Case Reports in Oncology

Case Rep Oncol 2016;9:826–832

DOI: 10.1159/000453314
Published online: December 8, 2016



**Case Report**

# Alectinib-Induced Erythema Multiforme and Successful Rechallenge with Alectinib in a Patient with Anaplastic Lymphoma Kinase-Rearranged Lung Cancer

Tatsuo Kimura[a, b] Junko Sowa-Osako[c] Toshiyuki Nakai[b]
Ayako Ohyama[c] Tomoya Kawaguchi[b] Daisuke Tsuruta[c]
Masahiko Ohsawa[d] Kazuto Hirata[a, b]

[a]Department of Premier Preventive Medicine, Graduate School of Medicine, Osaka City University, Osaka, Japan; [b]Department of Respiratory Medicine, Graduate School of Medicine, Osaka City University, Osaka, Japan; [c]Department of Dermatology, Graduate School of Medicine, Osaka City University, Osaka, Japan; [d]Department of Diagnostic Pathology, Graduate School of Medicine, Osaka City University, Osaka, Japan

**Keywords**
*EML4-ALK* · Alectinib · Lung cancer · Side effect · Erythema multiforme · Hypersensitivity syndrome · Rechallenge

**Abstract**
***Background:*** Alectinib is an oral drug developed for the treatment of patients with fusion gene encoding echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (*EML4-ALK*)-rearranged non-small cell lung cancer (NSCLC). Here, we present the case of a patient treated with alectinib who developed a hypersensitivity reaction with successful rechallenge treatment. ***Case Presentation:*** A 39-year-old woman who was a passive smoker was referred to Osaka City University Hospital for the evaluation of a skin event caused by treatment for NSCLC with the fusion gene *EML4-ALK*. The skin reaction was observed on the anterior chest, upper arms, and ear auricles on day 11 of treatment with oral alectinib. The skin event presented as widely distributed erythematous macules that were confluent, indi-



Tatsuo Kimura, MD, PhD
Department of Premier Preventive Medicine
Graduate School of Medicine, Osaka City University
1-1-43 Abeno Harukas 21F, Abenosuji, Abeno-ku, Osaka 545-6090 (Japan)
E-Mail kimutats@med.osaka-cu.ac.jp

cating a severe and life-threatening form. The skin lesions started to resolve after the initiation of treatment with 40 mg prednisolone. After regrowth of the tumor, she received a rechallenge program for alectinib for 2 weeks; thereafter, alectinib treatment was successfully reinitiated. ***Conclusion:*** To the best of our knowledge, we present the first case in which alectinib, which binds to the adenosine triphosphate site of *EML4-ALK*, induced erythema multiforme. Moreover, successful readministration of alectinib through our rechallenge program has not been reported so far.



## Background

The gene encoding echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (*EML4-ALK*) has been identified as a fusion oncogene in approximately 3–5% of cases with non-small-cell lung cancers (NSCLCs) [1]. The vast majority of these cases are adenocarcinomas. *EML4-ALK* fusions and mutations of the gene encoding epidermal growth factor receptor (*EGFR*) or *KRAS* are mutually exclusive [2]. Alectinib is an oral drug manufactured by Chugai Pharmaceutical (Tokyo, Japan) and is under development for patients with *ALK*-rearranged NSCLC. The crystal structure of the human *ALK* and of the alectinib complex shows that alectinib binds to the adenosine triphosphate site of *ALK* [3]. The Leu1196Met amino acid substitution confers resistance to crizotinib, and this substitution corresponds to gatekeeper mutations in the *EGFR* (Thr790Med) and *BCR-Abl* (Thr315Ile) genes [3].

The alectinib phase I/II studies (AF-001JP [4] and AF-002JG [5]) did not show dose-limiting toxicity, treatment-related deaths, or serious adverse reactions of grade 4 or higher as per the Common Terminology Criteria for Adverse Events. In each study, only 1 patient showed a grade-3 rash. The daily dose of oral alectinib was 600 mg.

Here, we report the case of a patient treated with alectinib who showed a hypersensitivity reaction with successful rechallenge treatment with alectinib. To our knowledge, ours is the first case in which alectinib, which binds to the adenosine triphosphate site of *EML4-ALK*, induced erythema multiforme (EM). Moreover, so far, successful readministration of alectinib through our rechallenge program has not been reported.

