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Case Report

Refractory Irinotecan-Induced Interstitial Pneumonitis after Treatment of Metastatic Lung Cancer from the Rectum : A Case Report

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ABSTRACT

A 64-year-old man underwent low anterior resection for rectal cancer at a local hospital in 1999. In February 2005, metastases to the brain and left lung were detected. The brain metastasis was treated with focal radiation therapy (gamma knife), and lung metastasis was treated with radio frequency ablation. The patient was referred to our department for systemic chemotherapy with irinotecan. Seventeen days after the first dose of irinotecan, he came to our emergency room with acute respiratory failure due to interstitial pneumonitis. Steroid pulse therapy was unsuccessful, and the patient's physical condition gradually worsened until his death in November 2005. Autopsy revealed no evidence of malignant cells in the left lung. However, interstitial pneumonitis with extensive fibrosis was confirmed. Myelosuppression and diarrhea are well-known adverse effects of irinotecan. Interstitial pneumonitis in cases of metastatic lung cancer from colorectal cancer accounted for only 0.05% (8 of 15,385) of all cases of irinotecan-induced side effects in one previous study. However, clinicians should be aware of the possibility of interstitial pneumonitis after the administration of irinotecan for metastatic lung cancer following colorectal cancer.

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Key words : irinotecan, interstitial pneumonitis, metastatic lung cancer

INTRODUCTION

Chemotherapy has been performed more frequently as outpatient therapy, which may improve the patient's quality of life[1]. Irinotecan is frequently used to treat colorectal cancer ; myelosuppression and diarrhea are common side effects[2,3], but pulmonary complications are rarely reported. We report herein a patient with rectal cancer metastatic to the brain and lung in whom autopsy-proven interstitial pneumonitis developed, presumably because of irinotecan.

CASE REPORT

A 64-year-old man underwent low anterior resection for rectal cancer at a local hospital in 1999. The pathological diagnosis was T2, n0, M0 by TNM classification.

He had been observed as an outpatient of the

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hospital since then. In February 2005, metastases to the brain and left lung were detected. The brain metastasis was treated with focal radiation therapy (gamma knife) at our hospital, and the left lung metastasis was treated with radio frequency ablation (RFA) at another University hospital. He was referred to our department for systemic chemotherapy.

After the patient recovered from pneumothorax following RFA, he began chemotherapy, which consisted of irinotecan, 80 mg/m² IV, 3 times every 2 weeks and withdrawal of treatment for 1 month. The first course of irinotecan was started in August 2005, after which no side effects were observed. Two weeks after the first administration of irinotecan, the second administration of irinotecan was started. Four days after the second one, he returned to the Emergency Department with a high fever (38.5°C) and chest discomfort. Blood tests revealed a white blood cell count of 3,700/ml and a C-reactive protein level of 4.3 mg/dl. In addition, a chest X-ray film failed to show pneumonitis (Fig. 1). Loxoprofen sodium was prescribed for pyrexia and pain relief.

Two days later, the patient again visited the emergency room because of acute respiratory failure, which required endotracheal intubation and admission to the intensive care unit. A chest X-ray film (Fig. 2) and computed tomography (CT) (Fig. 3) now clearly demonstrated interstitial pneumonitis. A diffuse ground-glass infiltrate was visible throughout both lungs. *Pseudomonas aeruginosa* was detected on sputum culture and was treated with antibiotics. The patient also received an antifungal agent because of high β-D glucan levels in blood. Because the respiratory status had improved by late September, the endotracheal tube was removed and the patient was

