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【 CASE REPORT 】

Pulmonary Adenocarcinoma, Harboring Both an *EGFR* Mutation and *ALK* Rearrangement, Presenting a Stable Disease to Erlotinib and a Partial Response to Alectinib

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Abstract:
A 63-year-old woman with pulmonary adenocarcinoma (stage IIIB) that was positive for an epidermal growth factor receptor (*EGFR*) mutation and an anaplastic lymphoma kinase (*ALK*) rearrangement was treated with erlotinib as the first-line treatment, resulting in a stable disease. Due to skin rashes, fatigue and anorexia, erlotinib was suspended on erlotinib day 44. Alectinib was administered as the second-line treatment, exhibiting a partial response. On alectinib day 56, drug-induced lung injury forced suspension of alectinib, which was cured with corticosteroid therapy. ALK-tyrosine kinase inhibitors may be more effective for patients positive for both *EGFR* mutation and *ALK* rearrangement than other agents.

Key words: non-small cell lung cancer, *EGFR* mutation, *ALK* rearrangement

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Introduction

Both epidermal growth factor receptor (*EGFR*) mutations and anaplastic lymphoma kinase (*ALK*) rearrangement are important gene drivers of non-small cell lung cancer (NSCLC). *EGFR* mutations occur in 19-20% of NSCLCs, and it is especially common in Asian populations, at 30-32% (1, 2). In contrast, *ALK* rearrangement occurs in 2-7% of NSCLCs (3-5), and ethnic differences are not as evident as with *EGFR* mutations. Although they were considered mutually exclusive (3), adenocarcinoma harboring both an *EGFR* mutation and *ALK* rearrangement have been recently observed in 0.1-1.3% of NSCLCs (4, 6-8).

We herein report a case of pulmonary adenocarcinoma with a concomitant *EGFR* mutation and *ALK* rearrangement in a single specimen and treated with both an EGFR tyrosine kinase inhibitor (EGFR-TKI) and an ALK-TKI.

Case Report

The patient was a 62-year-old woman with no remarkable medical history. She had smoked tobacco around 30 pack-years until a decade earlier. She was referred to us because of an abnormal lung shadow on plain chest X-ray at her health checkup. Computed tomography (CT) and positron emission tomography revealed a nodule (24 mm in maximum diameter) in the right upper lobe and hilar to mediastinal lymphadenopathy (Fig. 1A and B). Magnetic resonance imaging revealed no metastasis in the brain. A transbronchial lung biopsy revealed papillary adenocarcinoma (Fig. 1C), and we made a diagnosis of stage IIIB (T1bN3M0) pulmonary adenocarcinoma. Using a peptide nucleic acid-locked nucleic acid polymerase chain reaction-clamp method, an exon 19 deletion (E746-A750del) was identified with the adenocarcinoma specimen obtained at the biopsy. *ALK* rearrangement was also positive for the same specimen according to immunohistochemistry (IHC), and

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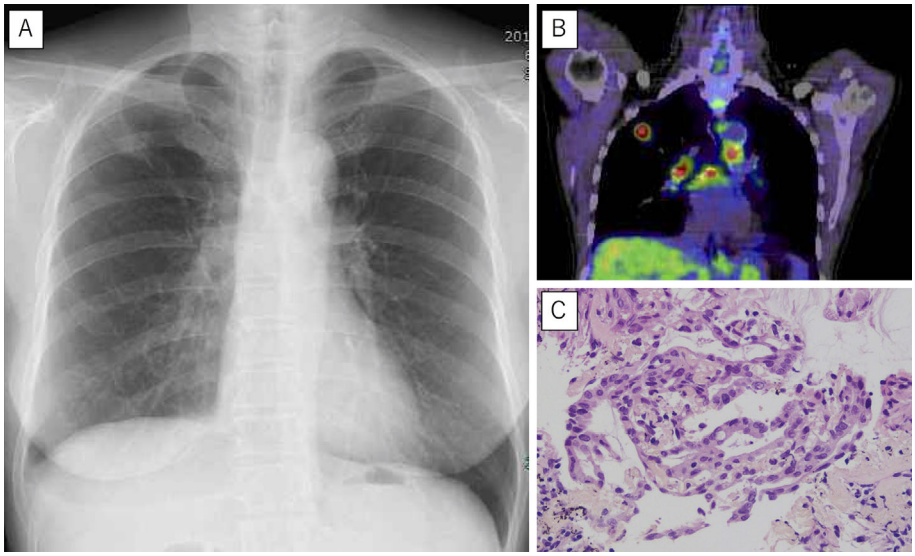

