Case Report

Acute lung injury following transcatheter hepatic arterial chemoembolization of doxorubicin-loaded LC beads in a patient with hepatocellular carcinoma

Ihsan Khan, Viswanath Vasudevan, Sasikanath Nallagatla, Farhad Arjomand, Rana Ali

Division of Pulmonary Medicine, Brooklyn Hospital Center, NY, USA

ABSTRACT

Transcatheter arterial chemoembolization (TACE) currently is being used as an effective palliative therapy for unresectable cancers especially hepatocelluar carcinoma (HCC). Accidental lipiodol embolism to the lungs is a rare but potentially fatal complication of TACE. This procedure involves injection of drug-eluting microspheres (LC Bead) loaded with doxorubicin, followed by embolization with embozene microspheres until stasis is evident, being used in advanced HCC. We report a patient with inoperable HCC with underlying Hepatitis C and liver cirrhosis, who developed acute lung injury following targeted chemoembolization of selective feeding hepatic artery with LC beads loaded with doxorubicin. Acute lung injury as a complication of unintended lung chemoembolization with doxorubicin has not been previously reported in the literature. Interventional radiologists screen patients for potential hepatic A-V shunt and take appropriate precautions to prevent unintended pulmonary embolization. These include appropriate selection of LC bead particle size especially in patients who are embolized with radiation pellets. This report highlights the need for a screening total body scintigraphy after injection of radionuclide Tc-99 MAA in the feeding hepatic artery to identify patients with hepatic A-V shunt. In such patients, appropriate size selection of LC bead particles is critical to prevent unintended pulmonary chemoembolization and acute lung injury. Other measures include careful patient selection, low dose of chemotherapy, and transient selective hepatic vein balloon occlusion.

KEY WORDS: Chest imaging, drug, lung injury

Address for correspondence: Dr. Ihsan Khan, Brooklyn Hospital Center, 121 DeKalb Ave, Brooklyn, NY 11201. E-mail: dr_ihsan71@hotmail.com

INTRODUCTION

Primary hepatocellular carcinoma (HCC) can be considered as a malignancy that have poor overall outcome. Transcatheter arterial chemoembolization (TACE) of hepatic artery is commonly used as a palliative management of HCC. TACE has been associated with complications such as inadvertent chemoembolizations.[1] Acute respiratory distress syndrome due to pulmonary embolization of lipiodol has previously been reported.[2]

Access this article online

Quick Response Code:

Website: www.lungindia.com

DOI: 10.4103/0970-2113.95335

Some strategies have been suggested previously for preventing chemoembolizations during TACE.[3] Doxorubin is one of the most commonly used chemotherapeutic agents for a wide variety of neoplasms. Systemic doxorubicin has been shown to cause lung injury.[4] Diffuse lung injury by chemoembolization with doxorubicin has not been reported in the literature. Here, we report a case of acute diffuse lung injury after TACE of hepatic artery with doxorubicin.

CASE REPORT

A 55-year-old male with hepatocellular carcinoma (HCC) was admitted to the intensive care unit with severe dyspnea, tachypnea and dry cough, four days after he received transcatheter arterial chemoembolization (TACE) of LC beads loaded with doxorubicin of left hepatic artery. He denied having fever, chills, chest pain, palpitation, and paroxysmal nocturnal dyspnea. One year ago, he was

diagnosed with hepatocellular carcinoma along with liver cirrhosis due to hepatitis C. His appetite had diminished over the past year, resulting in 20 pounds of weight loss over the last six months. His other medical history included type 2 diabetes mellitus, dyslipidemia, and hypertension. He had quit smoking marijuana and cocaine a year ago. He denied exposure to toxic organic or inorganic dusts and fumes like paints, pesticides, arsenic etc.

On physical examination, he was afebrile, with a heart rate of 85 beats/min and a respiratory rate of 18 breaths/min. His BP was 104/76 mm Hg, and his finger pulse oximetric saturation was 88% while breathing 2 liter/min of supplemental oxygen. He was in moderate respiratory distress without the use of accessory muscles. Oral thrush was present. On chest auscultation, he had bilateral diffuse rales. There was no palpable hepatosplenomegaly or ascites. His cardiovascular and central nervous system examination was unremarkable. His lower extremities revealed pitting edema. No cyanosis or clubbing was present.

