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【 CASE REPORT 】

Acute Exacerbation of Idiopathic Interstitial Pneumonia in a Patient with Hepatocellular Carcinoma after Transcatheter Arterial Therapy Using Miriplatin

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Abstract:
A 76-year-old Japanese woman with recurrent hepatocellular carcinoma presented with acute exacerbation of idiopathic interstitial pneumonia (AE-IIP) after transcatheter arterial therapy using miriplatin. She had a history of preexisting IIP five years before presenting at our hospital. On day 4 after transcatheter arterial therapy, she complained of shortness of breath. Subsequently, she developed acute respiratory failure on day 11 after transcatheter arterial therapy. Chest computed tomography revealed extensive ground-glass opacity and traction bronchiectasis in bilateral lung fields; subsequently, she was diagnosed with AE-IIP triggered by transcatheter arterial therapy using miriplatin. Despite systemic administration of high-dose corticosteroid and cyclophosphamide, she died of respiratory failure on day 36.

Key words: acute exacerbation, idiopathic interstitial pneumonia, miriplatin, transcatheter arterial therapy

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common types of cancer in Japan. Transcatheter arterial therapy, including transcatheter arterial chemoembolization (TACE) and transcatheter arterial infusion (TAI), has been widely used to treat advanced HCC (1). The 5-year survival rate of patients with advanced HCC who receive TACE has been reported to be as high as 26-39% (2, 3). In 2009, the Japanese Ministry of Health, Labour and Welfare approved miriplatin, a lipophilic cisplatin derivative used in TACE and TAI, for the treatment of HCC. Several studies have reported the efficacy and safety of TACE using miriplatin for treating HCC (1, 4-6). In recent years, TACE using miriplatin has become a standard protocol for treating HCC.

Miriplatin is known to induce several adverse effects in the hepatobiliary, hematologic, and gastrointestinal systems. However, the incidence of adverse events of miriplatin in the pulmonary system has rarely been reported. Thus far, only two cases of miriplatin-induced interstitial lung disease (ILD) (7, 8) have been reported. However, acute exacerbation (AE) of preexisting idiopathic interstitial pneumonia (IIP) caused by TACE and TAI using miriplatin has not been reported.

We herein report a patient with HCC who developed an AE of preexisting IIP after TACE and TAI using miriplatin.

Case Report

A 76-year-old woman with a 5-year history of chronic hepatitis C virus infection, liver cirrhosis, and HCC was admitted to our hospital. She had received TACE using epirubicin (50 mg/body) 5 years earlier. Chest computed tomography (CT) performed before TACE using epirubicin revealed bilateral subpleural reticulation. The differential diagnosis included secondary causes of ILD, such as connective tissue disease-associated ILD, vasculitis, hypersensitivity pneumonitis, pneumoconiosis, drug-induced pneumonia, infection, eosinophilic pneumonia, sarcoidosis, and others.

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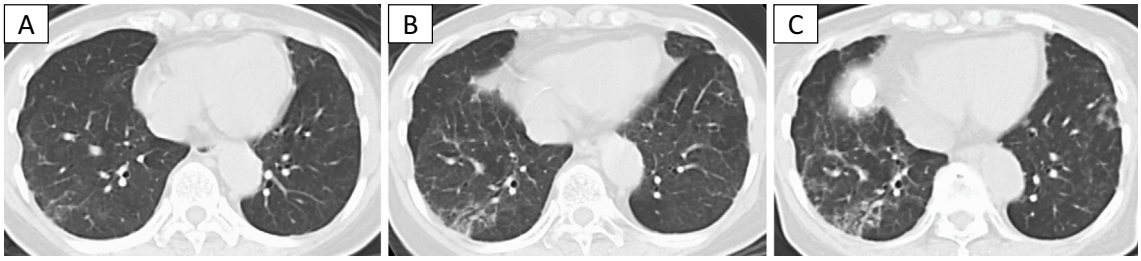

Figure 1. The course of CT scans before transcatheter arterial therapy using miriplatin. A: Chest CT scan obtained five years before presenting at our hospital, when she was first diagnosed with IIP, showing bilateral subpleural reticulation. B: Results of chest CT performed two years ago. C: Results of chest CT performed six months ago, when HCC recurred, demonstrating the slow progression of IIP over the past four years. CT: computed tomography, IIP: idiopathic interstitial pneumonia

