Organizing Pneumonia Associated with Oxaliplatin-Combined Chemotherapy: A Case Report

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Key Words

Interstitial pneumonia • Organizing pneumonia • Oxaliplatin • Pulmonary toxicity

Abstract

Objective: To report a case of oxaliplatin-combined chemotherapy-induced interstitial lung disease. **Clinical Presentation and Intervention:** A 57-year-old man was referred complaining of dyspnea and fever after treatment with an oxaliplatin-combined chemotherapeutic agent for metastatic colorectal cancer. Fever development and spontaneous subsidence were observed during the chemotherapeutic course repeatedly until the 9th cycle. A computer-tomographic (CT) scan revealed bilateral, peripherally distributed, patchy consolidation suggestive of an interstitial lung disease. As a confirmative step, video-assisted thoracoscopic surgical biopsy was attempted; the characteristic intraluminal organizing fibrous plug in the bronchioles and alveoli was seen. Corticosteroid therapy was administered, which rapidly improved the patient's symptoms and chest CT findings. **Conclusion:** This case showed that oxaliplatin may be implicated in the etiology of interstitial lung disease, since withdrawal of the drug resulted in improvement of interstitial lung disease.

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Introduction

The combination of oxaliplatin with leucovorin and 5-fluorouracil (FOLFOX regimen) has recently been accepted as first-line chemotherapy for advanced or metastatic colorectal cancer, and its use has been shown to significantly improve survival [1]. Common adverse events of oxaliplatin are hematological and gastrointestinal tract toxicities, and neuropathy [2]. Recently we observed a rare case of oxaliplatin-induced interstitial lung disease, specifically organizing pneumonia.

Case Report

A 57-year-old man was referred to our department complaining of dyspnea and fever. Three years previously, he had undergone surgical treatment with low anterior resection for a colonic adenocarcinoma with surgical stage T3N2M0 and had received adjuvant chemotherapy with oral tegafur/uracil.

During the follow-up, several metastatic pulmonary nodules appeared on a chest computer-tomographic (CT) scan, and the serum carcinoembryonic antigen level was elevated. The chemotherapy regimen was therefore changed to 5-fluorouracil, leucovorin and oxaliplatin (FOLFOX). This chemotherapy was a bi-monthly regimen with intravenous oxaliplatin (85 mg/m²) ad-

Fig. 1. Chest CT scan revealed bilateral, peripherally distributed, patchy consolidation (arrows).

Fig. 2. Video-assisted thoracoscopic surgical biopsy showed an intraluminal organizing fibrous plug (arrows) in the alveoli, consistent with an organizing pneumonia pattern. HE. $\times 400$.

ministered on day 1, leucovorin (200 mg/m^2) added on days 1 and 2, and 5-fluorouracil (400 mg/m^2 as a bolus and 600 mg/m^2 in continuous infusion for 22 h) added on days 1 and 2. No complications were noticed during the first 3 cycles of FOLFOX chemotherapy. However, the fourth cycle of oxaliplatin infusion was interrupted because of fever (38.7°C). Fever surveillance studies including chest radiography, sputum culture, urine culture and blood culture were not remarkable. Laboratory tests revealed a white cell count of $4,610/\text{mm}^3$, a hemoglobin concentration of 11.6 g/dl , a platelet count of $166,000/\text{mm}^3$ and an erythrocyte sedimentation rate of 67 mm/h . After the fever had spontaneously subsided, chemotherapy was continued with the remaining leucovorin and 5-fluorouracil. However, this episode (i.e. interruption of chemotherapy by a febrile period after infusing oxaliplatin and continuance after fever subsidence) occurred repeatedly until the 9th cycle of chemotherapy. Just prior to the 9th cycle, a follow-

up chest CT scan was made, and it revealed bilateral, peripherally distributed, patchy consolidation (fig. 1), suggesting interstitial lung disease. As a further evaluation, bronchoalveolar lavage was performed using a fiberoptic bronchoscope also for a microbiological study. The bronchoalveolar lavage study revealed no infectious cause, with a total cell count of $36 \text{ cells}/\mu\text{l}$ with 28% neutrophils, 64% lymphocytes and 1% eosinophils, also ruling out an eosinophilic pneumonia. A video-assisted thoracoscopic surgical biopsy was taken, and the histological finding showed a characteristic intraluminal organizing fibrous plug in the bronchioles and alveoli (fig. 2). With a presumptive diagnosis of oxaliplatin-induced organizing pneumonia, he was treated with prednisolone (1 mg/kg/day), and FOLFOX chemotherapy was discontinued. His symptoms and radiological abnormalities accordingly improved (fig. 3).

