

Case Report

# Adenocarcinoma of the Lung Acquiring Resistance to Afatinib by Transformation to Small Cell Carcinoma: A Case Report

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## Keywords

Adenocarcinoma · Afatinib · Small cell carcinoma · Irinotecan · Drug resistance · Transformation

## Abstract

A 65-year-old woman visited our hospital due to right chest pain and dyspnea on exertion. Chest radiography revealed decreased permeability of the right lung. Computed tomography demonstrated a huge mass in the right upper lobe and right pleural effusion. Right pleural effusion cytology yielded a diagnosis of adenocarcinoma and was positive for mutation of epidermal growth factor receptor (EGFR; exon 21 L858R). Afatinib was selected for the initial treatment. Multiple tumors regressed remarkably, but then rapidly progressed 3 months later. We performed re-biopsy to detect the mechanism of resistance to afatinib. Histopathology revealed a mixture of small cell carcinoma (SCC) and adenocarcinoma harboring same EGFR mutation. To the best of our knowledge, this is the first report of transformation to SCC after treatment with afatinib.

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## Introduction

Lung cancers harboring epidermal growth factor receptor (EGFR) mutations usually respond to EGFR tyrosine kinase inhibitors (TKIs), but most acquire resistance [1, 2]. Transformation of the tumor has been reported to be one of the mechanisms of acquired resistance after treatment with first-generation EGFR-TKIs [3]. However, few reports have described transformation during treatment with the second-generation EGFR-TKI afatinib [4]. We report a case of adenocarcinoma of the lung that acquired resistance to afatinib via transformation to small cell carcinoma (SCC).

## Case Report

A 65-year-old woman visited our hospital due to right chest pain and dyspnea on exertion. A chest radiograph revealed decreased permeability of the right lung (Fig. 1a). Computed tomography (CT) demonstrated a huge mass in the right upper lobe (Fig. 1b) and right pleural effusion. In addition, multiple masses were detected on the left lung, liver, and left adrenal gland, as well as mediastinal lymphadenopathy. Pathological examination of the right pleural effusion and a transbronchial biopsy from the right upper bronchus yielded a diagnosis of adenocarcinoma of the lung. Because an EGFR mutation (exon 21 L858R) was detected, treatment with afatinib was initiated.

Multiple tumors remarkably regressed in 1 month, but paronychia (grade 3) appeared in 2 months. Due to difficulties in daily life, the treatment was interrupted for 2 weeks. CT images 3 months after the initial treatment demonstrated growth of the tumors in the lung. We performed another transbronchial biopsy to determine the mechanisms of resistance to afatinib. Histopathological examination revealed a mixture of SCC and adenocarcinoma (Fig. 2) harboring the same EGFR mutation as the initial biopsy specimen. Systemic chemotherapy consisting of cisplatin and irinotecan was administered, but no tumor regression was evident and carcinomatous pericarditis occurred. In addition, the patient complained of consciousness disorder and convulsions. Lumbar puncture identified adenocarcinoma cells in the cerebrospinal fluid. The patient was diagnosed with carcinomatous meningitis and erlotinib treatment was administered. However, no symptomatic improvement occurred and the patient died 5 months after the initial diagnosis. Autopsy was not allowed.

## Discussion

In lung cancers harboring EGFR mutations, EGFR-TKIs demonstrate a favorable response, but drug resistance emerges in most cases. A transformation of adenocarcinoma to SCC is one of the resistance mechanisms in first-generation EGFR-TKIs and occurs in 14% of resistant cases, in which the same EGFR mutation is found before and after the changes [5]. An amplification of MET, a high affinity tyrosine kinase receptor for hepatocyte growth factor, and a T790M mutation have been reported as resistance mechanisms of the second-generation EGFR-TKI afatinib [4]. However, to the best of our knowledge, this is the first report of transformation to SCC after afatinib treatment.

In the current case, SCC cells were found 3 months after the initial treatment with afatinib. After the chemotherapy for SCC, the carcinomatous meningitis progressed rapidly. Thus, we hypothesized that a very early stage of SCC development was observed in the cur-

rent case. Although there is a possibility that adenocarcinoma and SCC coexisted from the initial diagnosis, a transbronchial biopsy from the same spot demonstrated adenocarcinoma alone at the time of the initial diagnosis and adenocarcinoma and SCC at the re-biopsy. We consider these findings to support our hypothesis.

