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Case Report

^{131}I-labeled lipiodol-induced interstitial pneumonia

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ABSTRACT

Drug-induced interstitial pneumonia is a severe disease that has been reportedly caused by more than 100 compounds, the most common being amiodarone, methotrexate and bleomycin. We report a case of fatal acute interstitial pneumonia occurring after a second injection of ^{131}I-labeled lipiodol for hepatocellular carcinoma treatment. Infectious pneumonia was ruled out and lung biopsy revealed a pattern of usual interstitial pneumonia. Despite early initiation of systemic corticosteroids and additionally, antioxidant medications, the patient's condition gradually worsened and he died 24 days after admission. ^{131}I-labeled lipiodol-induced interstitial pneumonia is probably frequently undiagnosed. A better knowledge of this disease would help to estimate its true incidence and may impact on the perceived risk/benefit ratio for its treatment. Moreover, this may have consequences on the prescription of ^{131}I-labeled lipiodol.

Drug-induced interstitial pneumonia is a severe disease that has been reportedly caused by more than 100 compounds (e.g. amiodarone, methotrexate and bleomycin). We report a case of fatal acute interstitial pneumonia following a ^{131}I-labeled lipiodol injection for hepatocellular carcinoma treatment.

In 2009, a 62-year-old man, with no history of smoking, was admitted for rapidly increasing shortness of breath. His past medical history was unremarkable including arterial hypertension treated with irbesartan and hydrochlorothiazide.

Eighteen months prior to admission, he was diagnosed with alcohol related liver cirrhosis (Child-Pugh grade A5) and a multifocal hepatocellular carcinoma, as shown by CT-scan. The serum alpha-feto-protein (AFP) level was 12,860 ng/mL (normal value <10 ng/mL). The patient was treated with doxorubicin, via intra-arterial chemotherapy. Portal vein thrombosis was discovered during an arterial opacification procedure, which contra-indicated the arterial embolisation that was initially planned to complete treatment for the carcinoma. The tolerance for this procedure was excellent.

Seven months prior to admission, the patient received his first intra-arterial injection, of ^{131}I-labeled lipiodol (60 mCi), *in situ*. Again, the tolerance for this procedure was rated as excellent. Thoraco-abdominal scintigraphy performed 7 days after this first injection revealed limited lung fixation.

Four months prior to admission, a thoraco-abdominal CT-scan found no abnormality in the lung parenchyma. The serum AFP level was 6 ng/mL. The patient received a second injection of ^{131}I-labeled lipiodol three weeks before admission. The patient had not reported any complaints during the week following this second injection while the scintigraphy revealed mild to moderate lung fixation.

Over the two weeks that preceded his admission, the patient progressively developed a dry cough and shortness of breath. On admission, the patient was in acute respiratory failure with a respiratory rate of 35 breaths/min and a pulsed-oxygen saturation level of 80% when the patient was breathing room air. A physical examination revealed cyanosis, bilateral crackles and a body temperature of 38.8 °C. Arterial blood gases on oxygen supplementation (8 L/min) were: $PaO_2 = 87$ mmHg, $PaCO_2 = 37$ mmHg. A chest X-Ray revealed bilateral opacities. Cefotaxime and ofloxacine were initiated on the day of admission (Day 0).

A broncho-alveolar lavage (BAL) was performed on Day 1. Cytological studies of BAL fluid revealed a cell count of 500,000 cells/mL with 53% lymphocytes (predominantly CD4 positive (73%)), 45% macrophages, 2% neutrophils and 1%

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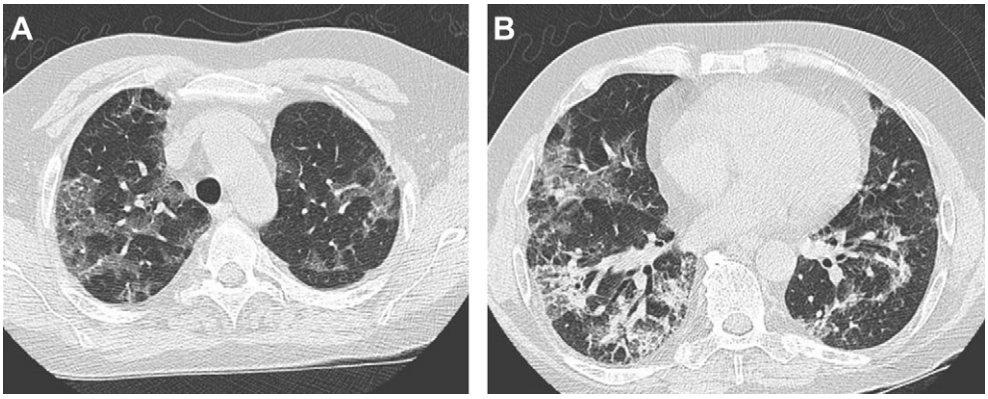