Discussion

This was a case of oxaliplatin-induced interstitial drug disease that was finally diagnosed by video-assisted thoracoscopic surgical biopsy. Generally, a drug-induced interstitial lung disease can be established by a definite temporal association between exposure to a specific drug and the development of respiratory symptoms and signs, and by compatible laboratory findings, such as radiology, bronchoalveolar lavage or a pathological pattern. However, drug-induced interstitial lung disease is rare, comprising fewer than 5% of all cases. It is an important etiology because withdrawal of the culprit drug frequently results in improvement of the condition [3], as happened with our patient. The exact mechanism of oxaliplatin-induced interstitial lung disease is not clearly understood, but the direct toxic effect of the drug, rather than an immunology-driven mechanism, has been suggested based on a negativity to lymphocyte stimulation testing [4].

Fig. 3. After steroid treatment, chest CT scan showed nearly complete resolution (arrows) of the consolidation.

Table 1. Reported cases of oxaliplatin-induced interstitial lung diseases

Ref. No.	Age, sex	Symp-toms	Final cycles	Radiology	Pathology or BAL	Diagnosis	Treatment	Prognosis
Present case	57, M	D, F	9	bilateral, patchy consolidation	VATS Bx: organizing pneumonia	organizing pneumonia	stop the drug, steroid	nearly complete resolution
4	60, M	D	7	GGO, consolidation in lower lobes	TBB: organizing diffuse alveolar damage pattern	acute lung injury	prednisone	complete remission
5	60, F	C, D	8	patchy bilateral nodular infiltrates in lower lobes	BAL: eosinophilia of 29%	eosinophilic pneumonia associated with oxaliplatin	stop the drug	progressive resolution
6	74, M	C, D, F	6	linear and nodular densities which were becoming confluent	TBB: did not show an infective process		methyl-prednisolone	death
7	64, M	D	2	reticular opacity and a honeycomb change in lower lobes	TBB: organizing pneumonia	pulmonary fibrosis	steroid	improvement
7	75, M	D	1	diffuse GGO and consolidation with interlobular thickening	TBB: diffuse alveolar damage with hyaline membrane formation	AIP	steroid	improvement
8	66, M	D	12	patchy bilateral consolidation in lower lobes	autopsy: diffuse alveolar damage with fibrous organization	pulmonary fibrosis	steroid	death
9	30, F	C, D	6	bilateral alveolar infiltrates	VATS Bx: organizing pneumonia	COP	prednisone	complete resolution
10	71, M	C, D, F	6	extensive fibrotic infiltrates and new GGO	none	hypersensitivity reaction	antibiotics, steroid	death
10	77, F	C, D	12	subpleural honeycombing and traction bronchiectasis	none	UIP	no therapy	gradual improvement of symptoms and stable findings on radiographs
10	69, M	H	6	bilateral honeycombing and traction bronchiectasis	TBB: a small focus of organizing pneumonia	UIP	N-acetyl-cysteine	improvement

M = Male; F = female; D = dyspnea; C = cough; F = fever; H = hypoxemia; GGO = ground glass opacity; BAL = bronchoalveolar lavage; TBB = trans-bronchial lung biopsy; VATS Bx = video-assisted thoracoscopic surgical biopsy; AIP = acute interstitial pneumonia; COP = cryptogenic organizing pneumonia; UIP = usual interstitial pneumonia.

Recently, a number of cases of oxaliplatin-induced interstitial lung disease were reported (table 1) [4–10]. Presumptive diagnoses varied, e.g. acute lung injury (acute interstitial pneumonia, hypersensitivity reaction), eosinophilic pneumonia, usual interstitial pneumonia or organizing pneumonia. The interval from chemotherapy infusion to the development of interstitial pneumonia also varied from less than 10 days to more than 6 months. The most common symptom was dyspnea; others were cough and fever, as in our case. Male gender was predominant. The principal treatment for oxaliplatin-induced interstitial lung disease was steroids, while a few patients were treated with antibiotics or N-acetylcysteine or no treatment. Most cases responded fairly well to appropriate treatment, but 3 out of 10 were fatal despite steroid treatment. Notably, most of these reports lacked a surgical lung biopsy, except for 2 cases of diffuse alveolar damage [8] and organizing pneumonia [9]. The case involving organizing pneumonia was a 30-year-old woman who complained of cough, which differs clinically from our case of an elderly man with fever.

Most previous reports failed to explain whether the lung disease was caused exclusively by oxaliplatin or by any other combined chemotherapeutic agent. In particular, one report of a cryptogenic organizing pneumonitis [9] may well have been corrected to organizing pneumonia instead. Our case was unquestionably caused by oxaliplatin rather than an unknown etiology.

Conclusion

This case showed that oxaliplatin is implicated in the etiology of interstitial lung disease and withdrawal may be well worth considering, as evidenced by the improvement in the condition of our patient after withdrawal of the drug.

Acknowledgement

This study was supported by a Korea University grant.

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