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Discrepancy between the Clinical Image and Pathological Findings of Non-Small Cell Lung Cancer Harboring an Epidermal Growth Factor Receptor Gene Mutation That Was Surgically Resected after Gefitinib Treatment

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Key Words

Gefitinib · Epidermal growth factor receptor · Non-small cell lung cancer · Pathological effect

Abstract

We herein describe a discrepancy between the clinical image and pathological findings in a non-small cell lung cancer patient with an epidermal growth factor receptor (EGFR) mutation who underwent surgical resection after gefitinib treatment. The patient was a 66-year-old female with c-stage IIIA lung adenocarcinoma harboring an EGFR gene mutation; she was surgically treated after receiving gefitinib. The pathological examination revealed adenocarcinoma, and the pathologically therapeutic effect was considered to be slight or of no response. EGFR T790M mutation and MET amplification were not present. The pathologically therapeutic effect is generally well correlated with the response rate after induction therapy. In this case, there was a discrepancy between the clinical image and pathological findings. Our findings, therefore, raise questions about the role of surgery after EGFR-tyrosine kinase inhibitor treatment.

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Introduction

The current standard of care for patients with locally advanced non-small cell lung cancer (NSCLC) is concurrent chemoradiotherapy (CRTx) or surgery with CRTx; however, the most effective treatment for patients with locally advanced (stage III) NSCLC remains controversial. When concurrent CRTx followed by surgery is performed, patients with a pathological complete response tend to show a longer overall survival than those without a pathological complete response [1, 2].

Epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) are effective against more than 70% of advanced NSCLC with EGFR gene mutations [3–5]. Some authors have reported the usefulness of surgical resection after gefitinib treatment for responding patients [6–8]. However, almost all the reported patients who underwent surgical resection after gefitinib treatment had distant metastasis.

In this report, we describe a patient in whom the pathological effect was a slight pathological response; however, she had a partial response (PR) after gefitinib treatment for NSCLC harboring an EGFR gene mutation. This finding raises questions about the role of surgery after gefitinib treatment.

Case Report

A 66-year-old female never-smoker with no significant medical history was referred to our hospital for the evaluation of an abnormal shadow observed on a chest X-ray film. Chest computed tomography (CT) revealed a 4.4-cm primary mass in the left upper lobe beside the main pulmonary artery and the growth of mediastinal lymph nodes (cT2aN2M0 stage IIIA) (fig. 1a, b). Fluorodeoxyglucose positron emission tomography (FDG-PET) showed FDG uptake in the mass with a maximal standardized uptake value (SUV) of 12.2, and in mediastinal lymph nodes with an SUV of 6.6 (fig. 1c). She was diagnosed with lung adenocarcinoma (fig. 2a) by a transbronchial lung biopsy. The L858R mutation in exon 21 of the EGFR gene was identified in the primary lung tumor. We gave the patient and her family three possible treatment options: concurrent CRTx (using standard platinum-based doublet chemotherapy), induction chemotherapy followed by surgery, or gefitinib therapy. They selected gefitinib therapy. Therefore, systemic chemotherapy with gefitinib (250 mg/body) was performed.

After 3 months of gefitinib treatment, a radiological CT evaluation revealed that there was a PR to gefitinib (regression rate was 35%) (fig. 1d, e), and a PET scan image showed positive accumulation of FDG (SUV max. 4.0) in the tumor (fig. 1f). Because of the good response, the patient wanted to undergo surgery. The gefitinib administration was stopped 2 weeks prior to surgery so that the drug would not interfere with tissue repair. We performed a left upper lobectomy and a combined resection of S6, which was involved by the tumor, and a systematic lymphadenectomy. Because the initially swollen lymph nodes had become thickened fibrous scars owing to the response to gefitinib, it was difficult to expose the superior trunk of the pulmonary artery. Finally, complete resection was achieved. The postoperative course was uneventful. The pathological examination revealed adenocarcinoma in the primary site, hilar lymph node (#12u) and mediastinal lymph node (#5), which also involved extra nodal disease. The tumor size was 37 × 32 × 30 mm, and the left S6 was considered to have higher than interlobar involvement (pT2aN2M0 stage IIIA). The pathologically therapeutic effect was considered to be slight or of no response (fig. 2b). EGFR

T790M mutation and MET amplification, which are often acquired following gefitinib treatment, were not observed [9].

Radiation therapy was performed for the mediastinal lymph nodes because of the extranodal invasion. Ten months after the operation, the patient developed recurrence in the cervical lymph nodes and multiple pulmonary metastases. Gefitinib therapy was tried again, and the effect was a PR of the lymph nodes and complete response of the pulmonary metastases. She is doing well and is still being treated with gefitinib, 16 months after surgery.

Discussion

Generally, when preoperative therapy is considered to have achieved a good response, the pathological effect is a moderate or complete pathological response. When induction therapy is performed, pathological downstaging and a pathological complete response are independent factors for a favorable overall survival [1, 2]. Some large-scale studies have been previously reported regarding preoperative EGFR-TKI in patients with early-stage NSCLC [10–13]. One such study mentioned the pathological response, but the clinical response did not clearly correlate with the pathological response in detail [13]. In addition, no large-scale studies have thus far been reported regarding the use of preoperative EGFR-TKI in patients with advanced NSCLC. There have been a few reports regarding the association between the clinical response after induction therapy and the pathological effect after surgery in advanced NSCLC. There were 12 patients who underwent surgery after gefitinib treatment for advanced NSCLC. Nine of these patients harbored EGFR gene mutations, and 4 of them had a known pathological effect. All 4 of these patients had a PR to induction therapy in the clinical images, and 3 out of the 4 had a complete pathological response, while 1 had a moderate pathological response [6–8].

