

# Erlotinib Treatment in a Case of Lung Adenocarcinoma Mimicking Interstitial Lung Disease

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## Abstract

Lung adenocarcinoma (LA) may occur with a radiographic appearance of localized tumor in the parenchyma or with diffuse parenchymal infiltration as interstitial lung disease (ILD). In our country, erlotinib is a tyrosine kinase inhibitor used in *Epidermal Growth Factor Receptor (EGFR)* mutation-positive patients who are resistant to first-line chemotherapy. A 48-year-old patient presented to our hospital with weakness and shortness of breath on exertion. Mediastinal enlargement and bilateral multinodules were observed in the chest X-ray. Ordinary blood laboratory values and arterial blood-gas analysis findings were normal. Lung function tests showed moderate restrictive ventilation and reduction of diffusing capacity based on the predicted value. A thorax computed tomography scan showed multiple mediastinal lymphadenopathies and bilateral diffuse perilymphatic nodule spread. The patient diagnosed with LA on the basis of endo-bronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA). Because of bilateral diffuse involvement of the lung, platinum-based combination chemotherapy was recommended. The progression of disease had occurred after two cycles, and a second-line treatment with erlotinib (150 mg/day) was initiated. A decrease in all lesions was observed in patient follow-up. The treatment with erlotinib was well tolerated. There was no adverse event for 6 months. This case was presented for the choice of LA that mimicked ILD and for the significant clinical and radiological responses to erlotinib in patients with EGFR mutation.

**Keywords:** Erlotinib, interstitial lung disease, lung adenocarcinoma

## INTRODUCTION

Lung adenocarcinoma (LA) most commonly manifests as a peripheral mass or a malignant pleural effusion (1). Different types of LA can show similar radiographic findings of pulmonary parenchymal infiltrates localized in the form of interstitial lung disease (ILD). *Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor (EGFR-TKI)* treatment has been demonstrated to significantly improve responses and outcomes in patients with advanced non-small-cell lung cancer (NSCLC) harboring an EGFR mutation. Here we report a response to erlotinib treatment in the case of a non-smoker female who was resistant to first-line platinum-based chemotherapy and had LA that mimicked ILD.

## CASE PRESENTATION

A 48-year-old non-smoker woman who was a housewife presented to our hospital with weakness and shortness of breath on exertion. She had a history of asbestos exposure for 6 years. Physical examination revealed no pathological findings in the examination of the entire system.

Arterial blood gas analysis showed no hypoxia. Findings of lung function tests were as follows: forced vital capacity (FVC), 2090 mL (61%); forced expiratory volume in 1 second (FEV<sub>1</sub>), 1950 mL (69%); FEV<sub>1</sub>/FVC, 119%; residual volume (RV), 780 (41%); ratio of RV to total lung capacity (RV/TLC), (28%); and diffusing capacity for carbon monoxide (DLCO), reduced to 4340 mL (53%). These findings showed a moderate restrictive ventilation disorder and a moderate reduction of diffusing capacity. Chest radiograph showed bilateral upper, mid, and lower zone alveolar interstitial shadows; bilateral multinodules in common; and mediastinal enlargement (Figure 1a). A thorax computed tomography (TCT) scan of her chest showed multiple mediastinal lymphadenopathies and bilateral diffuse perilymphatic nodule spread (Figure 1b).