Figure 1. **(A) Chest X-ray revealed a pulmonary nodule in the right upper lung field. (B) F18 fluorodeoxyglucose positron emission tomography showed the uptake in the tumor and the hilar and mediastinal lymph nodes. (C) Papillary adenocarcinoma was shown on Hematoxylin and Eosin staining (×20 magnification).**

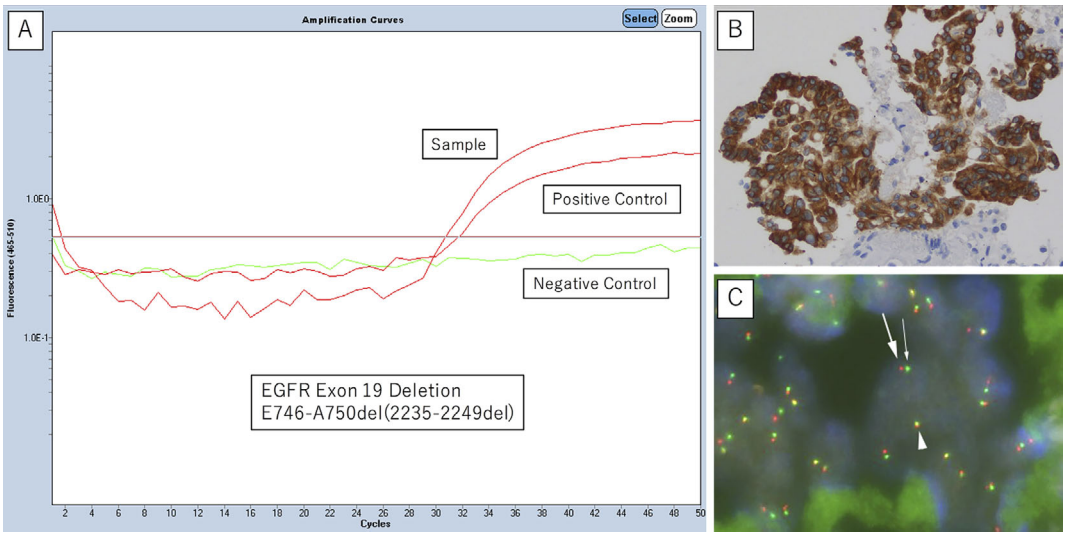

Figure 2. **(A) Positivity for an epidermal growth factor receptor (*EGFR*) mutation (exon 19 defect, E746-A750 deletion) was shown via a peptide nucleic acid-locked nucleic acid polymerase chain reaction-clamp method. (B) Immunohistochemistry of an anaplastic lymphoma kinase (*ALK*) rearrangement revealed that protein expression in tumor cells (×20). (C) Fluorescence *in situ* hybridization revealed a split of red and green probes flanking the *ALK* translocation site in the tumor cell (arrows).**

this was confirmed by fluorescence *in situ* hybridization (FISH), while the positive rate was 80% (Fig. 2).

Since metastases were present in the contralateral mediastinal lymph nodes, the patient was not considered appropriate for surgical resection even though her performance status was grade 0. Curative radiation therapy was also considered to be difficult because the radiation field was too wide. Among EGFR-TKIs or ALK-TKIs, offered as the first-line treatment options, the patient opted for erlotinib. The oral administration of erlotinib 150 mg/day was initiated. Since CT revealed no marked change in the size of the primary lesion (24 mm in maximum diameter) or mediastinal lymph nodes without any new lesions at 30 days after the initiation of erlotinib, the treatment was continued with the assessment of stable disease (SD). However, erlotinib was discontinued on day 44 based at the patient's request due to grade 2 skin rashes starting on day 20 and worsening fatigue and anorexia reaching grade 2, as it affected her work. These signs and symptoms disappeared after suspension of the erlotinib.

