Organizing pneumonia resembling disease progression in a non-small-cell lung cancer patient receiving ceritinib
A case report
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Abstract
Rationale: Echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK), a distinct molecular entity, is highly sensitive to ALK tyrosine kinase inhibitors (TKIs) such as crizotinib or ceritinib. Interstitial lung disease is a rare (1.2%) pulmonary toxicity that can result from ALK TKIs, however, organizing pneumonia has not been reported to date.
Patient concerns: A 45-year-old Korean female with ALK-rearranged metastatic lung adenocarcinoma underwent ceritinib treatment and exhibited a partial response, until she developed organizing pneumonia resembling disease progression.
Diagnoses: Multiple rebiopsies confirmed the involvement of organizing pneumonia in the pathology.
Interventions: Ceritinib was stopped and the patient was treated with intravenous antibiotics followed by oral antibiotics for two weeks.
Outcomes: After recovering from organizing pneumonia, ceritinib was successfully rechallenged and the patient attained a complete response.
Lessons: When a new mass-like lesion develops in the lungs of responding patients, benign lung conditions, including organizing pneumonia should be considered in differential diagnoses.

1. Introduction
Echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) is a distinct molecular entity that is highly sensitive to ALK tyrosine kinase inhibitors (TKIs), including crizotinib or ceritinib. In the first-line setting, crizotinib and ceritinib have demonstrated improved PFS compared to platinum-based doublet chemotherapy.1,2 Although patients dramatically respond to initial ALK inhibitor therapy, they invariably develop acquired resistance exhibiting regrowth of a lung tumor. Often, biopsies of regrowing tumor lesions are performed to elucidate the mechanisms of resistance to ALK inhibitor. Recently, approximately 50% of patients who progressed on ALK TKIs harbored newly acquired ALK mutations which can be further inhibited by newer generation ALK TKIs.3

Interstitial lung disease, a rare (1.2%) pulmonary toxicity, can result from ALK TKIs,1,2 but organizing pneumonia caused by ceritinib has not been reported to date. Herein, we report a case of organizing pneumonia resembling disease progression in a patient with non-small-cell lung cancer who received ceritinib. This study was approved by the Institutional Review Board of CHA Bundang Medical Center (South Korea), and the informed consent was waived due to the retrospective collection of data which secured the anonymity of the patient.

2. Case report
In September 2015, a 45-year-old Korean female with ALK-rearranged metastatic lung adenocarcinoma was administered ceritinib 750mg, a second-generation ALK inhibitor. Her brief
anticancer treatment history comprised right lower lobectomy (pT3N0M0) in February 2014, followed by adjuvant chemotherapy with vinorelbine and cisplatin. From September 2014, she received pemetrexed and cisplatin as the first-line therapy for the metastatic disease, followed by pemetrexed maintenance.

In the subsequent second-line therapy of ceritinib in October 2015, she exhibited a partial response in accordance with the response evaluation criteria in solid tumor (version 1.1) with substantial tumor shrinkage of 78% (Fig. 1B) compared with that in the baseline scan (Fig. 1A). She maintained the partial response until a follow-up computed tomography (CT scan in April 2016 (Fig. 1C), which revealed newly appearing mass-like lesions in the left apex and right middle lobe (Fig. 1E). Assuming the presumptive disease progression, we performed a rebiopsy of the new lesion in the left apex to consider it for a new clinical trial; however, the transbronchial lung biopsy of the left apex mass revealed organizing pneumonia, non-infectious pneumonia defined as granulation tissue plugs within the lumens of small airways and extending into the alveolar ducts and alveoli.

She underwent a repeat CT-guided gun biopsy of the left apex mass and a transbronchial lung biopsy of the right middle lobe mass to eliminate inappropriate targeting in biopsy; however, the

![Figure 1. Chest CT finding at (A) the baseline showing the right middle lobe mass; (B) after one cycle showing a partial response with 78% tumor shrinkage; (C) lung mass achieving near complete response; (D) lung mass in the complete response; (E) newly developed mass-like nodules on both upper lobes and right middle lobe; and (F) disappeared organizing pneumonia in both upper lobes and right middle lobe.](image)

![Figure 2. A, H&E staining of biopsy from the right middle lobe mass showing chronic inflammation. Some inflammatory cells and macrophages are present. B, H&E staining of a biopsy specimen from the left apex mass showing organizing pneumonia. Arrows indicate that aggregates of loose fibroblasts are present. Lymphocytes are present to a variable degree within the interstitium.](image)
pathology confirmed chronic inflammation (Fig. 2A) from the biopsy of the right middle lobe mass and organizing pneumonia (Fig. 2B) from that of the left apex mass. Because her symptoms included a mild cough without fever, she was presumably diagnosed with drug-induced organizing pneumonia. Thus, ceritinib was withheld, and the patient was treated with intravenous antibiotics, followed by oral antibiotics for two weeks. A 3-week follow-up CT scan revealed improved consolidation in the right middle lobe and left apex. Because the patient exhibited no specific symptoms, ceritinib was readministered at a one-level reduced dose from May 2, 2016. A 1-month follow-up CT scan revealed resolution of the consolidations in the left apex and right upper lobe (Fig. 1F). In July 2016, she attained a complete response (Fig. 1D); at present, she is still undergoing ceritinib treatment, having received 55 cycles of the treatment.

3. Discussion
This case presents the occurrence of organizing pneumonia, which was initially confused with disease progression in a patient with lung adenocarcinoma receiving ALK inhibitor therapy. Had the patient been withdrawn from ceritinib because of presumptive disease progression, she would not have attained a complete response. After ruling out disease progression, we rechallenged the drug and the patient showed favorable response to it.

Interstitial pneumonia associated with epidermal growth factor receptor (EGFR) TKI is estimated to occur in approximately 1% of patients with cancer and is radiologically classified into the following 4 types: acute interstitial pneumonia (AIP)-like; bronchiolitis obliterans organizing pneumonia (BOOP)-like; acute eosinophilic pneumonia-like; and nonspecific ground-glass opacity (GGO).[6–8] Endo et al.[5] reported that the most common type is the nonspecific GGO type (40%–50%), followed by AIP-like type (20%–30%). To the best of our knowledge, only a few cases of ALK inhibitor-caused interstitial pneumonia have been reported to date, and ours is the first BOOP-like case to be reported. The pathogenesis behind BOOP-like change is unclear at present, but the inflammatory response may be owing to ALK TKI.

In the era of targeted therapy, when encountered with the development of a new mass-like lesion in the lungs of responding patients with cancer, medical oncologists should consider benign lung conditions, including organizing pneumonia, in differential diagnoses. Furthermore, an aggressive diagnostic approach, including surgical rebiopsy, should be considered to avoid erroneous elimination of the therapeutic opportunity from responding patients.

Author contributions
Conceptualization: Sun M. Lim.
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