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Case report

A case of miriplatin-induced lung injury

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ABSTRACT

A 69-year-old man with an 8-year history of hepatocellular carcinoma (HCC) was hospitalized for treatment of recurrent tumour. In 2010, the first transcatheter arterial chemoembolization (TACE) using miriplatin with agents (Lipiodol Ultra-Fluid) was performed and did not occur any adverse events. In 2014, since his HCC recurred, the TACE using miriplatin with agents was performed. Following this therapy, pyrexia occurred on day 3, followed by respiratory failure with cough and dyspnea on day 5. Chest radiography revealed scattered infiltration in the right upper lung fields, and chest computed tomography revealed ground grass attenuations, indicating fibrotic non-specific interstitial pneumonia. These findings progressively deteriorated, and a diagnosis of miriplatin-induced lung injury was made. His respiratory failure also progressively deteriorated. Treatment with pulse methylprednisolone therapy resulted in a dramatic improvement in both patient symptoms and radiological abnormalities.

1. Introduction

Hepatocellular carcinoma (HCC) is not the most common cancer worldwide, although it is the most prevalent type of cancer in some developing countries. Although the 5-year-survival rate is almost 40% in Japan, the majority of HCC patients are not candidates for curative therapies [1]. The use of transcatheter arterial chemoembolization (TACE) as palliative therapy was first reported in the 1970s. TACE significantly reduces mortality and, therefore, is widely used [2,3]. Shibata et al. have reported that the combination of cisplatin and lipiodol may be more effective for advanced HCC [4]. In Japan, the use of miriplatin hydrate as a TACE agent was approved in 2010. Miriplatin is characterized by a long-term sustained release into the tumour tissue, and an efficacy equal to cisplatin [5,6].

Drug-induced lung injury (DILI) is observed occasionally. DILI can involve cytotoxic and immune-mediated types. The severity of DILI is variable, and respiratory failures are observed in severe cases of DILI. The radiographic and pathologic findings of DILI are so variable. Drug-induced lymphocyte stimulation test (DLST) may be effective, when DILI is diagnosed. In the treatment of severe DILI, the mechanical ventilation may be necessary and the steroid therapy may be effective. Although lung injury can occur as an adverse effect of any drug treatment, including miriplatin, this is the first reported case of miriplatin-induced lung injury.

2. Case report

A 69-year-old man with history of chronic HCV infection, liver cirrhosis, and HCC, diagnosed in 2006, was admitted to our hospital with suspected HCC recurrence in 2014. The first TACE with miriplatin and agents (Lipiodol Ultra-Fluid) was performed in 2010 and there were not any adverse events. There was no past history regarding the respiratory and allergic disease for the patients, and there was no sign of hepatopulmonary syndrome. Before this TACE, the blood gas analysis showed pH 7.412, $PaCO_2$ 42 torr and PaO_2 82 torr, and revealed the serum level of IgE of 70 UA/mL.

Laboratory examinations obtained at presentation revealed the serum level of prothrombin induced by vitamin K absence-II (PIVKA-II) of 22,652 IU/mL and alpha-fetoprotein (AFP) of 46 ng/mL (lens culinaris agglutinin-reactive AFP isoform 3 fraction; 85%).

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Chest radiography on admission showed no abnormal findings. The tumour was classified as Child-Pugh B (9 points; no existed encephalopathy and ascites, 42% of prothrombin time, 1.58 mg/dL of serum bilirubin, and 2.6 g/dL of serum albumin) and tumour-node-metastasis stage III ($T_3N_0M_0$). Abdominal computed tomography (CT) revealed multiple liver tumours (diameters: 30 mm in S7, and 23 mm and 19 mm in S5). As a result, TACE was performed with a suspension of miriplatin (60 mg) in Lipiodol (3.0 mL) through the anterior segmental branch of right hepatic artery, and with a suspension of miriplatin (50 mg) in Lipiodol (2.5 mL) through the post-anterior segmental branch of right hepatic artery. Three days following TACE therapy, pyrexia was noted, and respiratory failure, with associated cough and dyspnoea, occurred on day 5. On day 4 the chest radiography revealed a light infiltration in the right upper lung fields (Fig. 1a). On day 5, scattered infiltration was seen in the same fields (Fig. 1b). The P/F ratio had decreased to 205 on day 5 and the laboratory examinations obtained (Table 1). We diagnosed the left heart failure or the infectious disease firstly. Therefore, the oxygen therapy and the treatments with Levofloxacin and Furosemide were started. However, the chest CT revealed ground glass attenuations (GGAs) with organization of the alveolar exudate and dense consolidation in the right upper lobe, and an air-bronchogram was noted on day 5. Interlobular septal thickening was also noted (Fig. 1d). These findings were consistent with a diagnosis of fibrotic non-specific interstitial pneumonia (NSIP). Within 2 days, radiological findings and symptoms of respiratory failure had progressively deteriorated, with the observation of bilateral pleural effusions and expanded GGAs, and a P/F ratio of 70 (Fig. 1c and e).

A negative DLST was found in this case, and the serology test for autoantibodies was negative. His sputum and blood cultured were negative. And the biomarker of blood and urine (endotoxin, procalcitonin, beta-D-grucan, antigen of Streptococcus pneumoniae, antigen of Legionella, IgM and IgG of Cytomegalovirus, and so on.) were negative. Plasma N-terminal pro-Brain natriuretic peptide (NT-proBNP) was 334 pg/ml, and the ultrasound cardiography revealed that cardiac function was unaffected. Therefore, on day 7, we made a diagnosis of miriplatin-induced lung injury rather than infectious diseases and heart failure, although bronchoalveolar lavage could not be performed because of the severe respiratory

Table 1
Examination in day 5 after TACE.