Laboratory tests were negative for antineutrophil cytoplasmic antibody-associated vasculitis and autoantibodies associated with any connective tissue diseases. A physical examination revealed no findings such as rash or arthralgia. She had no history of antigen inhalation that might cause hypersensitivity pneumonitis or pneumoconiosis. In addition, she had not consumed any new drugs or supplements (9). Based on these findings and according to the American Thoracic Society/European Respiratory Society (ATS/ERS) International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias (10), she was ultimately diagnosed with IIP.

Chest CT demonstrated the slow progression of IIP over the past five years (Fig. 1). TACE using epirubicin for treating HCC was repeatedly administered until two years before she presented at our hospital. She received second-line treatment with TACE using miriplatin (120 mg/body) from 3 months before presenting at our hospital owing to HCC recurrence. Subsequently, she exhibited exertional dyspnea. Two months after the treatment initiation, CT revealed portal vein invasion of the HCC, so HCC was diagnosed as refractory to TACE using miriplatin, preventing further administration of TACE using miriplatin. Therefore, TAI using miriplatin (100 mg/body) was next initiated.

On day 4 after TAI initiation, the patient complained of dry cough and acute worsening dyspnea. On day 11, her peripheral oxygen saturation (SpO_2) was 98% as evaluated during face mask administration of oxygen (5 L/min), indicating acute respiratory failure. An arterial blood gas analysis showed that the partial pressure of arterial oxygen (PaO_2) was 131.6 mmHg with 5 L/min, and the PaO_2/fraction of inspiratory oxygen (FiO_2; P/F) ratio was estimated to be 329. On a physical examination, fine crackles were audible in the bilateral lower lung fields. Laboratory tests revealed elevated serum levels of the biomarkers Krebs von den Lungen-6 (KL-6: 4,303 U/mL), surfactant protein D (SP-D: 1,072 ng/mL), and lactate dehydrogenase (LDH: 648 U/mL). Serum levels of beta (β)-D-glucan and procalcitonin were below detectable limits, and cytomegalovirus-pp65 antigens in the blood were negative (Table). Chest radiography revealed bilateral ground-glass opacity and infiltrative shadow. High-resolution CT (HRCT) demonstrated even more extensive geographic distribution of ground-glass opacity and infiltrative shadow with traction bronchiectasis in both the lungs superimposed on underlying fibrotic opacities (Fig. 2). The miriplatin-triggered AE of preexisting IIP was diagnosed based on several factors: the clinical course of worsening preexisting IIP after the administration of miriplatin; an acute clinically worsening respiratory condition that developed within one month, meeting a new definition and diagnostic criteria for AE of idiopathic pulmonary fibrosis (IPF); new radiologic abnormalities on HRCT; and the absence of other obvious clinical causes, such as fluid overload and left heart failure (11).

Thus, miriplatin for treating HCC was discontinued, and systemic corticosteroid pulse therapy with intravenous methylprednisolone (1,000 mg/day for 3 days) was initiated. Despite 1 course of steroid pulse therapy, the P/F ratio decreased to 86.4, and the patient was intubated and mechanically ventilated. Thereafter, the patient was subsequently administered a pulse cyclophosphamide (500 mg/day) and an additional two courses of corticosteroid pulse therapy. However, her respiratory condition further deteriorated, and she ultimately died of respiratory failure on hospital day 36 (Fig. 3).

Discussion

AE-IIP, including IPF, is a severe and life-threatening condition. In 2016, a new definition and diagnostic criteria for AE-IPF were proposed by an international working group (11). Based on the absence or presence of a cause, AE-IPF can be classified as an idiopathic or a triggered event (e.g. infection, post-procedural/postoperative, drug toxicity, and aspiration), resulting in worsening respiratory status (12). To our knowledge, this is the first case report of AE-IIP triggered by miriplatin for the treatment of HCC that was refractory to aggressive therapy with a combination of high-dose corticosteroid and cyclophosphamide.

