Successful Resection of G719X-Positive Pleomorphic Carcinoma after Afatinib Treatment

Daisuke Nakamura, Kentaro Miura, Hirotaka Kumeda, Hiroyuki Agatsuma, Akira Hyogotani, Kazutoshi Hamanaka, Tomonobu Koizumi, Hiroshi Yamamoto, Hisashi Tamada, Ken-ichi Ito

Division of Breast, Endocrine and Respiratory Surgery, Department of Surgery, Shinshu University School of Medicine, Matsumoto, Japan; Department of Comprehensive Cancer Therapy, Shinshu University School of Medicine, Matsumoto, Japan; First Department of Internal Medicine, Shinshu University School of Medicine, Matsumoto, Japan; Department of Laboratory Medicine, Shinshu University School of Medicine, Matsumoto, Japan

Keywords
Pleomorphic carcinoma · Afatinib · Exon 18 · Epidermal growth factor receptor mutation

Abstract
We report a case of pleomorphic carcinoma with exon 18 mutation (G719X) of the epidermal growth factor receptor (EGFR), which showed good response to afatinib and resulted in successful resection. To our knowledge, this is the first report on the use of afatinib for pleomorphic carcinoma followed by the surgical resection. The patient was a 59-year-old woman, who visited our hospital because chest computed tomography showed a 28 × 28-mm nodule in the left upper lobe. Bronchoscopy was performed and the histological findings of transbronchial biopsy revealed adenosquamous carcinoma positive for G719X mutation in exon 18 of the EGFR. Since fluorodeoxyglucose (FDG)-positron emission tomography/computed tomography revealed a positive accumulation in the bilateral hilar and mediastinal lymph nodes, the disease was diagnosed as cT1bN3M0, stage IIIb. After 3 months of afatinib therapy, FDG accumulation in primary tumor was almost gone. However, FDG accumulation...
in lymph nodes remained unchanged. Video-assisted thoracic surgery was planned for further diagnostic information and left upper lobectomy with mediastinal lymph node dissection was performed. The resected tumor included adenocarcinoma, squamous cell carcinoma, and spindle cell components, without lymph node metastasis. Thus, the disease was diagnosed as pleomorphic carcinoma (pT2aN0M0, stage IB). All components in the resected specimen had the same G719X mutation in exon 18 of the EGFR. The patient has shown no signs of recurrence at 1 year after the operation. The present case indicates the possibility of minor EGFR mutations in pleomorphic carcinoma and successful outcome by the use of afatinib and surgical resection.

Introduction

Pleomorphic carcinoma accounts for 0.1–0.4% of all lung cancer cases [1]. Generally, the prognosis is worse for this type of lung cancer than for other histological types of non-small-cell lung cancer (NSCLC) because of a poor response to chemotherapy [2]. Some reports have mentioned successful chemotherapy, including chemotherapy with first-generation tyrosine kinase inhibitors (TKIs); however, effective treatments for pleomorphic carcinoma of the lung have not been established.

Epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase, and EGFR mutations have a very strong influence on chemotherapy for lung cancer. Particularly, lung cancers with EGFR mutations in exons 19 and 21 are known to show a therapeutic response to EGFR-TKIs, especially adenocarcinoma [3, 4]. Afatinib, which is a second-generation TKI, has been mentioned to be more active in uncommon EGFR mutations, especially mutations in exon 18, which are detected in approximately 3% of all EGFR mutations [5, 6].

Herein, we report the case of a patient with pleomorphic carcinoma having an exon 18 mutation (G719X) of the EGFR in all components (adenocarcinoma, squamous cell carcinoma, and spindle cell lesions), who was successfully treated with afatinib and resulted in successful resection. To our knowledge, this is the first report on the use of afatinib for pleomorphic carcinoma followed by the surgical resection.

