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CASE REPORT

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Interstitial pneumonia arising in a patient treated with oxaliplatin, 5-fluorouracil, and, leucovorin (FOLFOX)

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Abstract Information concerning the pulmonary toxicity of oxaliplatin with infusional 5-fluorouracil plus leucovorin (FOLFOX) is very limited. We herein report the case of a patient with FOLFOX-induced interstitial pneumonia. An 82-year-old man with unresectable colon cancer liver metastases was referred to our department for chemotherapy with the FOLFOX protocol. After the administration of ten cycles, he visited our outpatient clinic with a 2-week history of coughing and shortness of breath; he was afebrile. A chest radiograph showed reticular shadows with ground-glass opacities mainly involving the middle and lower zones of the right lung. Computed tomography depicted ground-glass opacities with superimposed reticulation in the right lung. A diagnosis of FOLFOX-induced interstitial pneumonia was made based on the clinical course and imaging findings. The symptoms disappeared within 3 days after the cessation of the FOLFOX regimen and the initiation of high-dose corticosteroid treatment. Two months after the initiation of the corticosteroid treatment, complete remission of the radiological abnormalities was confirmed; thereafter, interstitial pneumonia did not recur despite the reintroduction of 5-fluorouracil/leucovorin alone, suggesting that 5-fluorouracil/leucovorin alone was not responsible for the development of the interstitial pneumonia. Thus, oxaliplatin, alone or in combination with 5-fluorouracil/leucovorin, may have caused the interstitial pneumonia in this patient. Once interstitial pneumonia has occurred, cessation of the regimen is mandatory, and high-dose corticosteroid treatment is commonly given to rescue patients from this potentially lethal complication.

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Introduction

Oxaliplatin with infusional 5-fluorouracil plus leucovorin (FOLFOX) is a promising chemotherapeutic regimen for unresectable or metastatic colorectal cancer.[1] Based on the results of the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial, the United States Food and Drug Administration has approved the FOLFOX regimen for postoperative adjuvant therapy in patients with stage III colon cancer.[2]

Among known FOLFOX-induced toxicities, neurological, hematopoietic, and gastrointestinal toxicities are common.[3] Pulmonary toxicity of this regimen is unusual; only six such cases have been reported.[4–8] Because of the rarity of such cases, there has been no established guideline for the management of FOLFOX-induced interstitial pneumonia. We herein report the case of an additional patient with FOLFOX-induced interstitial pneumonia.

Case report

An 82-year-old man with unresectable colon cancer metastases to the liver was referred to our department for chemotherapy. He had no history of cigarette smoking, pulmonary disease, or significant occupational exposure. A chest radiograph before the initiation of chemotherapy showed no cardiopulmonary abnormalities (Fig. 1a). The patient received chemotherapy with the FOLFOX protocol, consisting of a biweekly regimen of l-leucovorin (100 mg/m^2) followed by bolus 5-fluorouracil (400 mg/m^2) and a subsequent 22-h infusion of 5-fluorouracil (600 mg/m^2), repeated on two consecutive days. Oxaliplatin (85 mg/m^2) was given on the first day only, concurrent with the

