

Fatal interstitial pneumonia caused by panitumumab-containing chemotherapy: a case report

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ABSTRACT A 49-year-old Japanese man visited our institution for the treatment of metastatic rectal cancer. He had no history of interstitial pneumonia or smoking. Although he achieved partial remission with combination chemotherapy consisting of 5-fluorouracil, leucovorin, and oxaliplatin plus bevacizumab, this regimen failed after 46 courses. A salvage chemotherapy consisting of 5-fluorouracil, leucovorin, and irinotecan plus panitumumab was initiated. However, 6 days after treatment initiation, asymptomatic hypoxia was detected. Chest computed tomography revealed interstitial lung disease; therefore, chemotherapy was discontinued and corticosteroid pulse therapy was immediately started. Chest computed tomography on day 20 of the salvage chemotherapy revealed progressive interstitial lesions with lung volume loss and mediastinal emphysema. He passed away a few days later because of respiratory failure. In conclusion, physicians should be aware of the adverse event wherein administration of chemotherapy containing an anti-epidermal growth factor receptor monoclonal antibody might result in a fatal outcome.

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Key words : **Rectal cancer, Interstitial lung disease, Panitumumab-containing chemotherapy, Fatal outcome, Corticosteroid pulse therapy**

INTRODUCTION

Most anti-neoplastic drugs have the potential to induce pulmonary toxicity in the lung parenchyma, airways, pleura, and pulmonary circulation. The mainstay of treatment of drug-induced pneumonia is to first identify and eliminate the causative agent as soon as possible¹⁾. Anti-epidermal growth factor receptor (EGFR) monoclonal antibodies, cetuximab

and panitumumab, are effective drugs for treating colorectal cancer (CRC) by competitively binding to the accessible extracellular domain of EGFR and inhibiting dimerization and subsequently, tumor growth and metastasis²⁾; however, they rarely induce interstitial lung disease (ILD). Only a few case reports have warned that anti-EGFR monoclonal antibody might potentially induce ILD in the treatment of a

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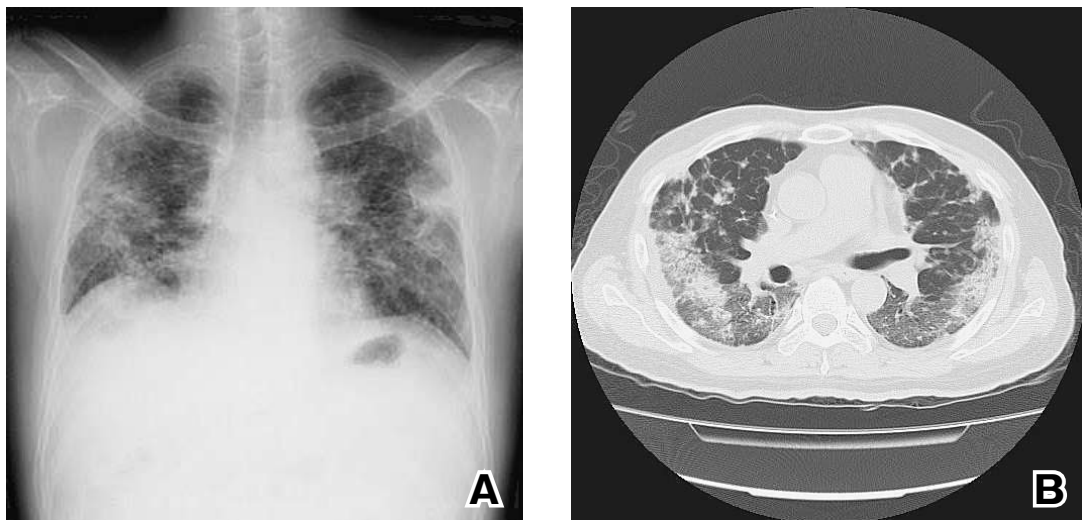


Fig. 1 Chest X-ray (A) and computed tomography (B) on day 11 of panitumumab-containing chemotherapy revealed bilateral patchy ground glass opacities and nodular lesions.

variety of malignancies, including CRC. Here we report a case of panitumumab-induced fatal ILD with a literature review.