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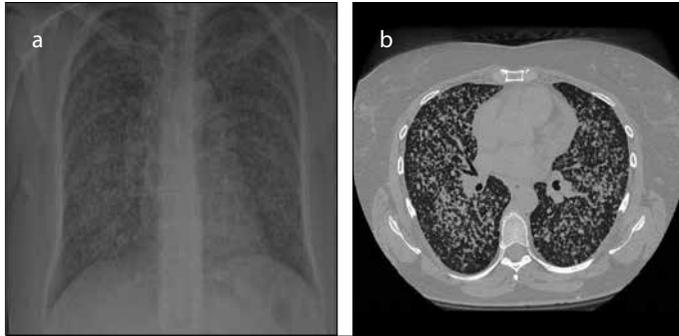
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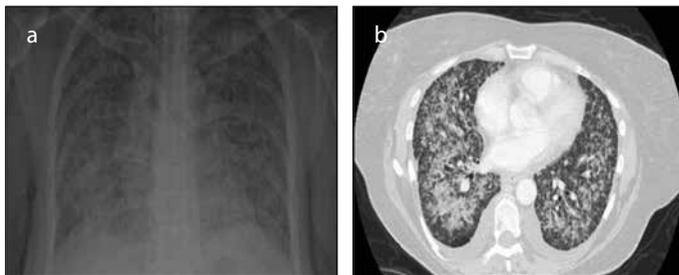
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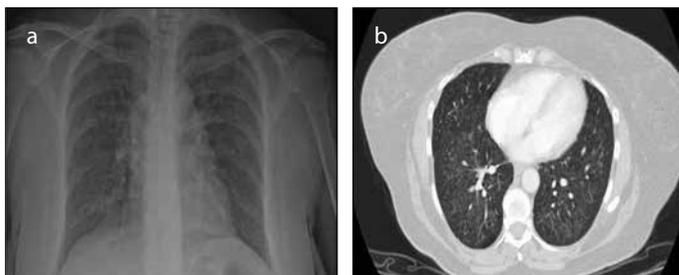
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**Figure 1. a, b.** A chest X-ray (a) and thorax computed tomography (b) of patient before the diagnosis of lung adenocarcinoma



**Figure 2. a, b.** A chest X-ray (a) and thorax computed tomography (b) after two cycles of platinum-based combination chemotherapy



**Figure 3. a, b.** A chest X-ray (a) and thorax computed tomography (b) after erlotinib treatment

Initially, from all clinical, laboratory and radiological findings, ILDs such as sarcoidosis, amiloidosis, and collagen tissue diseases were considered. Serum angiotensin-converting enzyme (ACE) and 24-hour urine calcium levels were normal. In terms of the history of connective tissue disease, physical examination and laboratory test findings revealed no abnormality. Two sputum samples were negative for acid-fast bacilli (AFB), and bacterial culture resulted in negative findings for tuberculosis. The result of the purified protein derivative (PPD) test was negative by the presence of anergy. T-helper and T-suppressor (Th /Ts) cell populations in bronchoalveolar lavage (BAL) were normal. However, any of the clinical, laboratory and microbiological tests did not support interstitial and infectious disease. Bronchogenic carcinoma and metastatic diseases were not excluded.

Bronchoscopy was performed including BAL and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) in the same session for differential diagnosis. Bronchoscopy revealed blunting of the carina. EBUS-TBNA cytology specimens of level 4R, 7, and 10L lymph nodes also showed LA. BAL cytology was not diagnostic for both malignancy and ILD. Mutational analysis of EGFR

was performed in specimens. After the diagnosis of malignancy, screening tests were performed for distant metastases. An  $^{18}\text{F}$  fluorodeoxyglucose-positron emission tomography (FDG-PET) scan showed bilateral heterogeneous metabolic activity and lymph node involvement. Magnetic resonance (MR) imaging of the brain revealed no metastasis.

Considering all the examination data and the bilateral involvement of lung, this case was diagnosed as an advanced stage. Direct platinum-based combination chemotherapy using cisplatin-gemcitabine was recommended. After two cycles of chemotherapy, a TCT scan showed progression in addition to the development of parenchymal lesions with minimal pleural effusion (Figure 2a, b). Meanwhile, we found that the EGFR mutation resulted as a positive variant at exon 21, codon 858 (CTG>CGG; L858R), and a second-line treatment with erlotinib (150 mg/day) was initiated. Three months later, a dramatic improvement in symptoms and radiographic regression were revealed with erlotinib (Figure 3a, b). The treatment with erlotinib was well tolerated. There was no adverse event for 6 months. At the time when this article was revised, our patient still undergoing treatment with erlotinib. Written informed consent was obtained from the patient.