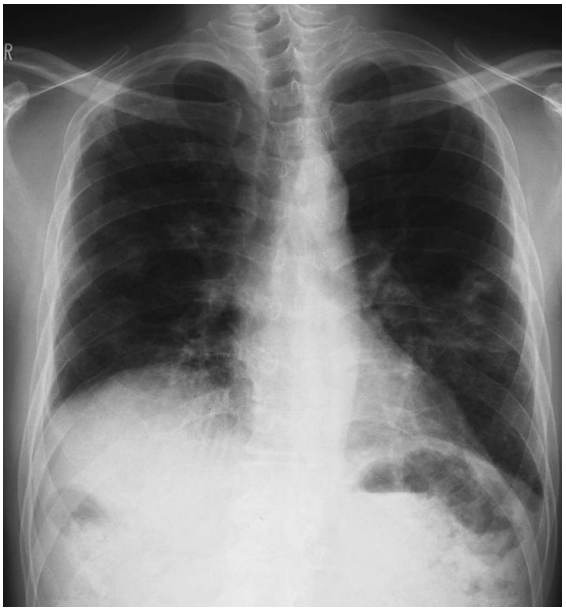

Fig. 1. Imaging diagnosis before admission
The pneumonitis image could not be evaluated for progression because of previous RFA of the lung metastasis.

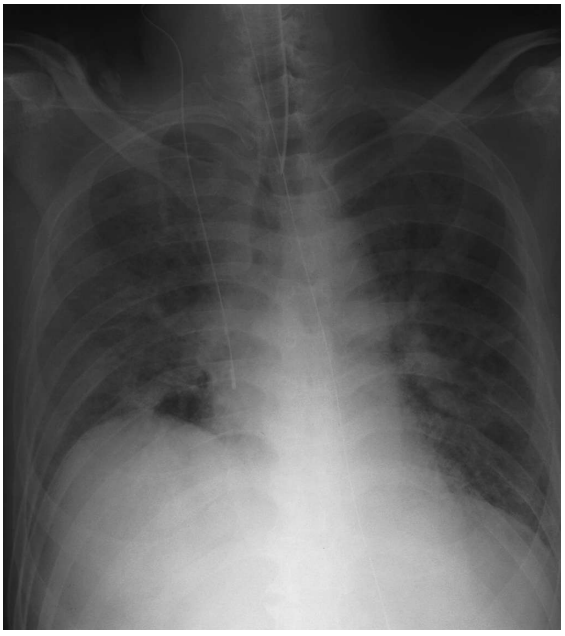

Fig. 2. Chest X-ray film on admission demonstrated interstitial pneumonitis in both lungs.

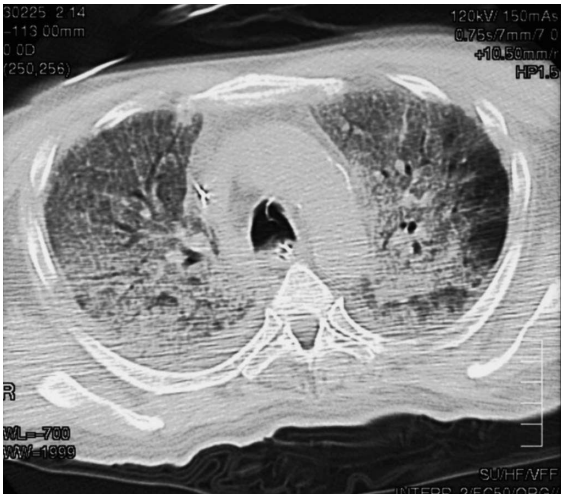

Fig. 3. Chest CT on admission demonstrated severe interstitial pneumonitis in both lungs.

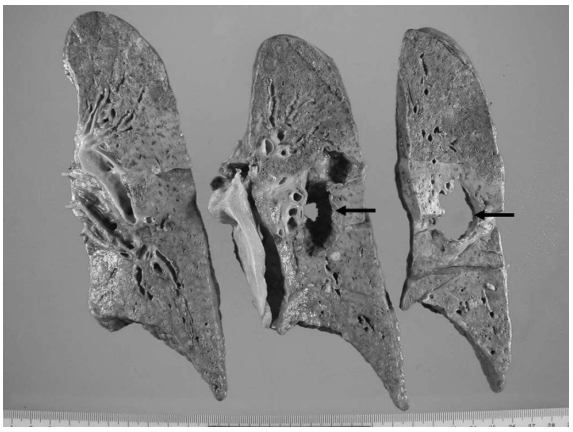

Fig. 4. Lungs at autopsy
No metastatic malignant lesions were detected in the left lung. The arrows indicate areas treated with RFA.