The patient's white blood cell count was 5,600/dL, hemoglobin was 10.4 g/dl, platelets count was 65,000/dL, and neutrophils count was 59.9%. There was no eosinophilia on the peripheral blood smear. Serum basic metabolic panel levels were normal except for a sodium level of 130 meq/dl. His liver function tests revealed the following: Total bilirubin of 2.2 mg/dl, direct bilirubin of 1.7 mg/dl, total protein of 8.4 g/dl, albumin of 1.9 g/dl, aspartate aminotransferase (AST) of 318 u/l, alanine aminotransferase (ALT) of 70 u/l, and alkaline phosphatase of 215 u/l. His prothrombin time, International normalized ratio (INR), and activated partial thromboplastin time were 15 seconds, 1.7, and 35 seconds, respectively. Duplex compression ultrasonography was negative for deep vein thrombosis in his lower extremity. Blood culture showed no growth. Respiratory culture grew only normal flora. His arterial blood gas was PH 7.40, PCO2 44 mmHg, and PO2 49 mm Hg while breathing room air. His plain chest X-ray and computed tomography (CT) pulmonary angiography are shown [Figures 1 and 2]. The concentration of blood α-fetoprotein (AFP) was 681 ng/mL. He was not deemed to be a candidate for surgical excision because of diffuse HCC involving both lobes of liver and advanced Liver cirrhosis of Pugh-Child score C.

Patient underwent selective left hepatic artery chemoembolization four days prior to admission. Hepatic arteriogram demonstrated a large number of hyper vascular lesions involving the left lobe of liver [Figure 3]. TACE was performed via left hepatic artery by using a mixture of LC Beads, 100 to 300 micron in size and 50 mg of doxorubicin, which was followed by bland embolization with 2cc of embozene 150 micron particle. Lipiodol was not used.

DISCUSSION

TACE of hepatic artery has been widely used as a palliative treatment of unresectable primary HCC.

The procedure involves mechanical occlusion of selective hepatic artery, supplying HCC with 100-300 micron drug eluting microspheres (LC Bead) loaded with 50 mg doxorubicin, followed by embolization with embozene microspheres of 150-micron size until stasis is evident. Slow local doxorubicin elution has an additive tumoricidal action.

Patient selection is critical to optimize outcome and avoid non-target organ complications. Complications as a result of unintended chemoembolizations associated with TACE have been reported. They include local complications such as ischemic necrosis of functioning hepatocytes resulting in acute hepatic failure, liver abscess, spontaneous rupture of tumor, gallbladder infarction, perforation of duodenum, acute renal failure, and gastrointestinal