Case Report

A 59-year-old woman who was a former smoker (25 pack-years) visited our hospital because of bloody sputum. On chest radiography, an abnormality was noted in her left lung. Her medical history included left breast cancer treated with mastectomy. The tumor markers carcinoembryonic antigen and cytokeratin 19 fragments were within normal limits, and the squamous cell carcinoma antigen level was high at 2.3 ng/mL. Chest computed tomography (CT) showed a 28 × 28-mm nodule with a cavity located in the left upper lobe and a swelling at the bilateral hilar and mediastinal lymph nodes (Fig. 1a). Bronchoscopy was performed and the histological findings of transbronchial biopsy revealed adenosquamous carcinoma positive for a G719X mutation in exon 18 of the EGFR. Since fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) revealed positive accumulation in the bilateral hilar and mediastinal lymph nodes (Fig. 2a), the disease was diagnosed as cT1bN3M0, stage IIIb. After 3 months of afatinib therapy (40 mg/day), the primary tumor decreased on CT findings (Fig. 1b), and FDG accumulation at the tumor disappeared on FDG-PET (Fig. 2b). However, the swelling of the bilateral hilar and mediastinal
lymph nodes remained on FDG-PET (Fig. 2b). There was a difference in the response in the primary tumor and the lymph nodes as regards afatinib therapy. Therefore, we considered that all of the swollen lymph nodes were not metastatic lymph nodes but included lymph nodes that had sarcoid reactions. Video-assisted thoracic surgery was planned for further diagnostic information and left upper lobectomy with mediastinal lymph node dissection was performed. The resected tumor included adenocarcinoma, squamous cell carcinoma, and spindle cell components, without any involvements of malignant cells in hilar and mediastinal lymph nodes (Fig. 3a–d). Histopathological findings of the resected lymph nodes show noncaseating epithelial cell granulomas (Fig. 3d). Thus, the disease was diagnosed as pleomorphic carcinoma (pT2aN0M0, stage IB). All components in the resected specimen had the same G719X mutation in exon 18 of the EGFR. Although postoperative adjuvant chemotherapy was not performed, the patient had no signs of recurrence at 1 year after the operation.

Discussion

We reported a case of pleomorphic carcinoma being positive for a G719X mutation in exon 18 of EGFR, which was successfully treated using afatinib followed by surgical resection.

G719X in exon 18 is an uncommon EGFR mutation. Although exon 18 mutations represent 3.6% of all EGFR mutations, most types are G719X mutations and are observed in patients with adenocarcinoma [5, 7]. To the best of our knowledge, there are no reports of patients with pleomorphic carcinoma being positive for G719X mutation. Thus, our case represents an extremely rare gene status in pleomorphic carcinoma. In addition, three different histological components in the present case had the same G719X mutation. Kaira et al. [8] reported that EGFR mutations were observed in 3 of 17 (18%) patients with pleomorphic carcinoma. All 3 patients had the pathological feature of an adenocarcinoma component; however, EGFR mutations (exon 19 mutations in 2 patients and an exon 21 mutation in 1 patient) were detected only in the adenocarcinomatous component and not in the sarcomatoid component [8]. On the contrary, Ushiki et al. [9] reported an autopsy case of pleomorphic carcinoma showing a resistance to gefitinib therapy. The tumor mass mainly occupied the spindle cell component with an exon 19 deletion and 20 T790M mutation, but a small minority of adenocarcinoma components in the mass showed exon 19 deletion. Thus, EGFR mutation status of pleomorphic carcinoma was complicated and different among the composed components and time dependence after EGFR-TKIs. In case of pleomorphic carcinoma, we should examine the EGFR mutation according to the histological components.

The clinical information about the response to EGFR-TKIs in patients with minor mutations, such as exon 18 mutations, is limited. In an experimental model, the preclinical efficacy of afatinib in cells expressing G719X in exon 18 was observed [5]. Based on the LUX-Lung 3 and 6 study, 14 among 18 positive patients with the G719X mutation showed good response to afatinib [6]. A similar clinical benefit was observed in another study [5] and it was described that the response rate of 78% (14/18) to afatinib was higher than 35% (8/23) in first-generation TKIs. In addition, Tanizaki et al. [10] mentioned that patients with NSCLC who are positive for uncommon EGFR mutations, including exon 18 mutations, might derive benefit from treatment with afatinib, but not from first- or third-generation agents. The present case was successfully treated with afatinib. To our knowledge, we believed that this is the first report on the use of afatinib for pleomorphic carcinoma with minor uncommon
mutation. Based on our clinical experience, we would like to emphasize that patients with NSCLC harboring uncommon G719X should be treated with EGFR-TKIs and afatinib might be a novel and effective agent for the uncommon mutation.

On the other hand, sarcoid reaction is thought to be caused by immunological hypersensitivity to antigens derived from tumor cell leading to granuloma formation. Such a sarcoid reaction occurs in 4.4% of carcinomas [11]. The appearance of enlarged lymph nodes on the CT or FDG-PET may be a sarcoid reaction instead of metastasis of cancer. In our case, in spite of decreasing primary tumor size, the bilateral hilar and mediastinal lymph nodes showed no change on CT and FDG-PET. The clinical course and radiographic findings changed our initial assessments and we speculated that malignant diseases did not involve the swelling lymph nodes. Indeed, resected specimen of lymph nodes showed no malignancy, only non-caseating epithelial cell granulomas. The clinical course in the present case was precious to recognize the tumor-induced sarcoid reaction and/or to make differential diagnoses in patients with malignant diseases.