When resistance to an EGFR-TKI occurs in lung cancer harboring an EGFR mutation, re-biopsy is recommended to reveal the resistance mechanisms. For cases with a T790M mutation in exon 20, osimertinib has been reported to be a promising treatment option [6]. Recently, the utility of liquid biopsy has been reported for the detection of the T790M mutation [7]. However, to date, SCC transformation cannot be detected by liquid biopsy. In cases in which EGFR-TKI treatment fails, re-biopsy should be applied to reveal the resistance mechanisms and aid in the selection an appropriate treatment.

Favorable results of systemic chemotherapy consisting of platinum and etoposide or irinotecan have been reported in cases of SCC transformation [8], but little response was observed in the current case and the adenocarcinoma progressed rapidly. The effect of EGFR-TKIs for transformed SCC is reported to be limited [9]. A treatment strategy for transformed SCC and existing adenocarcinoma should be established.

In conclusion, we reported a case of EGFR-mutated adenocarcinoma of the lung that transformed to SCC.

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### Statement of Ethics

The authors have no ethical conflicts to disclose.

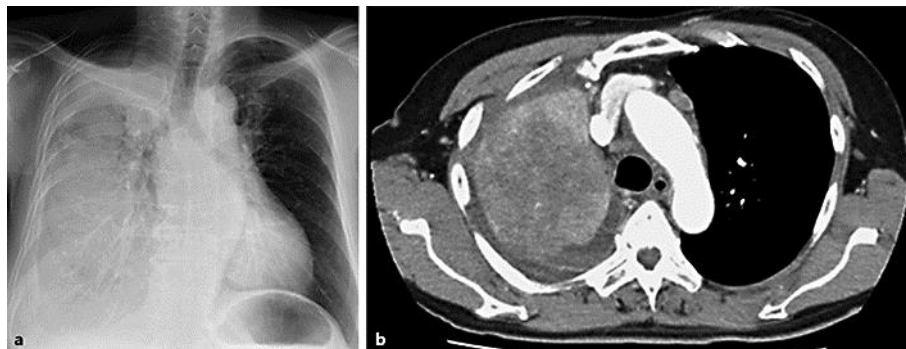
### Disclosure Statement

The authors have no conflicts of interest to declare.

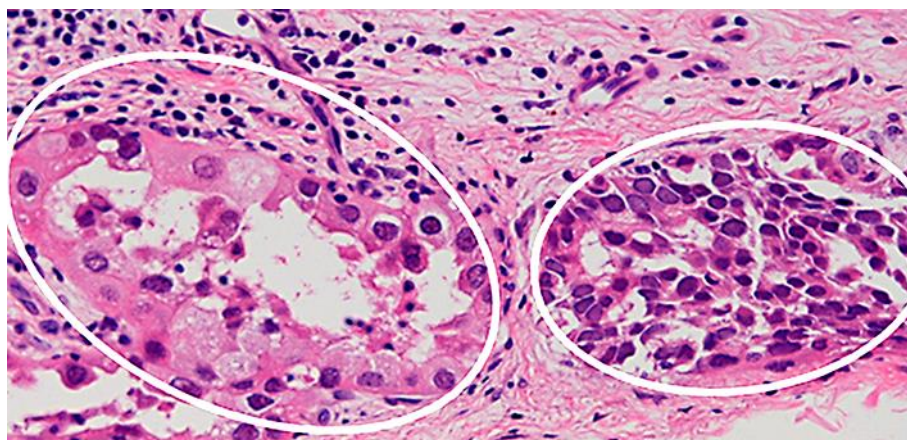
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**Fig. 1.** **a** Chest radiograph showing decreased permeability of the right lung. **b** CT image of the chest demonstrating a huge mass in the right lung and right pleural effusion.



**Fig. 2.** Pathological analysis of the transbronchial re-biopsy specimen revealed adenocarcinoma (left circle) and small cell carcinoma (right circle).