

[CASE REPORT]

Successful Re-administration of Osimertinib in Osimertinib-induced Interstitial Lung Disease with an Organizing Pneumonia Pattern: A Case Report and Literature Review

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Abstract:

Osimertinib is the standard therapy for epidermal-growth-factor-receptor (EGFR)-mutant lung cancers. We herein report a case of osimertinib-induced interstitial lung disease (OsiILD) with an organizing pneumonia (OP) pattern and provide a literature-based review. Six months after osimertinib administration, a 75-year-old woman with right pleural carcinomatosis developed ILD with an OP pattern. After salvage chemotherapy, osimertinib with corticosteroid was successfully re-administered. A literature review suggested that 1) OsiILD with an OP pattern was rare but should be recognized, and 2) re-administration of osimertinib in OsiILD was successful in select patients. A criterion that determines whether a patient would benefit from re-administration is warranted.

Key words: osimertinib, drug-induced ILD, reversed halo sign, organizing pneumonia pattern, re-administration

(Intern Med 59: 823-828, 2020)

(DOI: 10.2169/internalmedicine.3689-19)

Introduction

The discovery of driver mutations has drastically changed clinical practice in patients with lung tumors. The management of lung cancer with appropriate oncoprotein inhibitors is vital for the patient survival (1). Osimertinib is a third-generation irreversible epidermal-growth-factor-receptor (EGFR)-tyrosine kinase inhibitor (TKI) that has positively changed the standard treatment for non-small-cell lung cancer harboring an EGFR T790M mutation (2-4). Therefore, continued treatment with osimertinib is crucial for patients with EGFR-mutant lung cancer.

Unfortunately, some patients discontinue the use of EGFR-TKIs due to toxicities. Drug-induced interstitial lung disease (ILD) is the most common serious adverse event that occurs during EGFR-TKI treatment. Previous clinical

trials have reported that osimertinib-induced ILD (OsiILD) occurred in 2-4% of patients (2-4). However, only few case reports describing OsiILD have been published, and the specific clinical features are not fully understood. Notably, some cases reported successful re-challenge of patients with osimertinib, even in those with a history of OsiILD.

We herein report a patient who developed OsiILD with an organizing pneumonia (OP) pattern and was re-challenged with osimertinib, along with a literature-based review.

Case Report

A 75-year-old woman with no history of smoking or allergies had postoperative recurrence of lung adenocarcinoma harboring the EGFR exon 19 deletion. She developed cancer-related pleural effusion, which disseminated to the right lung. The patient's Eastern Cooperative Group Per-

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Received: July 21, 2019; Accepted: October 14, 2019; Advance Publication by J-STAGE: November 29, 2019
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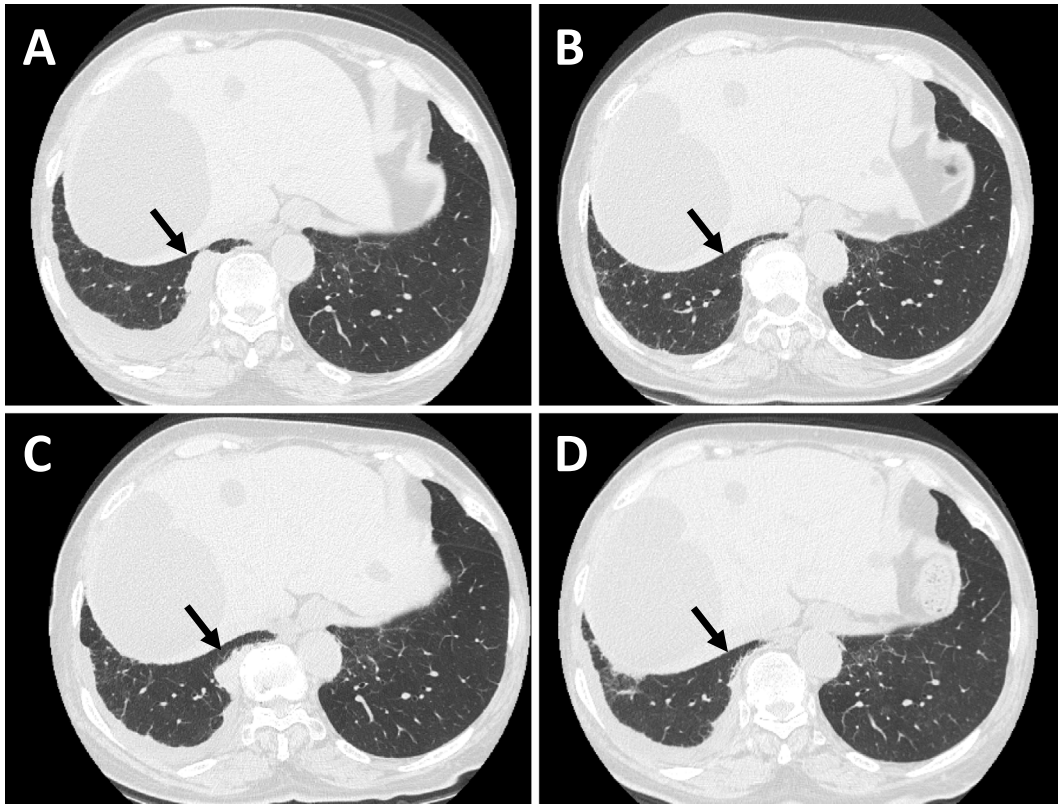