## Case Presentation

A 36-year-old woman was referred to Osaka City University Hospital with episodes of NSCLC since 2011. In 2011, she was diagnosed with stage-IIIb (T1aN3M0) lung adenocarcinoma in her right lower lobe. An *ALK* gene rearrangement was detected by an immunohistochemical examination and fluorescence in situ hybridization. Crizotinib was administered orally as a second-line treatment. During the crizotinib treatment, no skin events were noted. She was referred to our hospital in November 2014, at the age of 39 years, for the evaluation of a skin event, which was caused by alectinib treatment as the fifth-line treatment for NSCLC with the fusion gene *EML4-ALK*. She was a passive smoker and had routinely used medications including ambroxol hydrochloride, rabeprazole sodium, and sodium picosulfate hydrate for over 1 year. The skin reaction was observed on the anterior chest, back, upper arms, and ear auricles on day 11 of treatment with alectinib. The skin lesions were flat, atypical lesions, described as irregular purpuric macules (Fig. 1). A histamine-1 receptor antagonist, an external preparation of nadifloxacin, and a medium-class steroid were prescribed. On day 12, the skin reaction had rapidly spread to the abdomen and lower limbs. The patient

had a mild fever (body temperature, 37.2°C). An external preparation of a very strong steroid was prescribed. On day 13, the skin event presented as widely distributed erythematous macules that were confluent, indicating a severe and life-threatening form. Extensive mucosal involvement was also observed in the mouth and vulvar areas. The intensity of the itching of the skin lesions increased. Alectinib treatment was discontinued, and treatment with the oral histamine 2 receptor antagonist and oral prednisolone (20 mg) were initiated. On day 15, the patient was hospitalized because the skin condition did not improve. After admission, treatment with 40 mg oral prednisolone was initiated. The skin lesions started to resolve after 4 days of admission; thereafter, the prednisolone dose was gradually tapered, and treatment with prednisolone was discontinued on day 48.

Pathological findings of a skin examination on day 13 showed vacuolar degeneration of the basal cell layer with necrotic keratinocytes. The immunohistochemistry showed infiltration with CD4 and 8 T lymphocytes which led to the diagnosis of EM (Fig. 2a–c). Laboratory evaluation on day 14 showed elevated levels of aspartate transaminase (76 IU/L), alanine transaminase (55 IU/L), lactate dehydrogenase (300 IU/L), and C-reactive protein (0.86 mg/dL). Complete blood cell counts on day 14 showed no increase in the number of white blood cells, including eosinophils. Paired serum examinations on days 17 and 29 showed no elevation of the levels of the anti-human herpesvirus 6 IgG, anti-Epstein-Barr virus and cytomegalovirus IgG antibodies, or *Mycoplasma pneumoniae* antibody. The drug lymphocyte stimulation test was performed twice, on days 28 and 50. On day 28, steroid therapy was administered, and the drug lymphocyte stimulation index was 179%, which was slightly elevated, although it was within normal limits (<180%). The drug lymphocyte stimulation index on day 50 was 142%. A chest radiograph showed a remarkable decrease in the size of the tumor. Using the Naranjo criteria [6] to assess if the EM was caused by alectinib, "probable" adverse drug reaction (ADR) was found.

In January 2015, she showed brain and lymph node metastases on the contralateral side of the mediastinum. She underwent gamma-knife radiosurgery for the brain metastasis, followed by sixth-line chemotherapy with 4 courses of docetaxel, although she developed a progressive disease. In March 2015, she required emergency hospitalization due to increasing dyspnea. The cause of dyspnea was severe stenosis of the right and left main bronchus. At that time, she orally received 10 mg steroid (prednisolone) daily, because steroid reduced cerebral edema due to brain metastasis and gamma-knife radiosurgery. She received our rechallenge program for alectinib for 2 weeks, with 10 mg prednisolone. In brief, she received alectinib 20 mg once a day on days 1 and 2, 20 mg twice a day on days 3 and 4, 40 mg twice a day on days 5–7, 80 mg twice a day on days 8 and 9, 120 mg twice a day on days 10 and 11, and 160 mg twice a day on days 12–14. After each phase, the patient was observed for evidence of a hypersensitivity reaction. The patient tolerated this rechallenge program well with no symptoms of skin reaction or organ damage. Since completion of the rechallenge program, she continued treatment with alectinib (200 mg) twice daily. The result was a further decrease in tumor size and no signs of dyspnea.

## Discussion

EM is an acute, self-limiting, occasionally recurring skin disease. It is considered a type-IV hypersensitivity reaction and is associated with certain infections, including infections caused by herpes simplex virus, Epstein-Barr virus, and *M. pneumoniae*, drugs, and various other triggers [7]. In our case, paired serum examinations showed no elevation of anti-

human herpesvirus 6 levels, Epstein-Barr virus and cytomegalovirus IgG antibodies, or *M. pneumoniae* antibody. Additionally, the patient had no clinical symptoms before she received alectinib treatment. The patient routinely used ambroxol hydrochloride, rabeprazole sodium, and sodium picosulfate hydrate for over 1 year. There are reports of anaphylactic shock and allergic cutaneous reactions, including Stevens-Johnson syndrome, in the drug interview forms of these drugs; however, these reactions usually occur only as initial symptoms. These drugs are therefore unlikely to have contributed to her skin reactions.

