CASE REPORT

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

Akira Yokoyama, Atsuhisa Tamura, Kazuko Miyakawa, Kei Kusaka, Masahiro Shimada, Takashi Hirose, Hirotsushi Matsui, Masashi Kitani, Akira Hebisawa and Ken Ohta

Abstract:
A 63-year-old woman with pulmonary adenocarcinoma (stage IIIB) that was positive for an epidermal growth factor receptor (\textit{EGFR}) mutation and an anaplastic lymphoma kinase (\textit{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. \textit{ALK}-tyrosine kinase inhibitors may be more effective for patients positive for both \textit{EGFR} mutation and \textit{ALK} rearrangement than other agents.

Key words: non-small cell lung cancer, \textit{EGFR} mutation, \textit{ALK} rearrangement

(Intern Med 57: 2377-2382, 2018)

(DOI: 10.2169/internalmedicine.0383-17)

Introduction

Both epidermal growth factor receptor (\textit{EGFR}) mutations and anaplastic lymphoma kinase (\textit{ALK}) rearrangement are important gene drivers of non-small cell lung cancer (NSCLC). \textit{EGFR} mutations occur in 19-20% of NSCLCs, and it is especially common in Asian populations, at 30-32% (1, 2). In contrast, \textit{ALK} rearrangement occurs in 2-7% of NSCLCs (3-5), and ethnic differences are not as evident as with \textit{EGFR} mutations. Although they were considered mutually exclusive (3), adenocarcinoma harboring both an \textit{EGFR} mutation and \textit{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 \textit{EGFR} mutation and \textit{ALK} rearrangement in a single specimen and treated with both an \textit{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 IIIIB (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. \textit{ALK} rearrangement was also positive for the same specimen according to immunohistochemistry (IHC), and
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 (PaO₂) 89.7 mmHg, O₂ 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
response rate to TKIs. A few studies have reported that ALK that an
Yang et al. (7) and Baldi et al. (18) indicated in their reports
ing mechanism that contributes to ALK inhibitor resistance. Yang et al. (7) and Baldi et al. (18) indicated in their reports
that the activation of EGFR signaling was a bypass signaling
mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signal-
ing mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signal-
ing mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signal-
ing mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signal-
ing mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signal-
ing mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signal-
ing mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.

Sasaki et al. (17) found that the activation of EGFR signaling was a bypass signali-
g mechanism that contributes to ALK inhibitor resistance.
The authors state that they have no Conflict of Interest (COI).

References

1. Shigematsu H, Lin L, Takahashi T, et al. Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers. J Natl Cancer Inst 97: 339-346, 2005.
2. Mitsudomi T, Kosaka T, Yatabe Y. Biological and clinical implications of EGFR mutations in lung cancer. Int J Clin Oncol 11: 190-198, 2006.
3. Soda M, Choi YL, Enomoto M, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature 448: 561-566, 2007.
4. Koivunen JP, Merme C, Zejnullahu K, et al. EML4-ALK fusion gene and efficacy of an ALK kinase inhibitor in lung cancer. Clin Cancer Res 14: 4275-4283, 2008.
5. Inamura K, Takeuchi K, Togashi Y, et al. EML4-ALK lung cancers are characterized by rare other mutations, a TTF-1 cell lineage, an acinar histology, and young onset. Modern Pathology 22: 508-515, 2009.
6. Lee JK, Kim TM, Koh Y, et al. Differential sensitivities to tyrosine kinase inhibitors in NSCLC harboring EGFR mutation and ALK translocation. Lung Cancer 77: 460-463, 2012.
7. Yang JJ, Zhang XC, Su J, et al. Lung cancers with concomitant EGFR mutations and ALK rearrangements: Diverse responses to EGFR-TKI and crizotinib in relation to diverse receptors phosphorylation. Clin Cancer Res 20: 1383-1392, 2014.
8. Lee T, Lee B, Choi YL, Han J, Ahn MJ, Um SW. Non-small cell lung cancer with concomitant EGFR, KRAS, and ALK mutation: clinicopathologic features of 12 cases. J Pathol Transl Med 50: 197-203, 2016.
9. Zhao N, Zheng SY, Yang JI, et al. Lung adenocarcinoma harboring concomitant EGFR mutation and EML4-ALK fusion that benefits from three kinds of tyrosine kinase inhibitors: a case report and literature review. Clin Lung Cancer 16: e5-e9, 2015.
10. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin- paclitaxel in pulmonary adenocarcinoma. N Engl J Med 361: 947-957, 2009.
11. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 12: 735-742, 2011.
12. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 13: 239-246, 2012.
13. Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-negative lung cancer. N Engl J Med 368: 2385-2394, 2013.
14. Solomon BJ, Mok T, Kim DW, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med 371: 2167-2177, 2014.
15. Hida T, Nokihara H, Kondo M, et al. Alectinib versus crizotinib in patients with ALK-negative non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. Lancet 390: 29-39, 2017.
16. Shaw AT, Yeap BY, Mino-Kenudson M, et al. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. J Clin Oncol 27: 4247-4253, 2009.
17. Sasaki T, Koivunen J, Ogino A, et al. A novel ALK secondary mutation and EGFR signaling cause resistance to ALK kinase inhibitors. Cancer Res 71: 6051-6060, 2011.
18. Baldi L, Mengoli MC, Bisagni A, Banzi MC, Boni C, Rossi G. Concomitant EGFR mutation and ALK rearrangement in lung ade-
nocarcinoma is more frequent than expected: report of a case and review of the literature with demonstration of genes alteration into the same tumor cells. Lung Cancer 86: 291-295, 2014.