In patients with lung cancer, several studies have reported that chemotherapy-related AE-ILD, including IIP, occurs in 5.6-43% of patients and leads to death in 27.9% pa-

Table. Examination on Day 11 after Transcatheter Arterial Infusion Using Miriplatin.

Hematology		Serology	
WBC	7,200 /μL	CRP	2.06 mg/dL
Neu	79.4 %	KL-6	4,303 U/mL
Lym	11.8 %	SP-D	1,072 ng/mL
Mo	4.8 %	ANA (CLEIA)	<10
Eo	3.6 %	PR3-ANCA	<3.5 U/mL
Hb	10.8 g/dL	MPO-ANCA	<3.5 U/mL
PLT	80×10^3 /μL	anti-ss-DNA Ab	<25 AU/mL
Blood chemistry		anti-RNP Ab	<10 U/mL
TP	6.4 g/dL	anti-Sm Ab	<10 U/mL
Alb	2.4 g/dL	anti-SS-A Ab	<10 U/mL
Na	135 mmol/L	anti-SS-B Ab	<10 U/mL
K	4.3 mmol/L	anti-Scl-70 Ab	<10 U/mL
Cl	102 mmol/L	anti-Jo-1 Ab	<10 U/mL
BUN	18.2 mg/dL	anti-centromere Ab	<10 U/mL
Cre	0.59 mg/dL	anti-ARS Ab	(-)
T-Bil	2.2 mg/dL	RF	35 IU/mL
AST	122 U/L	anti-CCP Ab	<4.5 U/mL
ALT	60 U/L	Biological test	
LDH	540 U/L	β-D glucan	<6.0 pg/mL
PCT	0.19 ng/mL	CMV antigen	(-)
BNP	129.4 pg/mL	Blood gas analysis (F.M.: 5L/min)	
Coagulation		pH	7.470
PT	61 %	PaO_2	131.6 mmHg
APTT	80 %	$PaCO_2$	30.9 mmHg
D-dimer	4.8 μg/mL	HCO_3^-	22.0 mmol/L

Ab: antibody, ANA: anti-nuclear antibodies, ARS: aminoacyl tRNA synthetase, BNP: brain natriuretic peptide, CCP: cyclic citrullinated peptide, CLEIA: chemiluminescent enzyme immunoassay, CMV: cytomegalovirus, F.M.: face mask, KL-6: Krebs von den Lungen-6, MPO-ANCA: myeloperoxidase-anti neutrophil cytoplasmic antibody, PCT: procalcitonin, RF: rheumatoid factor, RNP: ribonucleoprotein, PR3-ANCA: proteinase 3-anti neutrophil cytoplasmic antibody, Scl-70: scleroderma-70, Sm: smith, SP-D: surfactant protein D, SS-A: Sjögren Syndrome-A, SS-B: Sjögren Syndrome-B, ss-DNA: single strand deoxyribonucleic acid

tients (13-15). In addition, Kudoh et al. reported that preexisting ILD is a strong risk factor for AE-ILD in patients with non-small cell lung cancer (odds ratio, 4.80-25.27) compared with those without ILD (13). However, there have been no reports of AE-IIP after transcatheter arterial therapy, including TACE and TAI, in patients with HCC and preexisting IIP. Neu et al. reviewed case reports, case series, and original studies of pulmonary complications after TACE in patients with HCC. Pulmonary complications, including acute lung injury and acute respiratory distress syndrome, occur in 0.05-2.3% of patients and are assumed to be related to lung damage caused by pulmonary oil embolism and chemotherapeutic agents. One underlying mechanism explaining these complications is the migration of oil emulsions into the pulmonary vasculature via arteriovenous shunts within the lesion of HCC (16).

Transcatheter arterial therapy, including TACE and TAI using lipiodol and anticancer agents, is widely used to treat HCC (17). In TACE, we administer anticancer agents and embolize the tumor nutrient arteries using gelatin sponge particles. Conversely, in TAI, although anticancer agents are injected, embolization using gelatin sponge particles is not performed. TACE is not always indicated, especially in patients with a poor liver function, large tumor size, and tumor metastasis in multiple lobes, because the risk associated with treatment-related death is relatively high in such patients (1, 18). Anticancer agents such as epirubicin, doxorubicin, mitomycin C, cisplatin, and neocarzinostatin are commonly used in TACE. In October 2009, miriplatin, belonging to the family of platinum agents, was approved as a TACE agent for treating HCC. The results of several previous studies on TACE using miriplatin suggest that miriplatin may be one of the safest and most efficacious therapeutic agents (1, 6, 17). However, TACE is not recommended in patients with distant metastases and vascular invasion. In our case, TAI using miriplatin was selected because of the presence of portal vein invasion.

