-MRI showed restricted diffusion in the acute disease phase.\textsuperscript{2-8} Hyperdensities on initial head CT are unusual in other causes of ischemic stroke. This is a useful early sign of ethiodized oil embolization. In contrast, DC beads are not radioopaque and thus are radiographically undetectable. The hyperdensities seen on our patient’s initial head CT scan (Fig 2) further confirm the role of ethiodized oil as the source of the emboli after TACE.

MRI is useful for the detection of acute ischemic strokes. Previous studies of post-TACE stroke have used 1.5-T scanners,\textsuperscript{6,7} which recently were shown to be more sensitive than 3-T scanners in detecting acute ischemia.\textsuperscript{17} MRI’s ability to detect ethiodized oil emboli remains controversial, however. Yoo et al\textsuperscript{2} found that MRI was unable to detect a weak lipid deposition signal, which was masked by a signal due to ischemia. Karapanayiotides et al\textsuperscript{5} argued that the hyperintense signals on DWI overestimate the true extent of the cytotoxic edema and reflect the presence of large quantities of sluggish lipids. They reported extensive reversal of DWI abnormalities on follow-up MRI in support of the idea that lipid was detected and was being degraded.\textsuperscript{5}

Cerebral emboli after TACE for HCC are devastating. Careful evaluation for shunts must be undertaken before the procedure. Ethiodized oil is the likely cause of cerebral...
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Sex</th>
<th>HCC description</th>
<th>TACE course/ injection site/ dose of iodized oil, mL</th>
<th>Shunt</th>
<th>PE</th>
<th>Chest imaging</th>
<th>Brain imaging</th>
<th>Symptoms/ outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-1</td>
<td>52M</td>
<td>Advanced</td>
<td>2/HA/35</td>
<td>None</td>
<td>Present</td>
<td>NA</td>
<td>CT: unremarkable. MRI: high-signal lesions on T2, FLAIR, or DWI; no hyperintense lesion on T1</td>
<td>Headache, confusion, left upper extremity weakness; recovered in 3 weeks</td>
</tr>
<tr>
<td>1-2</td>
<td>58M</td>
<td>NA</td>
<td>1/-/8</td>
<td>None</td>
<td>Present</td>
<td>NA</td>
<td>MRI: high signal lesions on FLAIR and DWI; no hyperintense lesion on T1</td>
<td>Vision loss, headache, shortness of breath, chest pain; recovered over several days</td>
</tr>
<tr>
<td>1-3</td>
<td>56M</td>
<td>NA</td>
<td>3/-/-</td>
<td>NA</td>
<td>Present</td>
<td>NA</td>
<td>MRI-high signal lesions on Flair and DWI, no hyperintense lesions on T1</td>
<td>Disorientation, irritability, blindness; recovered in 2 weeks</td>
</tr>
<tr>
<td>2</td>
<td>81F</td>
<td>14 × 10 cm, thoracic invasion with massive hemotherax</td>
<td>2/RIPA, RIMA/20</td>
<td>None</td>
<td>Present</td>
<td>CT: hyperdense oil deposition within the bilateral collapsed basal lungs</td>
<td>CT – hyperdensity MRI-hyperintense lesions</td>
<td>Vision loss, upper and lower limb weakness; died from respiratory complication 45 days later</td>
</tr>
<tr>
<td>3</td>
<td>76M</td>
<td>NA</td>
<td>16/epicholedochal artery, RIPA, HA/-</td>
<td>NA</td>
<td>Present</td>
<td>CT: deposition of iodized oil in the lungs, bilateral pulmonary consolidation and pleural effusions</td>
<td>CT- increased attenuation MRI(1.5-T unit)-restricted diffusion, isointense to hyperintense on T2 and FLAIR</td>
<td>Deteriorated level of consciousness, became comatose the next day; recovered over 6 weeks</td>
</tr>
<tr>
<td>4</td>
<td>70F</td>
<td>Recurrent HCC at the site of biloma resection that appeared to invade the diaphragm</td>