In conclusion, we presented a rare case of pleomorphic carcinoma with an exon 18 mutation of the EGFR, which was successfully treated using afatinib and subsequent surgical resection.

Statement of Ethics

The authors have no ethical conflicts to declare.

Disclosure Statement

The authors have no conflicts of interest to disclose.

References

[1] Chang YL, Lee YC, Shih JY, Wu CT: Pulmonary pleomorphic (spindle) cell carcinoma: peculiar clinicopathologic manifestations different from ordinary non-small cell carcinoma. Lung Cancer 2001;34:91–97.
[2] Mochizuki T, Ishii G, Nagai K, Yoshida J, Nishimura M, Mizuno T, Yokose T, Suzuki K, Ochiai A: Pleomorphic carcinoma of the lung: clinicopathologic characteristics of 70 cases. Am J Surg Pathol 2008;32:1727–1735.
[3] Kosaka T, Yatabe Y, Endoh H, Kuwano H, Takahashi T, Mitsudomi T: Mutations of the epidermal growth factor receptor gene in lung cancer: biological and clinical implications. Cancer Res 2004;64:8919–8923.
[4] Paez JG, Janne PA, Lee JC, Tracy S, Greulich H, Gabriel S, Herman P, Kaye FJ, Lindeman N, Boggon TJ, Naoki K, Sasaki H, Fujiy Y, Eck MJ, Sellers WR, Johnson BE, Meyerson M: EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 2004;304:1497–1500.
[5] Kobayashi Y, Togashi Y, Yatabe Y, Mizuuchi H, Jiangchul P, Kondo G, Shimoi M, Sato K, Suda K, Tomizawa K, Takemoto T, Hida T, Nishio K, Mitsudomi T: EGFR exon 19 mutations in lung cancer: molecular predictors of augmented sensitivity to afatinib or neratinib as compared with first- or third-generation TKIs. Clin Cancer Res 2015;21:5305–5313.
[6] Yang JC, Sequist LV, Geater SL, Tsai CM, Mok TS, Schuler M, Yamamoto N, Yu CJ, Ou SH, Zhou C, Massey D, Zazulina V, Wu YL: Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6. Lancet Oncol 2015;16:830–838.
[7] Shi Y, Au JS, Thongprasert S, Srinivasan S, Tsai CM, Khoa MT, Heeroma K, Ituoh Y, Cornelio G, Yang PC: A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER). J Thorac Oncol 2014;9:154–162.
Kaira K, Horie Y, Ayabe E, Murakami H, Takahashi T, Tsuya A, Nakamura Y, Naito T, Endo M, Kondo H, Nakajima T, Yamamoto N: Pulmonary pleomorphic carcinoma: a clinicopathological study including EGFR mutation analysis. J Thorac Oncol 2010;5:460–465.

Ushiki A, Koizumi T, Kobayashi N, Kanda S, Yasuo M, Yamamoto H, Kubo K, Aoyagi D, Nakayama J: Genetic heterogeneity of EGFR mutation in pleomorphic carcinoma of the lung: response to gefitinib and clinical outcome. Jpn J Clin Oncol 2009;39:267–270.

Tanizaki J, Banno E, Togashi Y, Hayashi H, Sakai K, Takeda M, Kaneda H, Nishio K, Nakagawa K: Case report: durable response to afatinib in a patient with lung cancer harboring two uncommon mutations of EGFR and a KRAS mutation. Lung Cancer 2016;101:11–15.

Sehgal S, Goyal P, Ghosh S, Mittal D, Singh S: Malignancy and granulomatosis: causality or coincidence? Narrative systematic review. Iran J Pathol 2014;9:237–244.

**Fig. 1.** a Chest computed tomography shows a 28 × 28-mm nodule with a cavity located in the lingular segment of the left upper lobe. b Three months after treatment with afatinib, the tumor decreased in size.

**Fig. 2.** a Fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) revealed a positive accumulation in the bilateral hilar and mediastinal lymph nodes. b FDG accumulation at the tumor disappeared on FDG-PET. However, the swelling of the bilateral hilar and mediastinal lymph nodes remained on FDG-PET.
Fig. 3. Pathological findings. **a** Microscopic assessment of the resected tumors shows spindle cells and giant cells in an alveolar arrangement. **b** Atypical cells with an intercellular bridge are stratified in the cavity. **c** Atypical cells with luminal formation show proliferation in the nodule. **d** Microscopic assessment of the resected lymph nodes show noncaseating epithelial cell granulomas and no cancer metastasis. The pathological diagnosis is pleomorphic carcinoma consisting of adenocarcinoma and squamous cell carcinoma.