Fig. 1. Chest CT-scan showing diffuse bilateral ground glass opacities (A and B) with retraction of both lower lobes suggestive of fibrosis (B).

eosinophils. There were no hemosiderophages or malignant cells found. Neither was there any detection of bacteria, virus, fungi nor parasites in the BAL. Urinary and serological testing for pathogens was negative and no precipitins for allergic alveolar pneumonia were found. Echocardiography was normal. Intravenous methylprednisolone (1.5 mg/kg/day) was initiated on Day 1. A chest CT-scan performed on Day 7 revealed diffuse bilateral ground glass opacities with retraction of both lower lobes suggestive of fibrosis (Fig. 1). No pulmonary embolism was found. Corticosteroid doses were increased to 3 mg/kg/day and antioxidant medications were introduced with tocopherol (500 mg/day) and *N*-acetyl cystein (900 mg/day). Tracheal intubation was necessary on Day 14 for mechanical ventilation, but the patient's condition gradually worsened. A videothoracoscopy-assisted lung biopsy was performed on Day 15. All microbiological studies were negative (bacteriology, virology, mycology and parasitology). The histological patterns were indicative of usual interstitial pneumonia. The patient died of intractable respiratory failure on Day 24.

^{131}I-labeled lipiodol is a viscous contrast product, used as intratumoral chemotherapy for non-resectable hepatocellular carcinoma when portal vein thrombosis contraindicates chemoembolisation.[1,2] This treatment is usually well tolerated.[1,2] However, some adverse events reported during the ^{131}I-labeled lipiodol studies, such as infectious pneumonia or cardiac failure, could actually be undiagnosed ^{131}I-labeled lipiodol-induced pneumonia.[3] Indeed, drug-induced pneumonia is not easily differentiated from other causes of lung infiltrates, especially when investigations are limited, which may be the case in patients with intractable hepatocellular carcinoma.

The lung is the second site of fixation for radioactive lipiodol, with an uptake of ^{131}I-labeled lipiodol during the first and second treatment of, respectively, 16% and 17% in the lungs, corresponding to 3 Gy.[3] In 2005, the "Agence Française de Sécurité Sanitaire des Produits de Santé" (AFSSAPS), the French Medicines Agency, issued a warning after 13 cases of interstitial pneumonia were reported following ^{131}I-labeled lipiodol administration.[4] However, 4 years on, the scarcity of data on ^{131}I-labeled lipiodol-induced interstitial pneumonia is striking and suggests that cases of interstitial pneumonia following ^{131}I-labeled lipiodol injection may remain undiagnosed.

The pathophysiology of ^{131}I-labeled lipiodol-induced pneumonia is not univocal, an allergic mechanism is possible, but a radioactive-induced mechanism is supported by many factors. The fact that these pneumonia have been most frequently reported after the second ^{131}I-labeled lipiodol injection could indicate that pre-radiation sensitisation is a necessary step in this disease's process.[5] Clinical and radiological features fit with the usual characteristics of radiation pneumonitis.[5] Moreover, the radiation dose delivered in the lungs during each ^{131}I-lipiodol injection is 3 Gy and it has been shown that a radiation dose per fraction greater than 2.67 Gy is significantly associated with the risk of radiation pneumonitis.[6,7]

Beside corticosteroids, antioxidant therapies could theoretically be of value given the suspected pathophysiology. In a mouse model, over-expression of manganese superoxide dismutase has been shown to protect against acute and chronic radiation pneumonitis.[8] In the observation reported herein, antioxidant drugs (tocopherol and *N*-acetyl cystein) were initated early (Day 7), in addition to high-dose corticosteroids, but no significant effect was observed throughout the hospitalization. Other drugs may be of interest in this setting – Imatinib had beneficial effects in a mouse model of radiation pneumonitis.[8] Cyclosporin A or pentoxifylline combined with tocopherol may be of value but their actions are delayed.[9,10]

In conclusion, ^{131}I-labeled lipiodol-induced interstitial pneumonia is a severe disease that may be frequently undiagnosed. Better knowledge of this disease's pathophysiology, incidence and clinical characteristics is necessary to better assess the risk/benefit ratio of ^{131}I-labeled lipiodol use in hepatocellular carcinoma treatment, especially when curative treatment such as liver transplantation or surgical resection are alternative options.

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