<td>1/RHA, MHA, R renal capsular artery/12</td>
<td>None</td>
<td>NA</td>
<td>NA</td>
<td>CT-hyperattenuating lesions MRI-hyperintense lesions on DWI, T2, FLAIR</td>
<td>Drowsy and disoriented, became comatose the next day; died from multiple organ failure in 2 weeks</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Sex</th>
<th>HCC description</th>
<th>TACE course/ injection site/ dose of iodized oil, mL</th>
<th>Shunt</th>
<th>PE</th>
<th>Chest imaging</th>
<th>Brain imaging</th>
<th>Symptoms/outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>62F</td>
<td>15 × 12 cm, exophytic growth contiguous to the diaphragm, no metastatic evidence to the regional lymph node and bone marrow</td>
<td>3/RIPA, RHA/30</td>
<td>None</td>
<td>Present</td>
<td>CT: hyperattenuation at the right lung base; chest X-ray: right pleural effusion and diffuse parenchymal infiltration</td>
<td>CT: increased attenuation; DWI-MRI: hyperattenuating lesions</td>
<td>Deteriorated level of consciousness, shortness of breath; recovered in 6 weeks</td>
</tr>
<tr>
<td>6</td>
<td>71M</td>
<td>NA</td>
<td>4/-/-</td>
<td>None</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>7</td>
<td>36M</td>
<td>Massive HCC in the right lobe of the liver invading the diaphragm</td>
<td>2/RHA/40</td>
<td>None</td>
<td>Present</td>
<td>CT: hyperattenuating lipiodol deposition in the bilateral basal lungs</td>
<td>CT: hyperdense lesions; MRI (1.5 T): restricted diffusion, hyperattenuating lesions on T2</td>
<td>Modest monoparesis of the right arm, transient dysarthria, dizziness; recovered over 48 hours</td>
</tr>
<tr>
<td>8-1</td>
<td>67M</td>
<td>4.3-cm mass at the medial segment of the left hepatic lobe, and three small lesions in the right hepatic lobe</td>
<td>4/RIPA/10</td>
<td>PFO</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Numbness and weakness of right hand, impaired fine motor activity in the right fingers; recovered in 10 days</td>
</tr>
<tr>
<td>8-2</td>
<td>63F</td>
<td>Right hepatic dome HCC</td>
<td>3/RIPA/10</td>
<td>PFO</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Right leg weakness; symptoms improved over the next 3 days</td>
</tr>
<tr>
<td>9*</td>
<td>66M</td>
<td>Multiple liver masses, largest 11.5 cm</td>
<td>1/RHA/4</td>
<td>None</td>
<td>Present</td>
<td>CT: hyperdense lesions along the gyri; MRI: acute ischemic lesions bilaterally</td>
<td>CT: hyperdense lesions along the gyri; MRI: restricted diffusion, unremarkable FLAIR</td>
<td>Deteriorated level of consciousness; returned to consciousness gradually, and CT normalized in 7 days</td>
</tr>
</tbody>
</table>

Abbreviations: PE, pulmonary embolism; HA, hepatic artery; RHA, right hepatic artery; MHA, middle hepatic artery; RIPA, right inferior phrenic artery; RIMA, right internal mammary artery; PFO, patent foramen ovale; NA, no available data; DWI, diffusion weighted imaging.

*Our patient.
emboli in this condition. The ethiodized oil dose should be kept below 20 mL to prevent extrahepatic embolism. Nonetheless, some of the previous cases, as well as our case, reported this complication even with appropriate doses.2-4,14 Further research with TCD for embolite detection during TACE is needed. Histological evaluation of brain tissue before the degradation of ethiodized oil may better characterize the mechanism of this disease.

Acknowledgment: We thank Dr Tamara Zach for her help with proofreading the manuscript.

References

15. Droste DW, Reisener M, Kemény V, et al. Contrast transcranial Doppler ultrasound in the detection of