CASE REPORT

A 49-year-old Japanese man visited our institution for the treatment of metastatic rectal cancer. He had no history of interstitial pneumonia or smoking and had been diagnosed with advanced rectal cancer 4 years earlier. He underwent low anterior resection and opted to receive adjuvant chemotherapy consisting of 5-fluorouracil (5-FU) and leucovorin (LV) for 6 months. Unfortunately, he was readmitted to our hospital 5 months later, because chest computed tomography (CT) revealed a recurrence with multiple lung metastases. A combination chemotherapy consisting of 5-FU, LV, and oxaliplatin (FOLFOX) plus bevacizumab was initiated and achieved a partial response. However, this regimen failed after 46 courses. Because his performance status was well preserved, a salvage chemotherapy consisting of 5-FU, LV, and irinotecan (FOLFIRI) plus panitumumab was initiated. Six days after the treatment began,

asymptomatic hypoxia was indicated. Chest X-ray and CT on day 11 of the salvage chemotherapy revealed interstitial pneumonia with multiple lung nodules (Fig. 1A and B). Differential diagnoses such as lymphangitis carcinomatosa, cardiac heart failure, and pulmonary infection were considered from the radiological findings, laboratory data, and negative sputum cultures; however, the patient's surfactant protein-D (226.6 ng/ml) and KL-6 (981 U/ml) levels were elevated, which is characteristic of ILD, and he was diagnosed with drug-induced ILD. The chemotherapy was discontinued and oral prednisone pulse therapy (70 mg/day) was immediately initiated. Chest CT on day 20 of salvage chemotherapy revealed progressive interstitial lesions with lung volume loss and mediastinal emphysema (Fig. 2). Although he received intensive therapy with mandatory ventilation, he passed away a few days later. No autopsy was performed.

DISCUSSION

Anti-EGFR therapies demonstrate certain activities in the treatment of CRC. Anti-EGFR monoclonal antibodies bind to the extracellular domain of EGFR

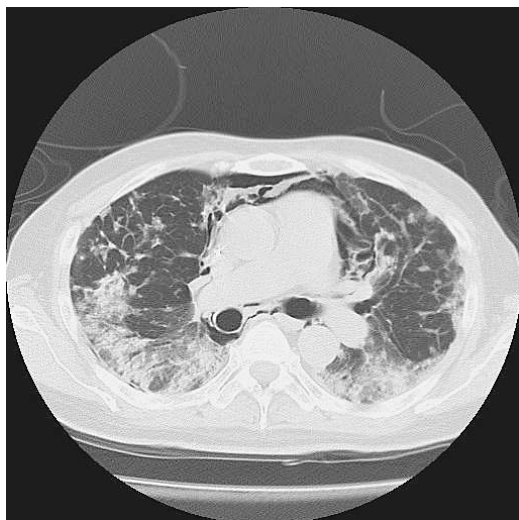


Fig. 2 Chest computed tomography on day 20 of panitumumab-containing chemotherapy revealed progressive interstitial lesions with lung volume loss and mediastinal emphysema.

preventing ligand binding and interrupting signal transduction. Phase II and III trials in patients with previously treated or untreated metastatic CRC, especially K-Ras wild type CRC, demonstrated antitumor activity of the anti-EGFR monoclonal antibody as a single agent or in combination with irinotecan- or oxaliplatin-based chemotherapies^{3, 4}). Moreover, the antibodies might cause severe non-hematological toxicities. A Japanese post-marketing surveillance of cetuximab in 2126 patients with metastatic CRC revealed that 21.5% experienced adverse drug reactions greater than grade 3⁵). While skin and gastrointestinal disorders were frequently observed, ILDs were observed in 1.2%