Figure 1. The effect of epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI). The black arrow indicates pleural dissemination. (A, B) Chest high-resolution computed tomography (HRCT) image three months after the initiation of erlotinib treatment. Right pleural dissemination and effusion were reduced. (C, D) Chest HRCT images three months after the initiation of osimertinib treatment. Right pleural dissemination and effusion were once again reduced.

formance Status (PS) was grade 1, so erlotinib was administered. Three months after the initiation of erlotinib, pleural dissemination and effusion were reduced. (Fig. 1A, B). However, the pleural dissemination and effusion increased one year after beginning the erlotinib treatment.

Genetic testing of the pleural fluid revealed EGFR exon 19 deletion and an EGFR T790M mutation in cancer cells. The patient's PS was maintained at grade 1. Thus, osimertinib was administered, and pleural dissemination to the right lung had almost disappeared by three months after the initiation (Fig. 1C, D); however, the patient complained of cough six months after starting osimertinib administration. Chest high-resolution computed tomography (HRCT) revealed patchy consolidation with a reversed halo sign in the left lower lung lobe (Fig. 2A, B). We suspected that ILD with an OP pattern had been induced by osimertinib; therefore, the anti-cancer drug was immediately discontinued, and she was admitted to our hospital for the diagnosis and treatment. At that time, her oxygen saturation was 98% in room air. Therefore, we considered the lung injury to be mild based on the "Consensus statement for the diagnosis and treatment of drug-induced lung injuries," edited by the Japanese Respiratory Society (5).

Bronchoscopy was performed on day 2 following hospitalization. We performed a transbronchial lung biopsy from

the right posterior segment (S2). The pathological examination did not reveal any specific findings, including the existence of malignant cells or granuloma. The cellular composition of the bronchoalveolar lavage (BAL) fluid was as follows: lymphocytes, 58.5%; eosinophils, 0.5%; neutrophils, 0%; monocytes, 3.0%, and macrophages, 38.0%. The CD4/CD8 ratio was 0.20. Cytology and a polymerase chain reaction test for *Pneumocystis jirovecii* of the BAL fluid were negative. The screening of general bacterial culture and acid-fast *Bacillus* smear and culture were all negative. Blood tests to rule out infections were performed, and the results were follows: procalcitonin <0.05 ng/mL; (1,3)-beta-D-glucan <6.0 pg/mL; cryptococcal antigenemia, negative; interferon-gamma release assay (T-SPOT.TB[®]), negative; cytomegalovirus viral antigen (pp65.C7-HRP), negative; and anti-mycoplasma pneumoniae IgM antibody, negative. The concentrations of serum Krebs von den Lungen-6 and surfactant protein-D were 1,011 U/mL (reference range, 0-500 U/mL) and 77.3 ng/mL (reference range, 0-110 U/mL), respectively. Therefore, the patient was diagnosed with OsILD.

As expected, the consolidation shadows gradually improved with 0.6 mg/kg prednisolone (30 mg) (Fig. 2C). Prednisolone was tapered as follows: 30 mg daily for 1 week, 20 mg daily for 1 week, 15 mg daily for 4 weeks,