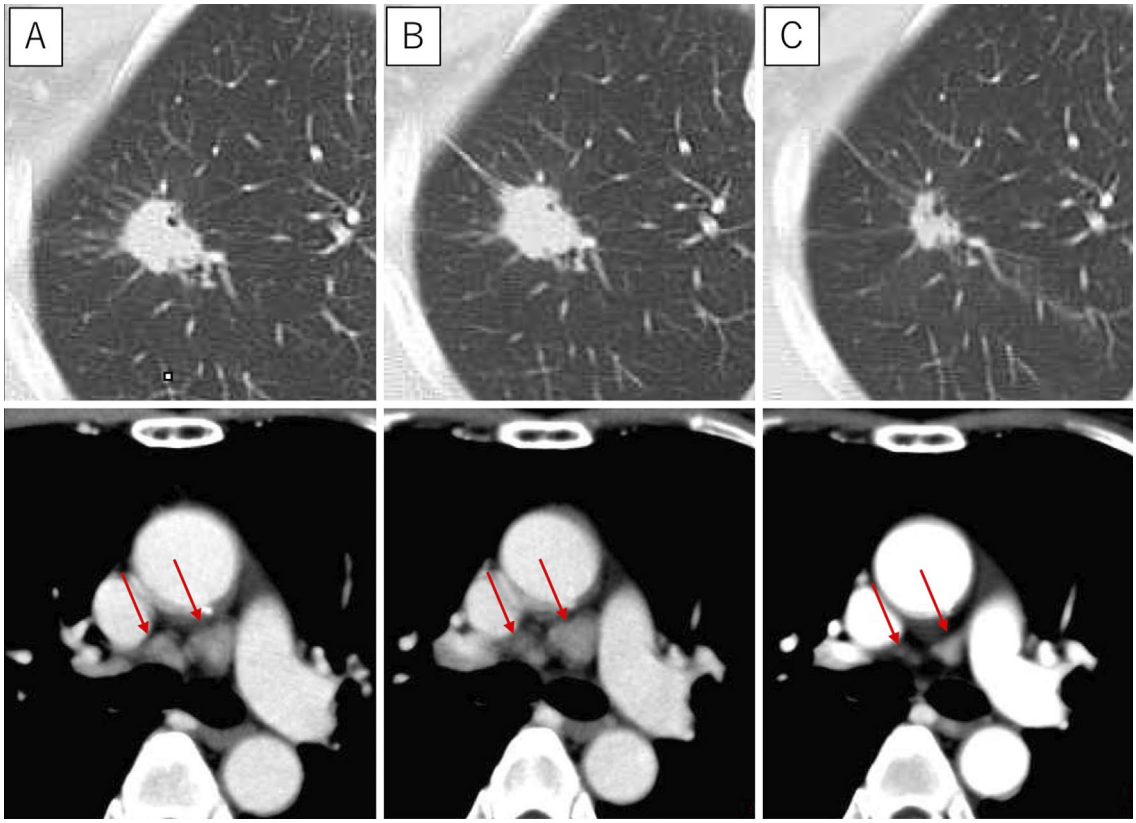

Figure 3. **(A) Chest CT showed a tumor in the right lung and mediastinal lymph nodes (arrows) before the treatments. (B) On day 30 after erlotinib treatment, the size of the tumor and mediastinal lymph nodes (arrows) showed no change. (C) On day 30 after alectinib treatment, the tumor and mediastinal lymph nodes (arrows) had shrunk.**

Although crizotinib was first considered as the second-line treatment, the oral administration of alectinib 600 mg/day was initiated because of her fear of recurrent anorexia. On day 30 of treatment with alectinib, chest CT indicated a reduction in the size of the primary lesion (15 mm in maximum diameter) and the lymph nodes. Accordingly, the effectiveness reached a partial response (PR) as the best response, and alectinib was continued (Fig. 3). On alectinib day 56, she made an unscheduled visit to the outpatient clinic because of dry cough along with a slight fever appearing a few days before the visit. Plain chest X-ray indicated interstitial shadows in both lungs, with chest CT revealing ground glass opacities in both lungs (Fig. 4). Hypoxemia [partial pressure of arterial oxygen (PaO_2) 89.7 mmHg, O_2 3 L/min inhalation] was observed. Blood tests revealed a slight increase in white blood cells, while the lactase dehydrogenase, C-reactive protein, and sialylated carbohydrate antigen Krebs von den Lungen (KL)-6 levels were within the normal range. Because infectious diseases, such as atypical pneumonia and pneumocystis pneumonia, were not suggested by blood tests and physical findings, alectinib-induced lung injury was suspected. Alectinib was discontinued on the admission day, and steroid pulse therapy (intravenous methyl-prednisolone 1,000 mg/day, for 3 days) was conducted. The patient's hypoxemia, fever and cough disappeared three days after the steroid pulse therapy, and the interstitial shadows on chest plain X-ray also significantly improved. Oral glucocorticosteroid was continued with prednisolone at a dose of 40 mg/day and then tapered by 5 mg every other week until it was discontinued 3 months later. During the reduction of the steroid therapy, there was no exacerbation of the fever, cough or interstitial abnormalities that had diminished by the time of the discontinuation of the steroid therapy. The tumor remained the same size on chest CT after the steroid therapy.

Discussion

In this report, we present a case of pulmonary adenocarcinoma, harboring both an *EGFR* mutation and *ALK* rearrangement presenting with SD to erlotinib and PR to alectinib.