In this report, there was a discrepancy between the clinical image and pathological findings in an NSCLC patient, harboring an EGFR gene mutation, who underwent surgical resection after gefitinib treatment. It is possible that the pathological effect after EGFR-TKI treatment might be overestimated. In fact, of the previously reported 4 cases, 3 were short-term outcomes, and 1 patient developed recurrence in the brain 2 years and 4 months after surgery [6–8].

In conclusion, surgery following induction therapy using EGFR-TKI should be carefully considered, even if the NSCLC harbors an EGFR gene mutation and the clinical imaging shows a complete clinical response.

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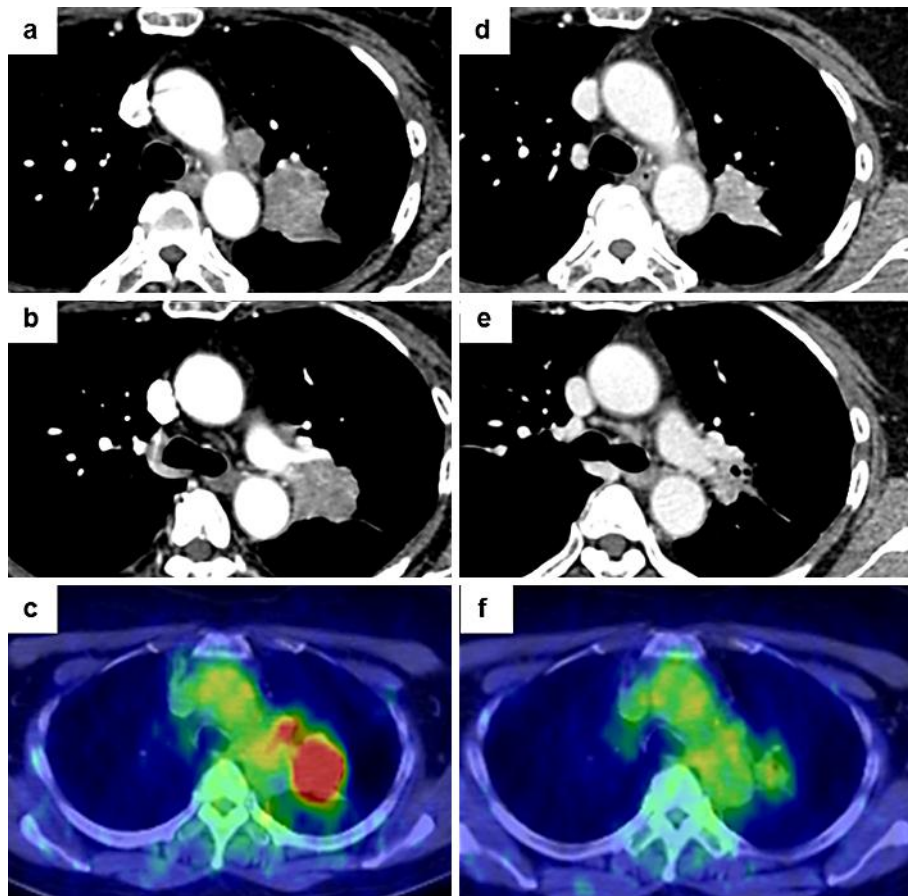


Fig. 1. Radiological evaluation by CT and PET scans. **a–c** Before treatment. **a** A mediastinal lymph node (#5) is observed. **b** A primary lesion in the left upper lobe can be seen invading the main pulmonary artery. **c** A PET scan image shows positive accumulation of FDG in the tumor. **d–f** After gefitinib treatment. **d** The mediastinal lymph node (#5) shows good regression. **e** Mild regression of the primary lesion and lymph node metastasis can be seen. **f** A PET scan image shows positive accumulation of FDG in the tumor.

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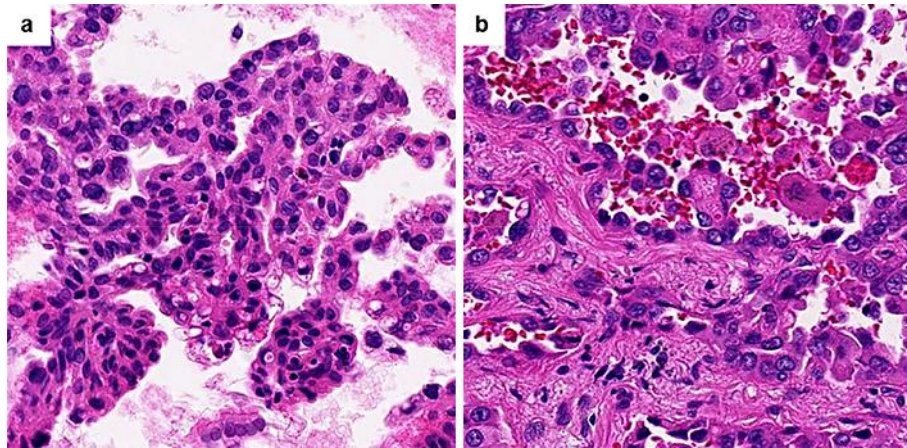


Fig. 2. The histological evaluation. **a** The histological findings of a section obtained by transbronchial lung biopsy (hematoxylin-eosin stain) reveal the proliferation of atypical cuboid-columnar epithelial cells with enlarged hyperchromatic nuclei, arranged predominantly in a papillary growth pattern. **b** The histological findings of the resected primary tumor (hematoxylin-eosin stain) show a papillary proliferation of viable adenocarcinoma cells, admixed with a small number of nonviable swollen carcinoma cells, thus suggestive of a slight therapeutic effect.