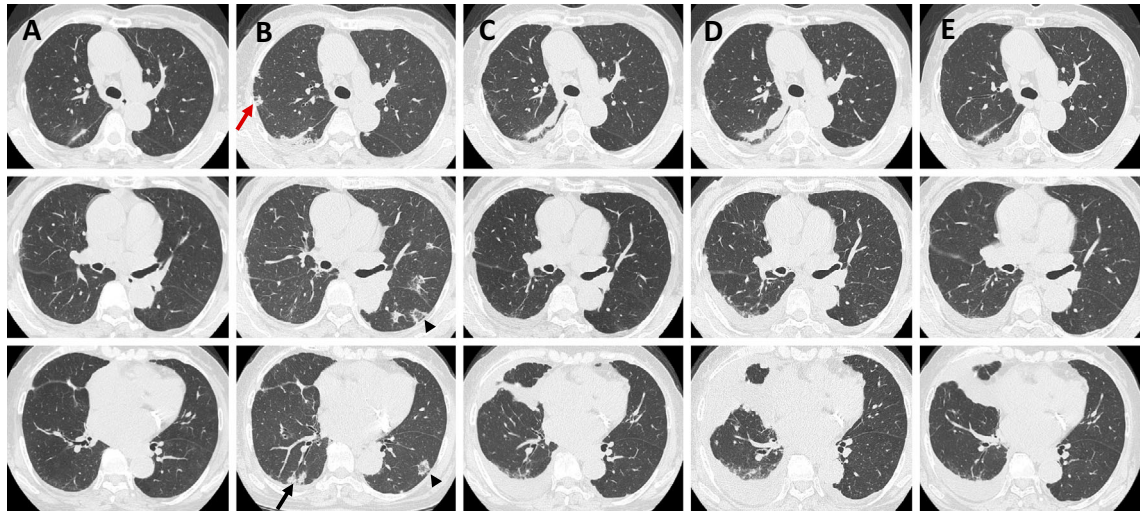


Figure 2. The clinical course of osimertinib-induced interstitial lung disease with an organizing pneumonia (OP) pattern. (A) Chest HRCT image three months after the initiation of osimertinib treatment. No evidence of lung tumor was detected in the lungs. (B) Chest HRCT image six months after starting osimertinib treatment, showing patchy consolidation (arrow). Some of the consolidation was accompanied by a reversed halo sign (arrowhead). The red arrow indicates a lung lesion on which a lung biopsy was performed. Lung cancer cells were not detected. (C) Chest HRCT image after 46 days of corticosteroid treatment, showing improvement in the abnormal shadow. (D) Chest HRCT image after cytotoxic chemotherapy, indicating increased right pleural effusion. (E) Chest HRCT image after four months of osimertinib re-administration, showing decreased right pleural effusion without recurrence of ILD.

and 10 mg daily for 2 weeks. After that, 5 mg of prednisolone was continued. Fortunately, ILD did not recur during the tapering. After tapering the prednisolone dose, the patient was treated with cytotoxic chemotherapy consisting of carboplatin, paclitaxel, and bevacizumab; however, her treatment was discontinued due to the onset of grade 3 peripheral neuropathy. In addition, right pleural effusion gradually increased again during the drug holiday (Fig. 2D). Her Eastern Cooperative Group PS was grade 1.

The patient and her family had a strong will to continue the treatment and provided informed consent to receive re-administration of osimertinib with a maintenance dose of 5 mg prednisolone daily. As a result, the patient has been successfully treated with osimertinib without recurrence of ILD for 7 months (Fig. 2E).

Discussion

We encountered a patient with OsiILD with an OP pattern who was successfully re-administered osimertinib. Table 1 shows previous case reports of OsiILD (6-13). Our literature-based review suggested that ground-glass opacity was the most common HRCT finding, but some cases showed an OP pattern. Our case presented with patchy consolidation with a reversed halo sign, indicating an OP pattern. The frequency of an OP pattern in OsiILD is unclear, and only a few cases of osimertinib-induced ILD with an OP pattern have been reported, although it was reported as a characteristic pattern of first-generation TKI-induced

ILD (14-16) (Table 2).

Interestingly, the re-administration of osimertinib was successful in 83% of cases (5 in 6 cases) in the literature-based review. In general, ILD induced by EGFR-TKIs, such as gefitinib or erlotinib, is severe, and approximately one-third of these cases are fatal (17, 18). Similarly, fatal cases have been reported in clinical trials for osimertinib (4). At present, there is no consensus regarding the safety and efficacy of re-administering EGFR-TKIs in patients with EGFR-TKI-induced ILD. However, even though the literature shows a high success rate with re-administration of osimertinib, we must be cautious. The high success rate may be due to positive publication bias.

Given that osimertinib has different biological features from other EGFR-TKIs, such as considerably less activity against wild-type EGFR (19), the disease severity, mortality, and biology of OsiILD might also differ from ILD induced by other EGFR-TKIs. Recently, several groups reported that osimertinib was able to induce transient asymptomatic pulmonary opacities (TAPOs) in 20-35% of patients (20-22). The radiological patterns of TAPOs included ground-glass opacity, peribronchial and subpleural nodules, and cryptogenic organizing pneumonia and/or simple eosinophilic pneumonia. According to the reports, these patients with TAPOs were able to be treated with continuous osimertinib therapy or a transient drug holiday followed by osimertinib re-administration (20-22). One explanation for the high success rates of osimertinib re-administration noted in our review might be that some patients developed TAPOs rather

Table 1. Previous Case Reports of Osimertinib-induced ILD in Patients with NSCLC Harboring EGFR T790M.