The response rate to EGFR-TKIs and ALK-TKIs among patients positive for both an *EGFR* mutation and *ALK* rearrangement (double-positive) is poorly understood. Zhao et al. (9) reported their case and a literature review; the objective response rate to TKIs for double-positive patients was reported to be 63.6% (14 of 22) for EGFR-TKIs and 55.6% (5 of 9) for an ALK-TKI (only crizotinib). The response rate to both TKIs appears to be slightly lower than that for either alone, given that the usual response rates of EGFR-TKIs are 71-83% in *EGFR* mutation-positive patients (10-12) while

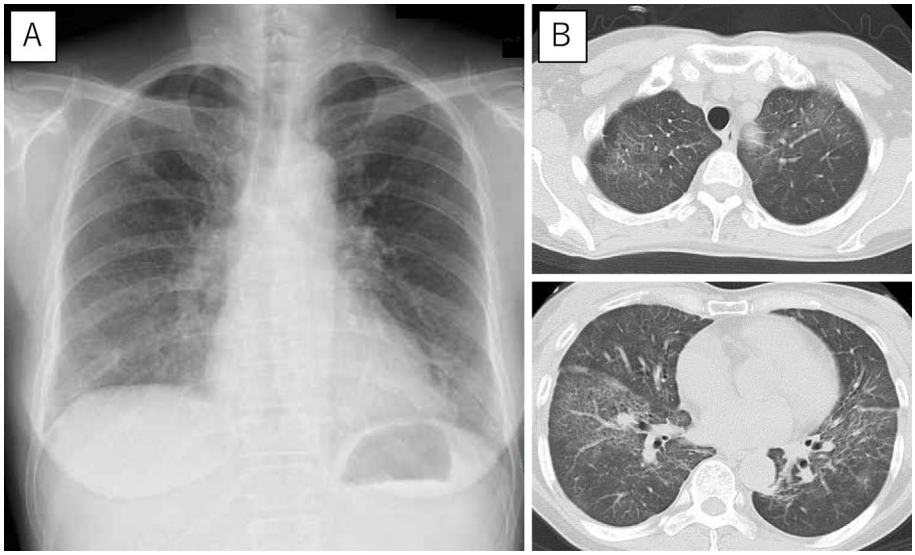

Figure 4. **(A) Plain chest X-ray at the onset of alectinib-induced lung injury revealed interstitial shadows in both lung fields. (B) Chest CT also revealed diffuse ground glass opacities in both lungs.**

those of ALK-TKIs are 65-74% (crizotinib) (13, 14) and 92% (alectinib) (15) in *ALK* rearrangement-positive patients.

Two possible mechanisms may underlie the relatively low response rate to TKIs. A few studies have reported that *ALK* rearrangement is associated with resistance to EGFR-TKIs (4, 16) and vice versa (17). Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signaling mechanism that contributes to ALK inhibitor resistance. Yang et al. (7) and Baldi et al. (18) indicated in their reports that an *EGFR* mutation and *ALK* rearrangement coexisted in the same tumor cells, as detected by IHC and serial sections. In double-positive tumor cells, EGFR and ALK may perform bypass signaling for each other, resulting in a poor response to both TKIs. Another possible mechanism was associated with the intratumoral expression of the *EGFR* mutation and *ALK* rearrangement in separate cells. Cai et al. (19) examined specimens of double-positive tumor tissues using various genetic tests and showed that *EGFR* mutation-negative/*ALK* rearrangement-negative cells, *EGFR* mutation-positive/*ALK* rearrangement-negative cells, *EGFR* mutation-negative/*ALK* rearrangement-positive cells and *EGFR* mutation-positive/*ALK* rearrangement-positive cells heterogeneously coexisted in the same tumor. If that is the case, *EGFR* mutation-positive/*ALK* rearrangement-negative cells and *EGFR* mutation-negative/*ALK* rearrangement-positive cells would be independently susceptible to EGFR-TKIs and ALK-TKIs, respectively, resulting in varying responses to either drug.