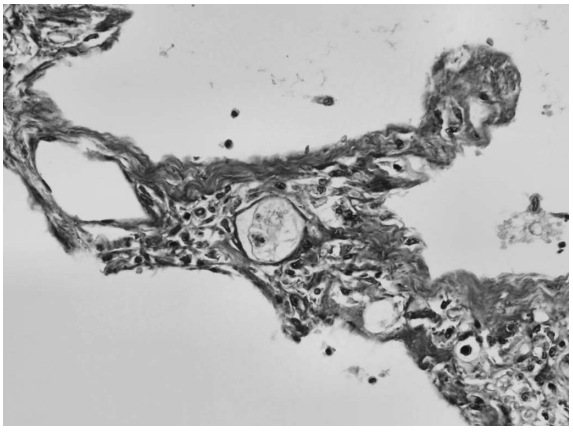

Fig. 5. Pathological examination of the lungs at autopsy (Masson-Noguchi staining ×50)
Interstitial pneumonitis with extensive fibrosis was confirmed in both lungs, and no metastatic malignant cells were detected.

returned to a general ward.

Ten days later, the patient's respiratory status worsened, necessitating endotracheal intubation and mechanical ventilation. The patient was given steroid pulse therapy, which was unsuccessful, and died in November 2005. At autopsy no metastatic malignant lesions were found in the left lung, but interstitial pneumonitis with extensive fibrosis had replaced much of the normal alveolar spaces in both lungs (Fig. 4). Masson-Noguchi staining showed diffuse interstitial lymphocytic infiltrates, especially around the blood vessels, and fibrosis of the alveolar septa (Fig. 5).

Discussion

In chemotherapy for colorectal cancer, 5-fluorouracil is an important drug. Regimens using irinotecan and oxaliplatin, such as FOLFOX[4] and FOLFILI[5], have attracted attention recently for their high response rates. Irinotecan is now one of the most favored anticancer drugs for colorectal cancer. Myelosuppression and diarrhea are well-known adverse effects of irinotecan, but interstitial pneumonitis has been reported only after treatment for primary lung cancer[6,7].

In a developmental trial of irinotecan for non-small cell lung cancer[8], pneumonic side effects developed in 15 of 1,134 patient (1.3%)[9]. Interstitial pneumonitis developed in 1 of 17 patients (6%) in a phase I study of weekly irinotecan and in 6 of 73 cases (8%) in a phase II study[10]. In a postmarketing study of the side effects of irinotecan[9], interstitial pneumonitis developed in 132 of 15,385 patients (0.9%), of whom 109 had primary lung cancer. Furthermore, interstitial pneumonitis developed in 33 patients with primary lung cancer, of whom 8 had metastasis from colorectal cancer. Therefore, interstitial pneumonitis in cases of metastatic lung cancer from colorectal cancer accounted for only 6% (8 of 132 cases) of all cases of interstitial pneumonitis and only 0.05% (8 of 15,385 cases) of all cases of side effects. Interstitial pneumonitis in cases of metastatic lung cancer from colorectal cancer accounted for an extremely small percentage of all cases of side effects. To our knowledge, our report is the first of irinotecan-induced interstitial pneumonitis confirmed at autopsy in a patient with lung cancer metastatic from colorectal cancer.

Drug-induced pneumonitis is divided into two categories, cytotoxic and noncytotoxic types, according to the mechanism of the disorder[11,12]. Cytotoxic drugs cause disorders in type II alveolar epithelium and alveolar capillaries. In contrast, noncytotoxic drugs may produce pneumonitis by an immunological mechanism. In other words, an allergic reaction may be responsible. Discontinuation of irinotecan and early administration of corticosteroids are important for the treatment of drug-induced pneumonitis.

Noncytotoxic pneumonitis tends to improve rapidly with treatment, but cytotoxic pneumonitis is usually irreversible.

Predisposing factors for the development of pulmonary toxicity by different categories of cytotoxic agents include the total cumulative dose, the age of the patient, prior or concurrent radiotherapy, oxygen therapy, and treatment with other cytotoxic drugs[11].

In conclusion, cases of interstitial pneumonitis in metastatic lung cancer from colorectal cancer account for only 0.05% of all cases of irinotecan-induced adverse effects; however, clinicians should be aware of the possibility of pulmonary disease after administration of irinotecan for metastatic lung cancer following colorectal cancer.

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