A severe drug reaction could be provoked by an imbalance of the immune system, such as an excessive activation of effector T cells and inadequate function of regulatory T cells [8]. Early in the disease process, the epidermis is infiltrated with CD8 T lymphocytes and macrophages, whereas the dermis displays a slight influx of CD4 lymphocytes [9]. In our case, CD4 lymphocytes were more abundant than CD8 T lymphocytes in the dermis, and there was a predominance of CD8 T cells in the epidermis. This immunological reaction may involve a hypersensitivity reaction that can be triggered by chemical products. In our case, the skin reaction began on the anterior chest, upper arms, and ear auricles, which were presumably exposed to sunlight. Sun exposure with alectinib administration might induce EM.

Drug-induced hypersensitivity syndrome is an adverse reaction resulting in clinical symptoms of fever, rash, and internal organ involvement [10]. The Naranjo algorithm is a questionnaire designed by Naranjo et al. [6] for determining the likelihood of whether an ADR is actually due to the drug rather than the result of other factors. The ADR probability scale consists of 10 questions, and different point values (–1, 0, +1, +2) are assigned to each answer. Total scores range from –4 to +13; the reaction is considered "definite" if the score is 9 or higher, "probable" if it is 5–8, "possible" if it is 1–4, and "doubtful" if it is 0 or less. The answers to the questions in the present case were as follows:

- Are there previous conclusive reports on skin reaction? Yes. The skin reaction was described as toxicity with alectinib. Score: +1.
- Did the adverse events appear after the suspected drug was given? Yes. Score: +2.
- Did the adverse reaction improve when a specific antagonist was given? Yes. Score: +1.
- Did the adverse reaction appear when the drug was readministered? No. Score: –1.
- Are there alternative causes that could have caused the reaction? No. Other drugs she used are unlikely to contribute to her skin reactions. Score: +2.
- Was the adverse event confirmed by any objective evidence? Yes. The immunohistochemistry showed infiltration with CD4 and 8 T lymphocytes which led to the diagnosis of EM. Score: +1.

The total score was +6; therefore, "possible" ADR was found to have occurred in our case.

The rechallenge test has often been done in our hospital, and our procedure is almost similar for other drugs, including antibiotics, antituberculosis drugs, and anticancer drugs including kinase inhibitors. The duration of our protocol is 2 weeks, and it was created on the basis of the desensitization program for antituberculosis drugs [11]. This procedure is a standard for antituberculosis drugs but not for alectinib. In our case, considering the significant mortality associated with suboptimal treatment, the patient had no choice except for the use of alectinib. Ceritinib was not released at that time in Japan. It is imperative to start the rechallenge test with dose reduction of the suspected drug. Combination with steroid may be considered for patients in such a case. The procedure environment should be provided with great caution by well-trained medical staff with continuous monitoring of the patient's condition. The rechallenge test should be regarded as serious and potentially dangerous and, therefore, should only be considered after balancing the risk-benefit ratio in the individual patient [12]. For the record, there are limited data to guide the rechallenge of

drugs in drug-induced EM. In a sorafenib-induced EM report, a dose reduction and oral prednisolone co-administration were performed [13].

In conclusion, we report the case of a patient treated with alectinib who showed a hypersensitivity reaction with successful rechallenge treatment with alectinib. Early systemic administration of a high dose of steroids may prevent these reactions. To our knowledge, ours is the first case of alectinib hypersensitivity and successful rechallenge with alectinib. Further studies will be needed to clarify the mechanism underlying hypersensitivity reactions to *ALK* inhibitors.

## Acknowledgements

We would like to extend our thanks to Assoc. Prof. Shinya Fukumoto, Assoc. Prof. Hiroyasu Morikawa, and Dr. Yoshihiro Tochino for the valuable and constructive suggestions for ethics issues.

## Statement of Ethics

Written informed consent was obtained from the patient for the publication of this case report and accompanying images.

## Disclosure Statement

The authors declare that they have no competing interests. There are no funding sources to report.