of patients (n = 24) and ILDs more than grade 3 were reported in 0.7% of patients (n = 15). The outcomes included recovery in 2 patients, lower severity in 6 patients, non-recovery in 5 patients, death in 10 patients, and unknown in 1 patient. This report indicated that approximately 40-60% of Japanese patients with cetuximab-induced ILD had poor prognoses. In their study, Kang *et al.*⁶) determined the incidence and clinical characteristics of adverse pulmonary reactions in patients treated with anticancer chemotherapy including monoclonal antibodies. They performed a retrospective cohort study that included patients who were treated with chemotherapy including rituximab, trastuzumab, cetuximab, or bevacizumab. In total, 1078 patients were included (418, 329, 122, and 209 were treated with rituximab, trastuzumab, cetuximab, and bevacizumab, respectively). Adverse pulmonary reactions were identified in 36 patients (3.5%) and the incidence differed among agents: cetuximab (9%), rituximab (5.3%), trastuzumab (0.6%), and bevacizumab (0.5%). In cases treated with cetuximab (n = 122), no patients experienced drug-induced ILD. ILD due to anti-EGFR monoclonal antibody has rarely been reported, unlike selective inhibitors of the EGFR tyrosine kinase domain⁷). Inhibition of EGFR signal transduction can induce fatal ILD in spite of different action mechanisms. We summarized the cases of severe ILD due to anti-EGFR monoclonal antibody⁸⁻¹¹) in Table 1. Three cases among the 5 in the English medical literature, including the present case, resulted in fatal outcomes

Table 1. Cases of severe ILD caused by chemotherapy including anti-EGFR monoclonal antibody

Author ^{Ref}	Age/Sex	Disease	Regimen	Time from initiation of chemotherapy to onset of ILD	Outcome
Chua W ⁽⁷⁾	78/M	Rectum	CPT-11/C-mab	60 days	Recovered
Shibahara H ⁽⁸⁾	60/M	Colon	CPT-11/C-mab	147 days	Dead
Lai JH ⁽⁹⁾	69/M	Colon	FOLFOX/C-mab	101 days	Dead
Yamamoto K ⁽¹⁰⁾	58/M	Colon	FOLFIRI/P-mab	15 days	Recovered
Present case	49/M	Rectum	FOLFIRI/P-mab	6 days	Dead

C-mab: cetuximab; CPT-11: irinotecan; EGFR: epidermal growth factor receptor; FOLFIRI: 5-fluorouracil, leucovorin, and irinotecan; FOLFOX: 5-fluorouracil, leucovorin, and oxaliplatin; ILD: interstitial lung disease; P-mab: panitumumab

due to ILD, although they were treated with steroid pulse therapy. To the best of our knowledge, ILD caused by panitumumab-containing chemotherapy has been described in two reports, including the present case.

Preexisting pulmonary fibrosis has been described as a risk factor for development of EGFR-TKI induced ILD and was likely a significant factor¹²⁾. In our present case, the patient had the history of repeated treatment of oxaliplatin, which had the significant potential to cause drug-induced ILD. It is possible that minute lung damage by the previous chemotherapy might lead to rapid progression of ILD by panitumumab-containing chemotherapy.

Chest CT clearly revealed the mediastinal emphysema in our present case. The most probable cause of mediastinal emphysema is the rupture of the alveolar walls caused by thoracic hyper pressure maneuvers, with the consequential escape of air into the interstitium and a further centripetal dissection along the broncho-vascular sheaths until it reaches the mediastinum through the hyllum. Occasionally, alveolar rupture can occur during an attack of asthma or as the result of a peripheral parenchymal affection of interstitial processes that lead to honeycombing¹³⁾.

From these findings, we inferred that rapid progression of ILD had caused the thoracic hyper pressure maneuvers and then mediastinal emphysema occurred.

In conclusion, our case indicated the need for physicians to be aware of the potential for ILD development and fatal outcomes in patients being treated with chemotherapy containing anti-EGFR monoclonal antibody.

Conflict-of-interest statement

All authors have no conflict of interest.

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