Mental Status Changes Postchemoembolization: The Role of Inflammatory Response

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Case Report

A 72-year-old woman with a history of end-stage liver disease (Child class A) secondary to cryptogenic cirrhosis presented for elective transarterial chemoembolization (TACE) of hepatocellular carcinoma (HCC). Recent imaging demonstrated increased size of a hypervascular 1.3-cm nodule in the left lobe consistent with recurrence at the margin of a previous radiofrequency ablation site. She reported episodic right upper quadrant pain and infrequent encephalopathy.

Chemoembolization was completed from a right transfemoral approach. A left hepatic arteriogram demonstrated segmental branches to segments 2 and 3 with marked tortuosity and a hypervascular mass with conspicuous contrast staining. An attempt to catheterize segmental arterial branches subselectively to hepatic segment 2 and 3 was unsuccessful. LC bead chemoembolization was then performed to near stasis from the level of the undivided left hepatic artery; a total of 60 mg of doxorubicin loaded onto 100- to 300-µm beads was delivered to the left hepatic artery distribution.

Following the procedure, the patient was admitted for overnight observation while receiving intravenous fluids, antiemetics, and pain relievers in addition to her home medications. That evening she developed signs of increasing confusion. She awoke not knowing who family members were, was making nonsensical statements, and exhibited impaired functioning and judgment, visuospatial integration, and so on. She was discharged in the morning on a new lactulose regimen for presumed hepatic encephalopathy.

Although the patient’s mental status was clearing by the following morning, her discharge was deferred for further observation. The following night was generally uneventful, and she was discharged in the morning on a new lactulose and rifaximin regimen for presumed hepatic encephalopathy.

The patient returned 11 weeks later for repeat chemoembolization of the left hepatic lobe; her overnight hospital course during this admission was uncomplicated, without evidence of delirium or significant manifestations of postembolization syndrome (PES).

Discussion

Postprocedural delirium is a well-documented phenomenon in the surgical and adult intensive care literature, but it has not previously been reported following TACE. Unpublished data from our institution suggest a post-TACE delirium incidence of ~5%. Delirium in these cases typically manifests within 36 hours and usually resolves by postprocedure day 3, which incidentally is the same time course that typical postembolization syndrome is known to develop and resolve.

To evaluate possible mental status changes properly in patients undergoing TACE, it is important to know how to distinguish dementia, delirium, and hepatic encephalopathy. Dementia refers to progressive and/or permanent cognitive impairment lasting at least 6 months affecting memory and deficits in two or more intellectual domains affecting daily functioning, such as sequencing and organizing tasks, executive functioning and judgment, visuospatial integration, and so on. Alzheimer disease is the most common form of dementia, but dementia can arise of a plethora of pathologies including strokes, head injuries, human immunodeficiency virus, Parkinson disease, and various other neurodegenerative syndromes. Delirium signifies an acute alteration in mental status, usually with dramatic fluctuations in levels of arousal, going from sleepy to agitated to calm in a short period of time. Hepatic encephalopathy is a subtype of delirium caused by acute metabolic effects of ammonia or other toxins not broken down by a failing liver, although patients with chronic liver disease often can have a baseline of milder chronic cognitive impairment that becomes much more recognizable in a state of hepatic encephalopathy.
patient gets acutely confused, psychotic, or agitated following TACE, by definition this is a form of delirium that probably has a major component of hepatic encephalopathy, perhaps superimposed on some underlying dementia.

It is not clear whether following serial ammonia levels aids in the management of patients with post-TACE delirium. The consensus for hepatic encephalopathy in general has been that ammonia will be elevated but that following changes in ammonia levels over time does not add anything; rather one gives lactulose and rifaximin and other medications until symptoms clear. Recent studies suggests that measuring ammonia levels and changes in ammonia levels may be useful for research studies but requires very finely calibrated laboratory instrumentation and standardization that may not be feasible when one is focused mainly on the clinical treatment of hepatic encephalopathy.

In our institutional cohort, ~20% of patients who develop post-TACE delirium have at least one other hospitalization for hepatic embolization that is also complicated by postprocedural delirium. In this cohort, most of the patients who developed post-TACE delirium were cirrhotic, but not all had prior episodes of hepatic encephalopathy. Those empirically treated with lactulose had variable improvement in mental status, and improvements that were seen may have been unrelated to lactulose intervention. Worsening hepatic encephalopathy is unlikely to account fully for the acute mental status changes observed in the case presented here, and the current literature on postembolization syndrome and postprocedural delirium suggests an alternative mechanism.

PES consists of a constellation of findings including pain, fever, nausea, and generalized malaise known to occur 24 to 72 hours following any embolization procedure, particularly those involving encapsulated organs. Postembolization syndrome is occasionally severe and can present with atypical symptoms. PES can become a significant complication when it prolongs hospitalization or deters patients from undergoing repeat TACE. Multiple studies report a widely differing PES incidence ranging from 26 to 100%. The risk of developing PES has a loose correlation with factors such as nontarget embolization (odds ratio [OR]: 2.8; \( p = 0.11 \)), chemoembolic dose (OR: 3.0; \( p = 0.08 \)), and a history of previous embolization (OR: 0.5; \( p = 0.24 \)). Severity of pain and nausea does not appear to vary between bland embolization and chemoembolization, or between conventional and drug-eluting bead TACE.

Early investigators of PES pathophysiology were divided in support of either tumor necrosis or ischemic injury to normal parenchyma as the primary cause of postembolization fever. More recent studies have demonstrated the induction of an acute systemic inflammatory response following hepatic embolization. Interleukin (IL)-6 is a known regulator of fever that targets the liver to induce synthesis of acute phase proteins such as C-reactive protein (CRP). IL-6 and CRP markedly increase after hepatic embolization, peak after 3 days, and remain above normal for 7 days. In vivo studies of HCC patients undergoing TACE demonstrated that these inflammatory mediators all rise and peak in 24 to 72 hours following the procedure, taking days to weeks to return to normal. A statistical correlation between inflammatory markers and delirium following TACE has yet to be demonstrated. However, studies in other patient populations such as the elderly undergoing cardiac bypass surgery, elderly hospitalized on medical wards, and elderly undergoing orthopedic surgeries have shown that elevated levels of inflammatory markers do indeed correlate with delirium, setting the stage for similar clinical studies in patients undergoing TACE. We are in the process of evaluating such a correlation.

**Conclusion**

This case describes a patient who experienced significant new-onset delirium following TACE for HCC. Although these symptoms were of limited duration and responded to empirical treatment, hospitalization was prolonged as a result. The mechanism responsible for post-TACE delirium remains to be determined, as is the degree to which post-TACE delirium may overlap in pathophysiology with other forms of postsurgical and intensive care unit delirium in noncirrhotic subjects. Although baseline hepatic encephalopathy is a common comorbidity in the hepatic chemoembolization population, post-TACE delirium may represent a pathophysiologically distinct entity requiring a different approach to treatment and prevention. Further studies are needed to determine the extent to which PES and post-TACE delirium overlap, and which pathophysiologic mechanisms might be shared.

**References**