Only two cases of drug-induced ILD by transcatheter ar-

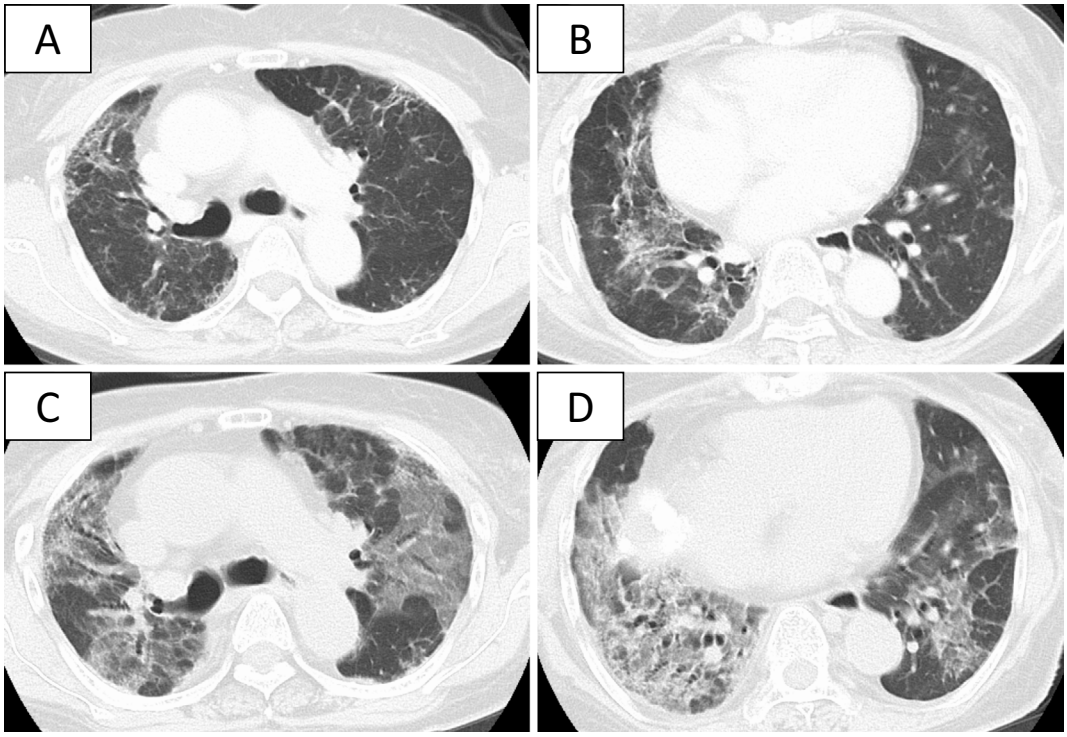

Figure 2. **Chest CT before and after transcatheter arterial therapy using miriplatin. A, B: Chest CT before transcatheter arterial therapy using miriplatin, showing interstitial pneumonia. C, D: Chest CT after transcatheter arterial therapy using miriplatin on day 11, demonstrating extensive ground-glass opacity, infiltrative shadow, and traction bronchiectasis in bilateral lungs. CT: computed tomography**