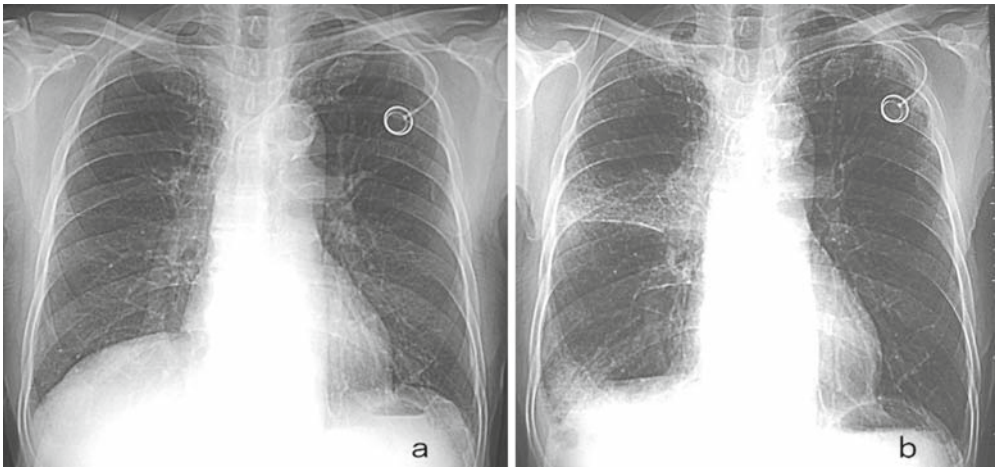

Fig. 1. **a** Chest radiograph before the initiation of oxaliplatin, 5-fluorouracil, and leucovorin (FOLFOX) treatment. There are no cardiopulmonary abnormalities. **b** Chest radiograph at the onset of FOLFOX-induced interstitial pneumonia. There are reticular shadows with ground-glass opacities mainly involving the middle and lower zones of the right lung, with no enlargement of the heart

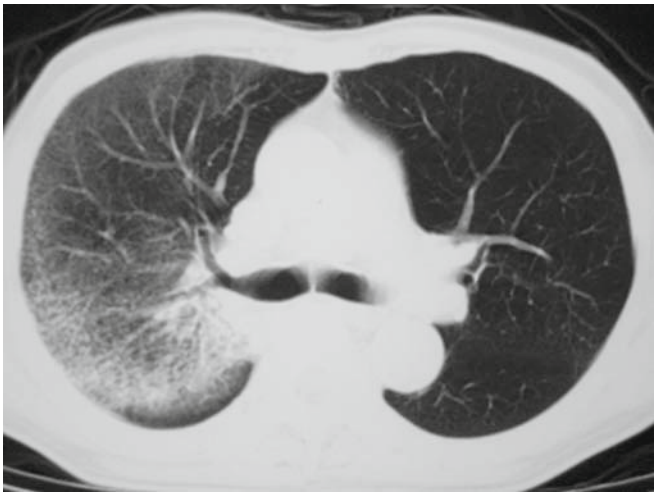

Fig. 2. Chest computed tomography at the onset of FOLFOX-induced interstitial pneumonia. There are ground-glass opacities with superimposed reticulation in the right lung

l-leucovorin. The hepatic tumors remained stable for 5 months.

After the administration of ten cycles of the FOLFOX regimen, he visited our outpatient clinic with a 2-week history of coughing and shortness of breath. On admission, he was afebrile; lung auscultation revealed inspiratory crackles in the right lung. Arterial blood gas analysis while he was breathing room air showed a pH of 7.42, a *P*aCO2 of 34.7 mmHg and a *P*aO2 of 61.5 mmHg. A chest radiograph showed reticular shadows with ground-glass opacities mainly involving the middle and lower zones of the right lung, with no enlargement of the heart (Fig. 1b). Chest computed tomography showed ground-glass opacities with superimposed reticulation in the right lung (Fig. 2). Based on the clinical course and imaging findings, a diagnosis of FOLFOX-induced interstitial pneumonia was made. After the cessation of FOLFOX and a high-dose infusion of corticosteroid (methylprednisolone sodium succinate; 1000 mg/day) for 3 days, the symptoms disappeared. Thereafter, prednisolone (30 mg once daily, then tapered down) was administered orally for 2 months. Two months after the initiation of the corticosteroid treatment, complete remission of the radiological abnormalities was confirmed.

As tumor progression was observed 1 month after the cessation of FOLFOX, chemotherapy using 5-fluorouracil/l-leucovorin alone (a biweekly regimen with l-leucovorin (100 mg/m^2) followed by bolus 5-fluorouracil (400 mg/m^2) and a subsequent 22-h infusion of 5-fluorouracil (600 mg/m^2), repeated on two consecutive days), was reintroduced. The interstitial pneumonia did not recur despite the administration of 5-fluorouracil/leucovorin alone for 3 months.

