CASE REPORT

Pulmonary pleomorphic carcinoma: A case harboring EGFR mutation treated with EGFR-TKIs

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Abstract

Pulmonary pleomorphic carcinoma (PPC) is a very rare type of primary lung cancer with an aggressive clinical course. Few reports have documented therapeutic options for PPC with EGFR mutations. Herein, we report a case of PPC with EGFR mutation treated with EGFR-tyrosine kinase inhibitors (TKIs). A 65-year-old Japanese woman was diagnosed with stage IV lung adenocarcinoma with L858R point mutation in exon 21. Despite treatment with erlotinib, the patient died after two weeks as a result of rapid disease progression. Postmortem examination indicated that the thoracic tumors consisted primarily of spindle/sarcomatous components, while expression of the mutated EGFR protein was only observed in adenocarcinoma components. We speculate that the tumor was not driven by EGFR mutation. Clinicians should bear in mind the possibility of pleomorphic carcinoma if EGFR-TKI treatment fails to achieve a clinical response for adenocarcinoma harboring an activating EGFR mutation diagnosed on the basis of small biopsy specimens.

Introduction

EGFR mutation was discovered in 2004 as the first example of oncogene addiction in lung adenocarcinoma. EGFR-tyrosine kinase inhibitors (TKIs) have been shown to be effective against lung adenocarcinomas harboring EGFR-activating mutations.1,2 Herein, we describe a case of pulmonary pleomorphic carcinoma (PPC) harboring an EGFR mutation treated with EGFR-TKIs.

Case report

A 65-year-old Japanese female non-smoker presented with a mass shadow that had been detected by chest radiography at a local clinic. Computed tomography (CT) revealed a 3 cm lesion in the right lower lung with no central necrosis and mediastinal lymphadenopathy extending to the contralateral side. Multiple metastases were observed in right pleural effusion, the adrenals, and bones (Fig 1). Transbronchial biopsy revealed primarily adenocarcinomatous cells with some spindle cells. Immunohistochemistry showed the cells to be diffusely positive for TTF-1 and Napsin A, but negative for vimentin. We diagnosed the primary tumor as adenocarcinoma, and detected a L858R point mutation in exon 21 by Cobas EGFR mutation assay (Roche Molecular Diagnostics Inc., South Branchburg, NJ, USA) (Fig 2). After 12 days of erlotinib treatment, the patient was admitted to our hospital because of dyspnea. CT revealed an increase of both pleural and cardiac effusion, and many subcutaneous metastases with acute renal injury and hypercalcemia. On day 15 of erlotinib treatment, the patient was admitted to our hospital because of dyspnea. CT revealed an increase of both pleural and cardiac effusion, and many subcutaneous metastases with acute renal injury and hypercalcemia. On day 15 of erlotinib treatment, the patient died as a result of aggressive tumor progression. An autopsy revealed that the thoracic masses consisted primarily of spindle/sarcomatous components, and immunohistochemistry showed the cells to be diffusely positive for vimentin. On the basis of these findings, we diagnosed the tumor as PPC (Fig 3).
Pulmonary pleomorphic carcinoma is a very rare type of primary lung cancer, accounting for 0.1–1.6% of all malignant tumors of the lung. PPC is defined as a poorly differentiated non-small cell lung cancer (NSCLC) containing spindle cells and/or giant cells, or a carcinoma that comprises spindle or giant cells alone, in at least 10% of the tumor. It has an aggressive clinical course and can show resistance to chemotherapy, which is an actively
applied treatment for NSCLC. The present case of PPC was unresponsive to EGFR-TKIs despite harboring an EGFR mutation.

Several researchers have reported that the frequency of PPC harboring EGFR mutations is approximately 15%. However, it is still unclear whether EGFR-TKIs are active against this type of PPC. Tamura et al. reported a case of PPC expressing mutated EGFR protein in both the adeno-carcinomatous and sarcomatoid components that showed a good response to gefitinib. By contrast, Kaira et al. reported a case of PPC with L858R point mutation that did not respond to gefitinib. In the latter case, expression of the mutated EGFR protein was detected in the adeno-carcinomatous component, but not in the sarcomatoid component. Similarly, the present case of PPC, which expressed the mutated EGFR protein only in the adenocarcinomatous component, showed no response to EGFR-TKIs. We speculate that the EGFR mutation had not caused oncogene addiction in this case.

Pulmonary pleomorphic carcinoma shows distinctive heterogeneity, being composed of poorly differentiated NSCLC containing spindle cells and/or giant cells. The molecular origin of PPC remains largely obscure. Lee et al. reported that 30 (49%) of 61 resected PPC cases had molecular alterations such as EGFR, KRAS, and c-kit, and amplification of MET. Of these cases, eight had EGFR deletion in exon 19 and one had L858R mutation in exon 21. Furthermore, four cases also had c-kit mutation, and one had KRAS mutation with activating EGFR mutations. Another study detected KRAS mutations in 10 out of 110 PPC cases that occurred in never smokers. Recently, MET skipping mutations were found in nine out of a series of 45 PPC cases. We suggest that the biology of PPC, including driver gene alteration, should be investigated further.

In conclusion, we have described a case of PPC with EGFR mutation for which erlotinib was not effective. We speculate that the tumor was not driven by EGFR mutation. If adenocarcinoma harboring an activating EGFR mutation diagnosed from small biopsy specimens shows no clinical response to EGFR-TKI therapy, clinicians should consider the possibility that the tumor may be a pleomorphic carcinoma.

Disclosure
No authors report any conflict of interest.

References
1. Maemondo M, Inoue A, Kobayashi K et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 2010;362:2380–8.
2. 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 2011; 12: 735–42.
3 Travis WD, Travis LB, Devesa SS. Lung cancer. (Published erratum appears in Cancer 1995; 75: 2979.). Cancer 1995; 75 (Suppl. 1): 191–202.

4 Mochizuki T, Ishii G, Nagai K et al. Pleomorphic carcinoma of the lung: Clinicopathologic characteristics of 70 cases. Am J Surg Pathol 2008; 32:1727–35.

5 Ito K, Oizumi S, Fukumoto S et al. Clinical characteristics of pleomorphic carcinoma of the lung. Lung Cancer 2010; 68: 204–10.

6 Kaira K, Horie Y, Ayabe E et al. Pulmonary pleomorphic carcinoma: A clinicopathological study including EGFR mutation analysis. J Thorac Oncol 2010; 5: 460–5.

7 Lee S, Kim Y, Sun JM et al. Molecular profiles of EGFR, K-ras, c-met, and FGFR in pulmonary pleomorphic carcinoma, a rare lung malignancy. J Cancer Res Clin Oncol 2011; 137:1203–11.

8 Tamura Y, Fujiwara Y, Yamamoto N et al. Retrospective analysis of the efficacy of chemotherapy and molecular targeted therapy for advanced pulmonary pleomorphic carcinoma. BMC Res Notes 2015; 8: 800.

9 Jia X, Chen G. EGFR and KRAS mutations in pulmonary pleomorphic carcinoma and their correlation with clinicopathologic features. Contemp Oncol (Pozn) 2015; 19: 22–7.

10 Kwon D, Koh J, Kim S et al. MET exon 14 skipping mutation in triple-negative pulmonary adenocarcinomas and pleomorphic carcinomas: An analysis of intratumoral MET status heterogeneity and clinicopathological characteristics. Lung Cancer 2017; 106: 131–7.