Mutually Exclusive or Not? A Case with Concurrent EGFR Mutation, ALK Rearrangement, and 50% PD-L1

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Abstract
EGFR is the most common driver mutation detected in NSCLC. ALK rearrangement is found in about 4-5% of NSCLC patients. Although it is historically known that EGFR mutations and ALK rearrangements are mutually exclusive, recently identified cases show that this is not always true. A 48-year old male patient admitted with hoarseness, after a suspicious mass in the left hilar region on chest x-ray. 18F-FDG positron emission computed tomography performed. Pathological findings were consistent with pulmonary adenocarcinoma infiltration. Brain MRI and genomic tests were performed. EGFR mutation, ALK rearrangement and 50 PD-L1 positivity were detected. With the diagnosis of metastatic lung adenocarcinoma, treatment with erlotinib 150 mg per day orally started and the response was continued for 8 months. After progression on erlotinib, crizotinib is started. Although EGFR mutation and ALK rearrangement have been reported to be mutually exclusive, it has also been shown to coexist in several studies. Optimal treatment decision is difficult, there is no consensus for initial treatment.

Introduction
Lung cancer is the most common cancer in the world with 2,093,876 new cases and 1,761,007 deaths [1]. In the United States, an estimated 228,820 new cases and 135,720 deaths are expected in 2020 [2]. Lung cancer is divided into two main groups as small cell and non small cell (NSCLC). NSCLC's rate is about 85% in all lung cancers.

A better understanding of molecular pathways in NSCLC has led to the development of specific agents that go beyond traditional chemotherapy and target these pathways, and significant advances in advanced NSCLC treatment. Epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), proto-oncogene tyrosine-protein kinase 1 ROS (ROS1), v-Raf murine sarcoma viral oncogene homologue B (BRAF) are targeted pathways in NSCLC [3]. Guidelines recommend routine testing for genetic mutations, especially EGFR, ALK, ROS1 in all non-squamous NSCLC.

EGFR is the most common driver mutation detected in NSCLC. It can be detected in approximately 10-15% of western societies and 50% of Asian origin patients [4,5]. Tyrosine kinase inhibitors (TKI) such as erlotinib, gefitinib, afatinib, osimertinib can be used in advanced NSCLC patients with driver mutations in EGFR [6-8]. The less frequent ALK rearrangement is found in about 4-5% of NSCLC patients [9,10]. TKIs such as crizotinib, ceritinib, alectinib, brigatinib can be used in advanced NSCLC where ALK rearrangement is detected [11-13].

Although, it is historically known that EGFR mutations and ALK rearrangements are mutually exclusive, recently identified cases show that this is not always true [14]. There are case series and studies have been published...
regarding the coexistence of EGFR mutation and ALK rearrangement [15-19]. Here, we present a case with lung adenocarcinoma diagnosed with EGFR mutation, ALK rearrangement and PD-L1 positivity.

Case Presentation

A 48-year old male patient admitted with hoarseness, after a suspicious mass in the left hilar region on chest x-ray was seen he was referred to our hospital. The patient have never smoked and has no known previous disease history. With suspected lung cancer 18F-FDG positron emission computed tomography was performed. It revealed increased FDG uptake in the mass in left lung upper lobe of left lung, left supraclavicular lymph node, mediastinal lymph nodes, and L3 vertebra. Endobronchial ultrasound bronchoscopy was performed and fine needle aspiration biopsies were taken from lymph nodes 4R, 2R and 11L. Pathological findings were consistent with pulmonary adenocarcinoma infiltration. Metastasis was not detected in brain magnetic resonance imaging (MRI). Genomic tests were performed; deletion of exon 19 (EGFR mutation analysis with real-time polymerase chain reaction), %20 ALK rearrangement positivity and ROS1 negativity (fluorescent in situ hybridization) and %50 PD-L1 positivity (Ventana-SP263) were detected.

With the diagnosis of metastatic lung adenocarcinoma and EGFR exon 19 deletion and ALK rearrangement positivity, treatment with erlotinib 150 mg per day orally started. Serial chest radiographies of case were shown at Figure 1. Due to bone metastasis intravenous 4 mg of zoledronic acid per 28 days also administered. After 3 months, partial response was seen on thorax CT scan and the response was continued for 8 months. After progression on erlotinib, crizotinib is started recently and patient is taking crizotinib for 1 months. Until now any treatment related grade 3-4 toxicity or progression suspect is not seen.

Discussion

Here we present a rare case with EGFR exon 19 deletion, ALK rearrangement and PD-L1 positivity. In this rare situation, it is difficult to make treatment choices since the clinical features of patients are not well defined.

Although EGFR mutation and ALK rearrangement have been reported to be mutually exclusive, it has also been shown to coexist in several studies. In the study conducted by Ulivi et al. EGFR mutation and ALK rearrangement was found to be concurrent in 1.6% of patients [17]. In this study, 5 of 6 patients with concurrent mutations were women and 3 of them never smoked. Six patients were treated with EGFR TKI; complete response was obtained in 1 patient and partial response was obtained in 2 patients.

In another study mutation concurrence was found 1.3% [20]. In that study, those with exon 19 deletions were younger than those with exon 21 mutations (mean age 53.6 vs 62.7). Treatment was started with EGFR TKI in 10 of 13 patients. Partial response was seen 8 of 10 patients (4 erlotinib, 3 gefitinib and 1 afatinib).

In another study, those with concurrent mutations were younger than those with EGFR mutations alone [16]. Our patient also had exon 19 deletion and patient was 48 years old. We treated the patient first line with erlotinib, time to progression was about 9 months. In that mentioned study, 5 of 10 patients with concurrent mutation that received EGFR TKI had partial response, 3 had stable disease. Progression free survival was worse than those with EGFR mutation alone (p = 0.04) [16]. In second line treatment with ALK TKIs, partial response was seen in 3 of 5 patients. However, while Lo Russo et al. reported that ALK TKIs are slightly more effective than EGFR TKIs, Schmid et al. reported that better results were obtained with EGFR TKIs compared to ALK TKIs [15, 21].

Immune checkpoint inhibitors, especially anti-PD-1 and anti-PD-L1 agents, provided significant survival benefit in advanced NSCLC patients with phase 3 studies [22-24]. However, many studies have shown that checkpoint inhibition is less effective in patients with EGFR mutation than in those without. In the Checkmate 057 study, progression-free survival and overall survival benefit could not be demonstrated for the subgroup of patients with EGFR mutation [22]. Also in the Keynote-010 and OAK studies, no survival benefit
was found in the EGFR mutant subgroup [24,25]. In the light of these information we did not started second line treatment with a checkpoint inhibitor.

**Conclusion**

Concurrent mutation of EGFR and ALK is a rare condition. Optimal treatment decision is difficult, there is no consensus for initial treatment. In targeted therapies, targeting one of the driver mutations can lead to activation of other existing driver mutations and eventually lead to progression. It may be promising to find an agent that targets both EGFR and ALK pathways in the future.

**References**


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