We summarized 12 previously reported double-positive patients who were treated by both EGFR-TKIs and ALK-TKIs along with this case in Table (6-9, 20-24). This is the first case treated by alectinib. All patients received EGFR-TKIs prior to ALK-TKIs, and in these 12 patients, the response rate of the second ALK-TKI (crizotinib) was 100% (6/6 cases) in patients manifesting progressive disease (PD) with the first EGFR-TKI. While the response rate for each TKI in double-positive patients was low, ALK-TKIs were effective in the patients not responding to EGFR-TKIs, as in this case. Regarding the mechanism underlying the success with ALK-TKI administration in this case, *ALK* rearrangement may be superior to the *EGFR* mutation as a driver gene in tumor cells (7). As another potential mechanism, since 80% of *ALK* rearrangement-positive cells were detected by FISH in this case, ALK-TKIs may be more effective than EGFR-TKIs in cases with many *ALK* rearrangement-positive cells. ALK-TKIs may be effective for cases with predominantly *ALK* rearrangement, and alectinib may be the preferred agent, as it has a higher response rate than crizotinib (15).

Lung injury from alectinib has been reported to affect 0.4% (25, 26) and 1.4% of cases in Japan (27). To our knowledge, this is the first case of alectinib-induced lung injury in a patient double-positive for an *EGFR* mutation and *ALK* rearrangement. The prognosis of alectinib-induced lung injury is reported to show a favorable outcome (28, 29), as in this case. Chino et al. (30) reported a case wherein the patient demonstrated drug-induced lung injury during treatment with crizotinib that was successfully switched to alectinib. The re-administration of alectinib after it has caused lung injury is inappropriate, but in addition to the standard platinum-doublet chemotherapy, switching to crizotinib administration may be an option for the next pharmacotherapy in this case, given the patient's good response to alectinib.

In Japan, many NSCLC patients do not undergo tests for *ALK* rearrangement when exhibiting positivity for *EGFR* mutations. As such, there may be a fair few as-yet-undetected double-positive patients. Particular attention should be paid to the *EGFR* mutation-positive EGFR-TKI-resistant patients who may be positive for *ALK* rearrangement. *ALK* rearrangement should be assessed even if a patient is shown to have an *EGFR* mutation. Further studies may be required to establish TKI treatment strategies for

Table. Summary of the Clinicopathological Characteristics of Non-small Cell Lung Cancer Patients with a Concomitant *EGFR* Mutation and ALK Rearrangement Treated by EGFR-TKIs and ALK-TKIs.

Case	Age	Sex	Histology	Stage	Smoker	EGFR	EGFR-TKI	Best response / PFS	ALK	ALK-TKI	Best response / PFS
1 (6)	73	M	Adeno	IV	Yes	exon19	gefitinib	PD	FISH/IHC	crizotinib	PR/9months
2 (20)	55	F	Adeno	IV	No	exon19	gefitinib erlotinib	SD/2months SD/3months	FISH/IHC	crizotinib	SD/4months
3 (21)	56	M	Adeno	IV	Yes	exon19	erlotinib	SD/8months	FISH/ RT-PCR	crizotinib	CR/22months
4 (22)	67	F	Adeno	IV	No	exon21	gefitinib afatinib	PR/24months PD	FISH/IHC	crizotinib	PR/25months
5 (7)	65	F	Adeno	IIIA	No	exon19	erlotinib	PD	FISH/IHC	crizotinib	PR/2months
6 (7)	65	F	Adeno	IV	No	exon20	afatinib	PR/5months	FISH/ RT-PCR	crizotinib	PD
7 (7)	54	F	Adeno	IV	No	exon19	erlotinib	PR/12months	FISH/IHC/ RT-PCR	crizotinib	SD/3month
8 (9)	48	F	Adeno	IV	No	exon21	erlotinib	SD/5months	FISH/IHC	crizotinib	SD/3.5months
9 (23)	73	M	Adeno	IV	Yes	exon19	gefitinib	PD	FISH/IHC	crizotinib	PR/19months
10 (24)	67	M	Adeno	>IIIB	No	exon19	erlotinib	PD	FISH/IHC	crizotinib	PR/unknown
11 (24)	74	M	Adeno	>IIIB	No	exon18	erlotinib	SD/8months	FISH/IHC	crizotinib	SD/unknown
12 (8)	62	F	Adeno	IV	No	exon18 exon21	gefitinib	SD/unknown	FISH/IHC	crizotinib	PR/unknown
our case	63	F	Adeno	IIIB	Yes	exon19	erlotinib	SD/1.5months	FISH/IHC	alectinib	PR/5months

F: female, M: male, Adeno: adenocarcinoma, FISH: fluorescence in situ hybridization, IHC: immunohistochemistry, RT-PCR: real-time polymerase chain reaction, EGFR-TKI: EGFR inhibitor, ALK-TKI: ALK inhibitor, PFS: progression-free survival, PR: partial response, SD: stable disease, PD: progression disease, CR: complete response

double-positive pulmonary adenocarcinoma patients, since some patients might benefit more from first-line ALK-TKIs and others from first-line EGFR-TKIs.

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

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