Discussion

Drug-induced interstitial pneumonia is one of the serious adverse reactions that can be induced by various anticancer agents.[9] The manifestations of drug-induced pulmonary injury are usually nonspecific, making an accurate diagnosis difficult.[9] In the English-language literature, we found six cases of FOLFOX-induced interstitial pneumonia.[4–8] The demographic and clinical details of the reported cases (including the present case) are listed in Table 1. In all the reported patients, a median eight cycles of the FOLFOX regimen were administered before the onset of interstitial pneumonia; the FOLFOX treatment was abandoned immediately after the onset of the interstitial pneumonia.[4–8] Jung and colleagues[4] reported two cases of FOLFOX-induced interstitial pneumonia (cases no. 4 and no. 5 in Table 1) that occurred after the administration of only one or two cycles of the regimen. Thus, it should be noted that interstitial pneumonia may occur soon after the initiation of FOLFOX treatment.

Interstitial pneumonia induced by 5-fluorouracil appears to be extremely rare; we found no such cases in the English-language literature, and only one such case was found in the Japanese-language literature.[10] In our patient, the interstitial pneumonia did not recur despite the reintroduction of 5-fluorouracil/leucovorin alone. Gagnadoux and colleagues[7] reported a similar case of FOLFOX-induced interstitial pneumonia, which did not recur after the reintroduction of 5-fluorouracil/leucovorin and irinotecan. These findings

Table 1. Reported cases of FOLFOX-induced interstitial pneumonia

Case no.	First author	Sex/age (years)	FOLFOX treatment before the onset of interstitial pneumonia		Shortness of breath	Interstitial pneumonia	
			No. of cycles administered	Total dose of OHP (mg/m^2)		High-dose corticosteroid treatment	Outcome
1	Trisolini[5]	M/60	7	700	At rest	Given	Complete remission
2	Gagnadoux[7]	F/60	8	680	On exertion	Not given	Complete remission
3	Ruiz-Casado[6]	M/67	11	1100	None	Not given	Complete remission
4	Jung[4]	M/64	2	200	At rest	Given	Complete remission
5	Jung[4]	M/75	1	100	At rest	Given	Complete remission
6	Pasetto[8]	M/74	12	1020	At rest	Given	Progression (died of the pneumonia)
7	Muneoka (present patient)	M/82	10	850	On exertion	Given	Complete remission

OHP, oxaliplatin

imply that 5-fluorouracil/leucovorin alone was not responsible for the development of FOLFOX-induced interstitial pneumonia in these patients. In 2005, Yagues and colleagues[11] first reported a case of interstitial pneumonia induced by oxaliplatin alone. Taken together, the above observations suggest that oxaliplatin, alone or in combination with 5-fluorouracil/leucovorin, contributes to the development of FOLFOX-induced interstitial pneumonia.

Once FOLFOX-induced interstitial pneumonia has occurred, cessation of the FOLFOX regimen is mandatory.[4–8] High-dose corticosteroid treatment is commonly given for serious cases of this potentially lethal complication.[9] Of the seven cases reported thus far (Table 1); five of the patients were treated with high-dose corticosteroid. Although high-dose corticosteroid treatment was not given in the two remaining patients (cases no. 2 and no. 3 in Table 1; one who had a mild degree of shortness of breath, and the other who had no shortness of breath), the interstitial pneumonia in both of these patients resolved spontaneously following the cessation of the FOLFOX regimen. Thus, the role of high-dose corticosteroid treatment in the management of FOLFOX-induced interstitial pneumonia remains unclear.[9] The administration of antibiotics for patients with FOLFOX-induced interstitial pneumonia is indicated only if bacterial infection is superimposed on the interstitial pneumonia.[9]

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