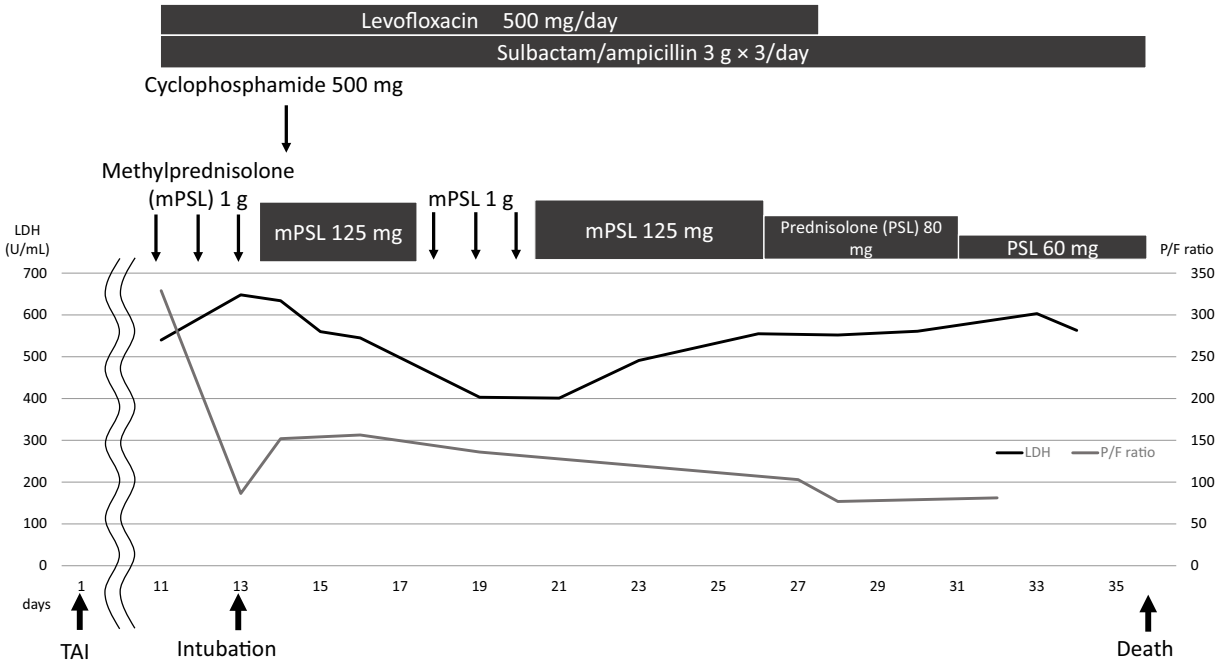

Figure 3. **The clinical course of the patient in our study. TAI: transcatheter arterial infusion**

terial therapy using miriplatin have been reported (7, 8). Both patients demonstrated progressively worsening respiratory failure after the initial administration of miriplatin and recovered after treatment using corticosteroid pulse therapy and respiratory care, including mechanical ventilation or noninvasive positive pressure ventilation. Prior to transcatheter arterial therapy using miriplatin, the patients in these reported cases had no preexisting ILD, including IIP, or any respiratory symptoms. In contrast, our patient died of respiratory failure, despite treatment with a high-dose corticoster-

oid and cyclophosphamide and respiratory care with mechanical ventilation. In another report, the CT findings of a patient revealed a fibrotic nonspecific interstitial pneumonia pattern (8). Our patient's CT findings showed a diffuse alveolar damage (DAD) pattern. Patients with DAD patterns have poorer a prognosis than those without DAD patterns (19). In addition, our patient had a 5-year history of IIP and suffered shortness of breath in her daily life. Considering her clinical course, she was eventually diagnosed with AE-IIP triggered by transcatheter arterial therapy using miriplatin.

Several limitations associated with the present case study warrant mention. Lipiodol is generally used for TACE and TAI. In our case, however, lipiodol was used for TACE and TAI while also using miriplatin before the development of AE-IIP. AE-IIP may therefore have been caused by either or both miriplatin or lipiodol. However, our patient had been previously administered lipiodol several times for the treatment of HCC. We therefore concluded that the administration of miriplatin rather than lipiodol triggered AE-IIP. The influence of lipiodol alone on lung complications in the present case is unclear; however, lipiodol and miriplatin may synergize and potentiate the risk of AE-IIP when used together.

To our knowledge, a case of fatal AE-IIP after transcatheter arterial therapy using miriplatin has not yet been reported. Serious complications of AE-IIP should be carefully monitored when providing transcatheter arterial therapy using miriplatin in patients with HCC with preexisting IIP.

The authors state that they have no Conflict of Interest (COI).

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