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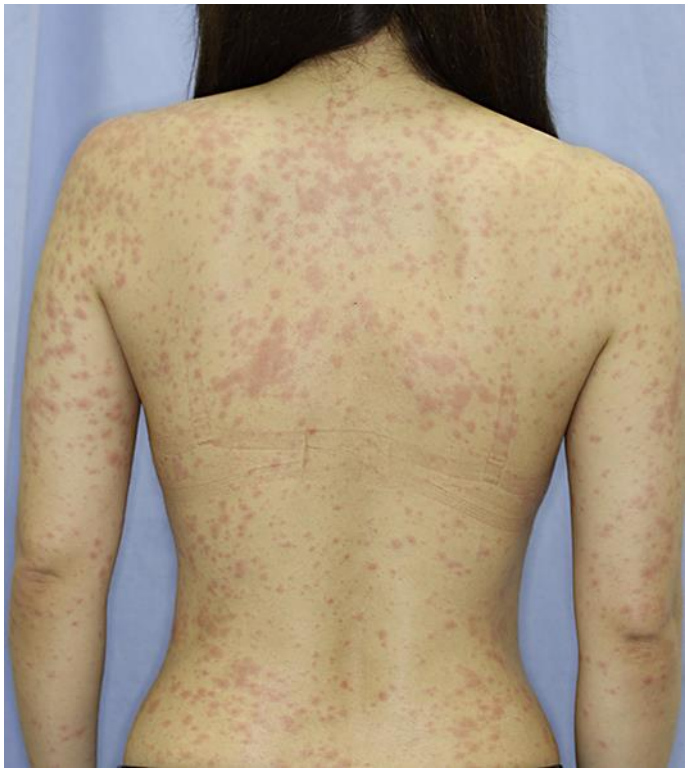

**Fig. 1.** Alectinib-induced erythema multiforme. Numerous erythematous macules of varying sizes are symmetrically distributed on day 11, at an early stage in the disease process.

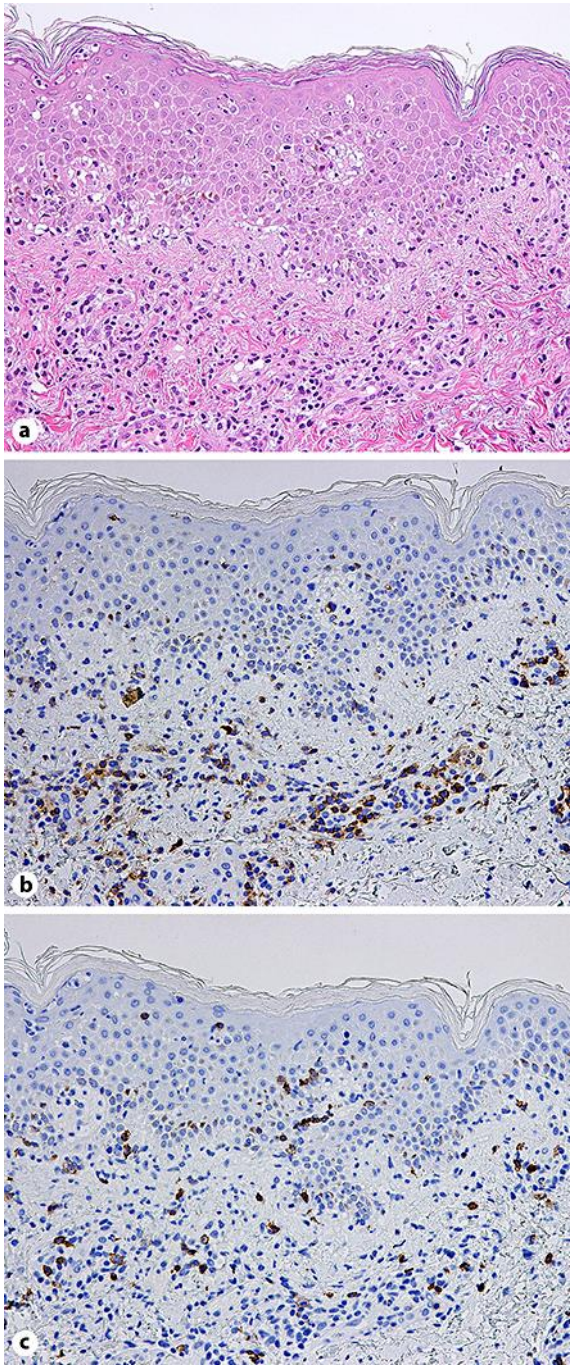


**Fig. 2.** Immunohistochemical analysis of CD4 and CD8 in erythema multiforme. Histopathological features indicating vacuolar dermatitis with perivascular lymphocytic infiltration at the superficial and mid-dermis; lymphocyte-mediated necrosis of keratinocytes, which was referred to as satellite cell necrosis; and vacuolar degeneration of the basal cell layer. CD4 lymphocytes were more abundant than CD8 T lymphocytes in the dermis, and there is a predominance of CD8 T cells in the epidermis. **a** Hematoxylin and eosin stain. **b** Immunohistochemistry of CD4. **c** Immunohistochemistry of CD8. Original magnification ×200.