19. Cai W, Lin D, Wu C, et al. Intratumoral heterogeneity of ALK-rearranged and ALK/EGFR coalterred lung adenocarcinoma. J Clin Oncol 33: 3701-3709, 2015.

20. Miyanaga A, Shimizu K, Noro R, et al. Activity of EGFR-tyrosine kinase and ALK inhibitors for EML4-ALK-rearranged non-small-cell lung cancer harbored coexisting EGFR mutation. BMC Cancer 13: 262, 2013.

21. Chen X, Zhang J, Hu Q, Li X, Zhou C. A case of lung adenocarcinoma harboring exon 19 EGFR deletion and EML4-ALK fusion gene. Lung Cancer 81: 308-310, 2013.

22. Chiari R, Duranti S, Ludovini V, et al. Long-term response to gefitinib and crizotinib in lung adenocarcinoma harboring both epidermal growth factor receptor mutation and EML4-ALK fusion gene. J Clin Oncol 32: e30-e32, 2014.

23. Won JK, Keam B, Koh J, et al. Concomitant ALK translocation and EGFR mutation in lung cancer: A comparison of direct sequencing and sensitive assays and the impact on responsiveness to tyrosine kinase inhibitor. Ann Oncol 26: 348-354, 2015.

24. Sahnane N, Frattini M, Bernasconi B, et al. EGFR and KRAS mutations in ALK-positive lung adenocarcinomas: biological and clinical effect. Clin Lung Cancer 17: 56-61, 2016.

25. Ou SH, Ahn JS, De Petriss L, et al. Alectinib in crizotinib-refractory ALK-rearranged non-small-cell lung cancer: a Phase II Global Study. J Clin Oncol 34: 661-668, 2016.

26. Shaw AT, Gandhi L, Gadgeel S, et al. Alectinib in ALK-positive, crizotinib-resistant, non-small-cell lung cancer: a single-group, multicentre, phase 2 trial. Lancet Oncol 17: 234-242, 2016.

27. Seto T, Kiura K, Nishio M, et al. CH5424802 (RO5424802) for patients with ALK-rearranged advanced non-small-cell lung cancer (AF-001JP study): a single-arm, open-label, phase 1-2 study. Lancet Oncol 14: 590-598, 2013.

28. Ikeda S, Yoshioka H, Arita M, et al. Interstitial lung disease induced by alectinib (CH5424802/RO5424802). Jpn J Clin Oncol 45: 221-224, 2015.

29. Yamamoto Y, Okamoto I, Otsubo K, et al. Severe acute interstitial lung disease in a patient with anaplastic lymphoma kinase rearrangement-positive non-small cell lung cancer treated with alectinib. Invest New Drugs 33: 1148-1150, 2015.

30. Chino H, Sekine A, Kitamura H, Kato T, Ogura T. Successful treatment with alectinib after crizotinib-induced interstitial lung disease. Lung Cancer 90: 610-613, 2015.

The Internal Medicine is an Open Access article distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (https://creativecommons.org/licenses/by-nc-nd/4.0/).