Case	Age	Sex	EGFR status	Smoking pack-year	Onset of ILD	Chest CT pattern	Treatment for ILD	Outcome	Re-challenge (mg/body)	Corticosteroid during re-challenge	Recurrence of ILD	Effect of osimertinib (Initial/ Re-challenge)
1 (ref6)	32	M	Exon 19 deletion, T790M	NA	4.5 months	GGO	Dexa 10 mg/day	Improved	No *	Dexa 10 mg/day	No	PR/NA
2 (ref7)	38	F	L858R, T790M	Never	31 days	Diffuse GGO	Cessation	Improved	Osimertinib (80 mg)	No	Yes	PR/PR
3 (ref8)	75	F	Exon 19 deletion, T790M	Never	64 days	ILST	PSL 0.5 mg/kg	Improved	Osimertinib (40 mg)	PSL 0.5 mg/kg → tapered 5 mg/day	No	PR/PR
4 (ref9)	77	F	L858R, T790M	Never	14 days	Diffuse GGO	Cessation	Improved	No	NA	No	PR/NA
5 (ref10)	82	M	Exon 19 deletion, T790M	Never	8 months	Diffuse GGO	Steroid	Improved	Osimertinib (80 mg)	PSL 40 mg/day → tapered off	No	PR/PR
6 (ref10)	60	M	Exon 19 deletion, T790M	NA	6 weeks	Diffuse GGO	Steroid	Improved	Osimertinib (NA)	PSL 20 mg/day → tapered off	Yes	NA/PR
7 (ref11)	75	M	L858R, T790M	Never	34 days	Diffuse GGO Peribronchial consolidation	mPSL 500 mg/day	Improved	No	NA	No	NA/NA
8 (ref12)	59	F	Exon 19 deletion, T790M	NA	63 days	Patchy GGO and consolidation	Steroid pulse	Improved	No	NA	No	PR/NA
9 (ref13)	62	M	Exon 19 deletion, T790M	30	82 days	Multiple GGO	PSL 0.5 mg/kg	Improved	Osimertinib (40 mg)	PSL 25 mg/day	No	NA/SD
10	75	F	Exon 19 deletion, T790M	Never	6 months	OP pattern	PSL 0.6 mg/kg	Improved	Osimertinib (80 mg)	PSL 20 mg/day → tapered 5mg/day	No	PR/SD

ILD: interstitial lung disease, CT: computed tomography, GGO: ground-glass opacity, ILST: interlobular septal thickening. This patient also suffered pleural effusion
 DEXA: dexamethasone, PSL: prednisolone, mPSL: methylprednisolone, NA: not available, PR: partial response, SD: stable disease
 *Osimertinib was continued with a dose reduction.

Table 2. CT Pattern of First-generation EGFR-TKI-induced ILD.

Reference	EGFR-TKI	CT pattern					Total
		GGO pattern ^a	OP-like pattern ^b	AEP-like pattern ^c	AIP-like pattern ^d	Others	
(14)	gefitinib	24 (47.1%)	7 (13.7%)	1 (2.0%)	12 (23.5%)	7 (13.7%)	51
(15)	gefitinib	8 (34.8%)	3 (13.0%)	5 (21.7%)	7 (30.4%)	0	23
(16)	erlotinib	NA	NA	NA	63 (22.3%)	NA	283

EGFR-TKI: epidermal growth factor receptor tyrosine kinase inhibitor, GGO: ground-glass opacity, OP: organizing pneumonia, AEP: acute eosinophilic pneumonia, AIP: acute interstitial pneumonia, NA: not available, ILD: interstitial lung disease, CT: computed tomography

^aGGO pattern: Only nonspecific area with ground-glass opacity

^bOP-like pattern: Multifocal areas of airspace consolidation

^cAEP-like pattern: Patchy distribution of areas with ground-glass opacity accompanied by interlobular septal thickening

^dAIP-like pattern: Extensive bilateral ground-glass opacity or airspace consolidations with traction bronchiectasis

than OsiILD. At present, there are no definitive ways of confirming whether pulmonary opacities are drug-induced ILD or TAPOs. Further assessments of the radiological patterns and BAL data will be required to investigate this clinical issue.

In conclusion, re-administration of osimertinib for OsiILD might be feasible in select cases. Further studies are required in order to determine the clinical features or specific biomarkers of OsiILD to select which ILD patterns or patients can be treated with or safely re-administered osimertinib.

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

Financial Support

This work was supported by the JSPS Grants-in-Aid for Scientific Research (Grant-in-Aid for Young Scientists [B]: KAKEN 16K19454) to K.O. and JSPS Grants-in-Aid for Scientific Research (Scientific Research [B]: KAKEN 15H04830) to K.O. and K.K.

Acknowledgement

First, we would like to thank the patient who participated in this study and her family. We are also grateful to Hiromi Nakashima and Kyoko Maeda for the technical support and to Hirofumi Inoue from the Department of Pathology of the Okayama University Hospital for their support with the pathological studies.

Junko Itano and Hisao Higo contributed equally to this work.

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Intern Med 59: 823-828, 2020