#### DISCUSSION

Radiological appearance of LA is either a pure ground-glass nodule or partly solid nodule with a predominant ground-glass component (2). It may produce no symptoms until the disease is at an advanced stage. The tumor doubling time is long in most patients; extrathoracic metastases have a low tendency. In these cases, shortness of breath is dominant in the clinical progress. Pneumonia, pulmonary edema, and diffuse ILD must be distinguished in differential diagnosis combined with clinical and radiological findings (3).

Our patient was admitted to our clinic with shortness of breath on exertion and bilateral multiple nodules in common and mediastinal enlargement on chest X-ray. Some tests were primarily performed for the etiology of ILD. Mediastinal lymphadenopathy and multiple nodules primarily suggest sarcoidosis. Laboratory and clinical examination findings were not compatible with sarcoidosis. Physical examination and laboratory values revealed no abnormality in terms of connective tissue disease. Atypical radiological findings of pulmonary tuberculosis can mimic ILD (4). In our case, two sputum specimens were microscopically examined for the presence of AFB by Ziehl-Nielsen staining and were found to be negative with sputum culture for tuberculosis. Findings of the PPD test were negative by the presence of anergy.

Adenocarcinoma is the most common subtype of NSCLC in developed countries and is increasing in our country. Adenocarcinoma can show similar clinical and radiological features to ILD. Imaging methods may be useful for differential diagnosis, but the confounding radiological appearance should always be remembered. Despite all these, a tissue biopsy should be performed as soon as possible to reach a final diagnosis. EBUS-TBNA is a reliable technique for the investigation of unexplained mediastinal lymphadenopathy and staging of lung cancers (5). EBUS-TBNA is preferred over transbronchial biopsy (TBB) for sampling mediastinal lymph nodes (6). Because we considered all differential diagnoses such as tuberculosis and sarcoidosis, our patient underwent EBUS-TBNA rather than TBB as it is considered more appropriate and adequate amount of sample can

be taken from lymph nodes according to the parenchyma. However, it is an underutilized technique with a poor diagnostic yield and high risk of complications (7). She was diagnosed with LA on the basis of 4R and 10L lymph node aspiration. Aspiration materials were sufficient for the genetic mutation tests. We have also shown that EBUS-TBNA can be effectively used not only for diagnosis but also for complete mutational testing. With the increasing availability and emphasis on minimally invasive diagnostic procedures such as EBUS-TBNA, testing for EGFR mutations and ALK rearrangements is increasingly attempted on small specimens, including biopsy samples or paraffin cytoblocks prepared from fine needle aspiration (FNA) samples. In addition, ALK rearrangement by FISH analysis was negative and ROS1 rearrangement was not evaluated in our patient.

The standard treatment for NSCLC patients is platinum-based combination chemotherapy. In recent years, targeted therapies have allowed for a personalized approach to the treatment of advanced NSCLC. They may have fewer side effects than traditional chemotherapy (8). The most important change during the last decade was the introduction of treatment guided by the genetic profile of the tumor (9). Treatment with EGFR-TKI such as gefitinib or erlotinib is an effective targeting therapy, particularly for advanced NSCLC (10). According to clinical characteristics of the patient and histological and genetic results, erlotinib was started as second-line chemotherapy. Three months later, a dramatic improvement in symptoms and radiographic regression were observed with erlotinib. We emphasize that erlotinib treatment is efficient and well-tolerated in NSCLC patients with an EGFR mutation.

## CONCLUSION

At first, which has been taken care of in all relatively similar cases, is the view that "LA must be come to the fore in differential diagnosis, although clinical harmony with diffuse parenchymal involvement is visible on X-ray". Secondly, it has to be discussed that targeted therapeutic agents now in our country should be used as first-line therapy agents if there is appropriate laboratory support.

**Informed Consent:** Written informed consent was obtained from patient who participated in this study.

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