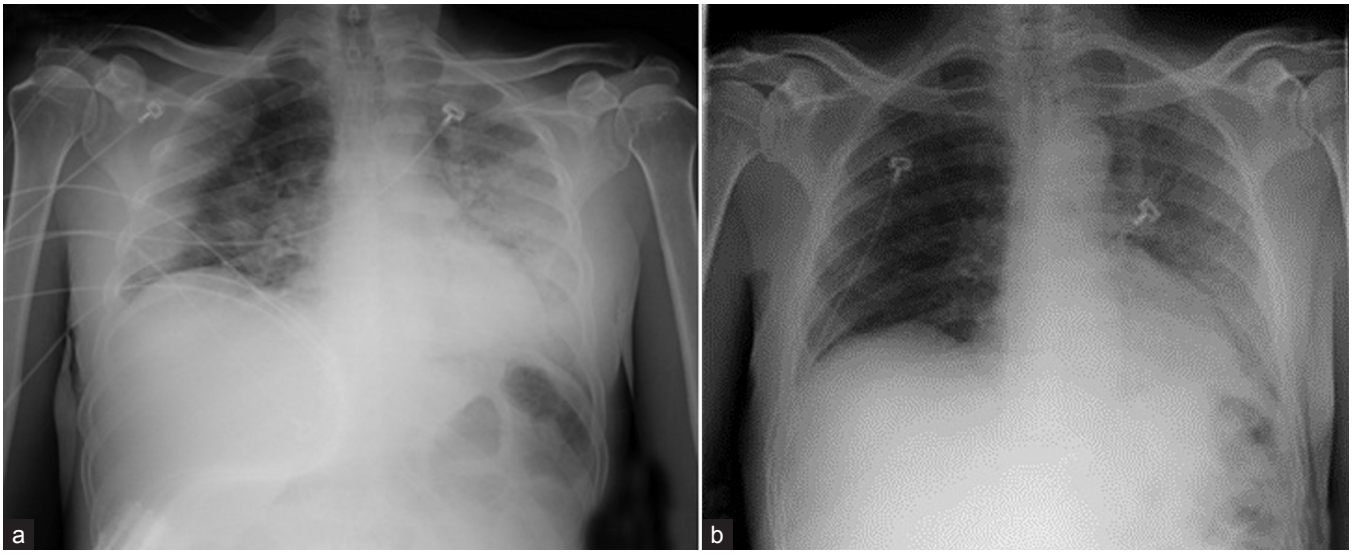

Figure 1: a) Before treatment; b) After treatment

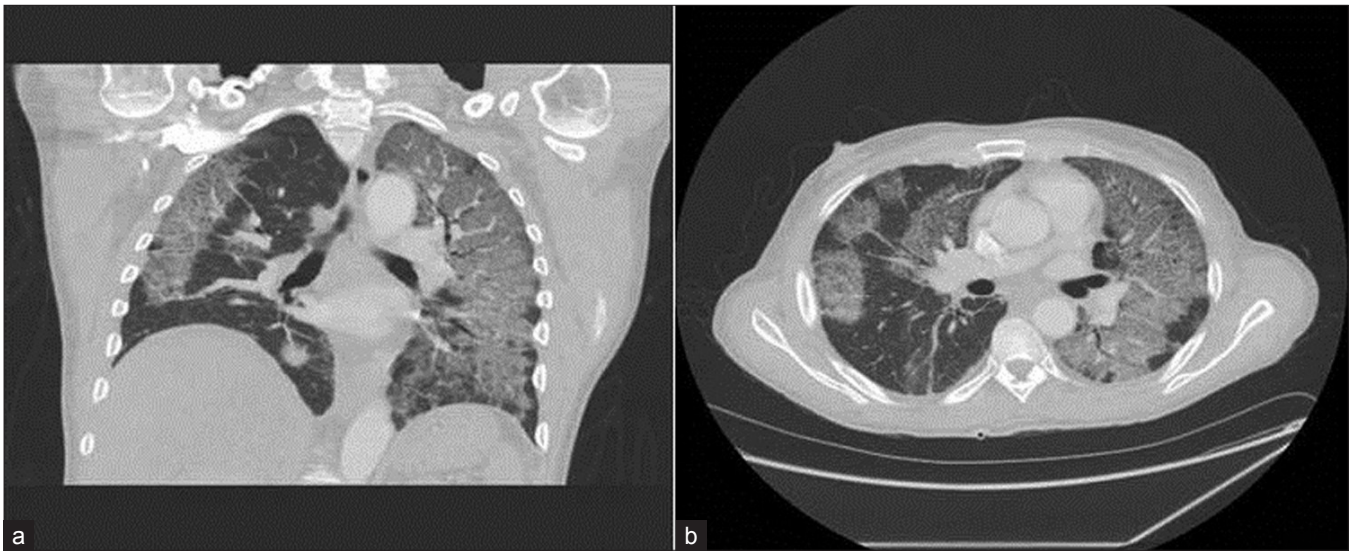

Figure 2: (a-b) Computed tomography scan of the chest at the time of admission

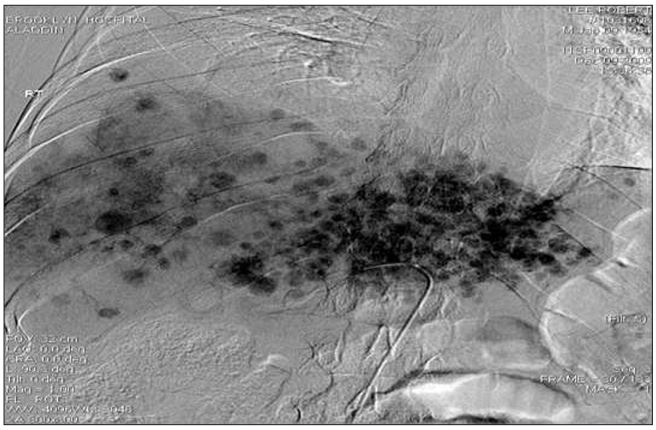

Figure 3: Hypervascular hepatocellular carcinoma

mucosal ulceration.[1] Acute respiratory distress syndrome due to lipiodol (iodized oil) pulmonary embolization has been reported in the literature.[2] Acute lung injury has been attributed to enzymatic digestion of lipiodol by lipase and formation of free fatty acid, which is toxic to alveolar-capillary membrane. Lipiodol was not used in our patient. In patients at high risk for pulmonary chemoembolization, temporary balloon occlusion of corresponding draining hepatic vein has been useful in preventing lung chemoembolization.[3]

High dose of IV systemic doxorubicin has been implicated in acute lung injury,[4] but diffuse lung injury by chemoembolization has not been reported in the literature.

Doxorubicin is an anthracycline antibiotic, it works by intercalating DNA. It is commonly used for the treatment of a wide range of different cancers, includes hematological malignancies, many types of carcinoma, and soft tissue sarcomas. Vahid *et al* reported acute dyspnea associated with transient neutropenia during systemic infusion of pegylated-liposomal doxorubicin. This phenomenon ascribed to acute lung injury caused by adhesion and sequestration of neutrophils to the pulmonary capillary endothelial cells and producing injury to alveolar-capillary membrane. Systemic infusion of doxorubicin in patients with lymphoma has also been reported to produce organizing pneumonia.[4,5]

Our patient developed acute lung injury following selective left hepatic artery chemoembolization with 50 mgm of doxorubicin loaded on to LC beads with particle size of 150-300 microns. It is very likely because of hepatic A-V shunt in our patient with hepatocellular carcinoma resulted in accidental chemembolization in pulmonary circulation and slow doxorubicin elution resulted in lung injury.