Hematology		**Serology**	
WBC	5900/μl	CRP	5.58 mg/dl
Neut	84.5%	IgE	202 IU/ml
Lym	9.0%	KL-6	301 U/ml
Mo	5.0%	ANA	(−)
Eo	1.0%	PR3-ANCA	(−)
Hb	11.2 g/dl	MPO-ANCA	(−)
PLT	5.7 × 104/μl	anti-Scl-70 Ab	(−)
PT	44%	anti-Jo-1 Ab	(−)
Fib	159 mg/dl	anti-CCP Ab	(−)
D-dimer	12.58 ng/ml	**Biological test**	
Blood chemistry		endotoxin	(−)
TP	5.1 g/dl	β-D grucan	(−)
T-Bil	4.36 mg/dl	sputum culture	(−)
AST	69 IU/l	blood culture	(−)
ALT	48 IU/l	**Blood gas analysis**	
LDH	315 IU/l	pH	7.434
BUN	20.8 mg/dl	$PaCO_2$	46.8 torr
CRE	0.86 mg/dl	PaO_2	41.1 torr
Na	143 mEq/l	HCO_3	30.6/mmol/l
K	3.9 mEq/l	**DLST**	
FBS	104 mg/dl	miriplatin	(−)
		Lipiodol	(−)

ANA; anti-nuclear antibody PR3-ANCA; proteinase 3- anti-neutrophil cytoplasmic antibody MPO-ANCA; myeloperoxidase-ANCA Ab; antibody anti-Scl-70 Ab; antiscleroderma-70 Ab anti-CCP Ab; anti-cyclic citrullinated peptide Ab.

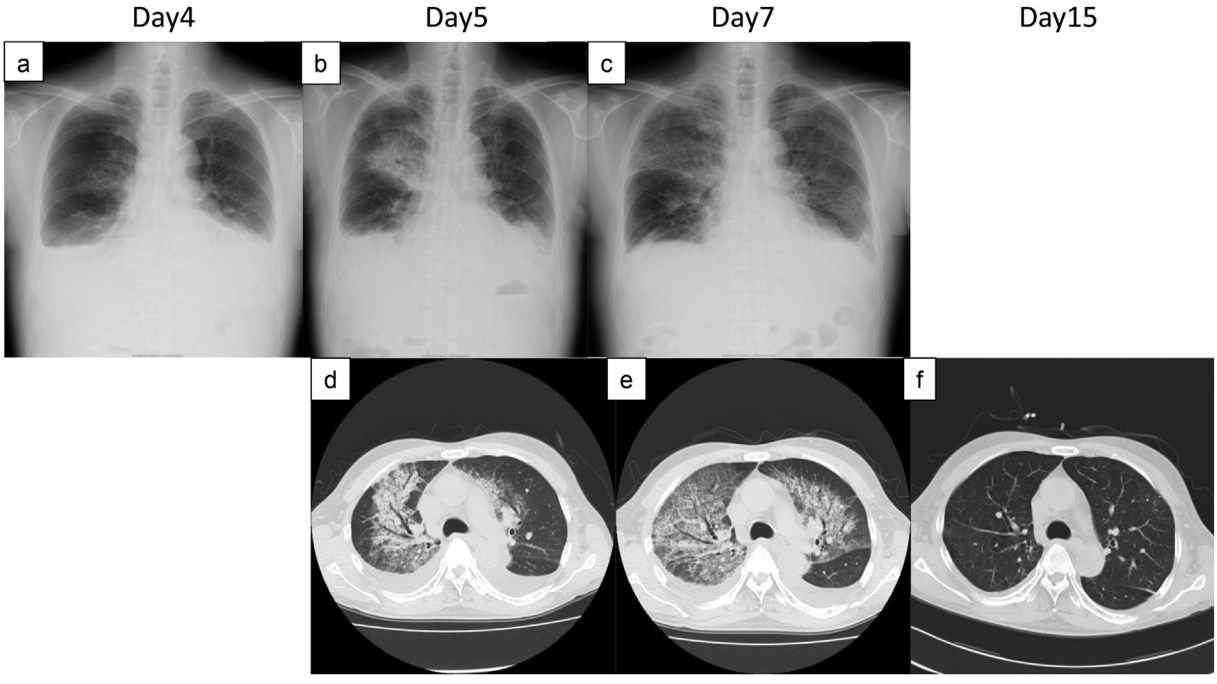

Fig. 1. Chest X-ray and CT findings after TACE. (a) On day 4, A chest radiograph obtained following treatment with TACE showed an infiltration in the right middle lung fields. (b) On day 5, the infiltration had progressively expanded and become denser, and new infiltrations were visible in the left lower lung field. (c) On day 7, the infiltrations had been replaced with ground glass opacities and expanded to the whole lung field. (d) Chest CT on day 5 revealed dense consolidations, an air bronchogram, and thickening of the interlobular septum in both upper lobes. These consolidations involved traction bronchiectasis. Bilateral pleural effusions were present, but no mediastinal lymph node enlargement was seen. (e) On day 7, these dense consolidations had expanded and been replaced by GGOs, and the thickening of the interlobular septum was more marked. (f) On day 15, the radiographic findings had dramatically improved.