The mainstay of therapy is supportive care with supplemental oxygen and systemic corticosteroids. Although corticosteroids are used widely to treat drug-induced pneumonitis, this treatment has not been evaluated in controlled clinical trials. It is important to exclude an infectious etiology prior to initiating corticosteroid therapy. High-dose IV methylprednisolone, 1 g/d for 3 days, is recommended for patients with respiratory failure. Lower doses IV methylprednisolone, 60 mg every 6 h may be used in less severe cases of pneumonitis.[6,7] Mechanical ventilation is indicated in patients with severe respiratory failure.

Prevention

A high risk of pulmonary embolization has been reported when very small micro particles are used for liver embolization because of hepatic AV shunt in HCC with cirrhosis. The percentage of pulmonary shunting is variable and the size of these connections is unpredictable. For these reasons, whole-body scintigraphy after hepatic arterial injection of albumin Tc99 labeled macro-aggregates (MAA) is mandatory. If lung shunting is detected, microparticles for embolization are up-sized from 40 μm to 100 μm, or more. In very few selected cases

where the shunting is more than 20%, embolization with microparticles should be considered contraindicated.[8] Physicians should be aware of the clinical and radiographic presentations of the pulmonary toxicities associated with antineoplastic agents.[4]

Clinical course

Our patient developed dyspnea four days after he underwent TACE. This is as a result of slow elution of doxorubicin from the bypassed and embolized loaded LC beads in the pulmonary capillaries. He was hypoxemic and CT scan of thorax revealed bilateral ground glass opacities with interlobular septal thickening, which was diffuse in the left lung and patchy peripheral opacities on the right [Figure 2]. He was treated with oxygen supplement and IV methyl Prednisolone 60 mg every six hourly. Patient's oxygen saturation improved to 96-98% on repeat assessment (RA) and he was discharged from the hospital. Follow-up chest X-ray showed complete resolution of lung infiltrate in five days [Figure 1b].

CONCLUSION

Patients with HCC, who are at high risk for accidental pulmonary embolic complications following TACE should be closely monitored for dyspnea. Supportive therapy with supplemental oxygen and IV methyprednisolone helps improve outcome. Careful patient selection, appropriate LC bead size, low dose of chemotherapy, and transient selective hepatic vein balloon occlusion may help avoid pulmonary embolic complications.

REFERENCES

1. Dai H, Ding H, Liu F, Yao Z, Li L, Li C, *et al*. Complications of chemoembolization for hepatic neoplasms. Saudi Med J 2007;28:1208-12.
2. Wu GC, Perng WC, Chen CW, Chian CF, Peng CK, Su WL. Acute respiratory distress syndrome after transcatheter arterial chemoembolization of hepatocellular carcinomas. Am J Med Sci 2009;338:357-60.
3. Lee JH, Won JH, Park SI, Won JY, Lee do Y, Kang BC. Transcatheter arterial chemoembolization of hepatocellular carcinoma with hepatic arteriovenous shunt after temporary balloon occlusion of hepatic vein. J Vasc Interv Radiol 2007;18:377-82.
4. Vahid B, Marik PE. Pulmonary complications of novel antineoplastic agents for solid tumors. Chest 2008;133:528-38.
5. Skubitz, KM, Skubitz, AP. Mechanism of transient dyspnea induced by pegylated-liposomal doxorubicin (Doxil). Anticancer Drugs 1998;9:45-50.
6. Higenbottam T, Kuwano K, Nemery B, Fujita Y. Understanding the mechanisms of drug-associated interstitial lung disease. Br J Cancer 2004;9:31-7.
7. Camus P, Kudoh S, Ebina M. Interstitial lung disease associated with drug therapy. Br J Cancer 2004;91:18-23.
8. Bonomo G, Monfardini L, Vigna PD, Orgera G, Pedicini V, Orsi F. Does Microparticle Size Affect Bland Embolization Outcome of Local Treatment for Liver Malignancies? Jr Vasc Disease Management 2009;6:129-34.

How to cite this article: Khan I, Vasudevan V, Nallagatla S, Arjomand F, Ali R. Acute lung injury following transcatheter hepatic arterial chemoembolization of doxorubicin-loaded LC beads in a patient with hepatocellular carcinoma. Lung India 2012;29:169-72.

Source of Support: Nil, **Conflict of Interest:** None declared.