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Case Report

Rebiopsy with Thoracoscopy under Local Anesthesia for the Detection of EGFR T790M Mutation

Asako Matsuda[a] Yasuko Fuchimoto[a] Sae Wada[a] Takaaki Tanaka[a] Tetsuya Takeguchi[a] Sho Mitsumune[a] Yuki Takigawa[a] Yosuke Miyamoto[a] Shinji Ozaki[a] Norichika Iga[b] Hideyuki Nishi[b] Nobukazu Fujimoto[c]

[a]Department of Respiratory Medicine, Okayama Rosai Hospital, Okayama, Japan; [b]Department of Surgery, Okayama Rosai Hospital, Okayama, Japan; [c]Department of Medical Oncology, Okayama Rosai Hospital, Okayama, Japan

Keywords
EGFR-mutated non-small cell lung cancer · Osimertinib · Rebiopsy · T790M · Thoracoscopy

Abstract
A 70-year-old woman underwent right upper lobectomy for adenocarcinoma of the lung (pT1bN2M0 stage IIIA). Five years after the surgery, lymph node recurrence was detected. Gefitinib was administered because epidermal growth factor (EGFR) exon 19 deletion mutation was detected in the previously resected surgical specimen. After a treatment of first-generation EGFR tyrosine kinase inhibitors, an FDG-PET/CT scan demonstrated abnormal FDG uptake in the pleura indicating pleural dissemination. Pleurocentesis revealed tumor cells in the pleural fluid; however, EGFR mutation testing failed due to inadequate tumor cellularity. Thoracoscopy under local anesthesia revealed multiple nodules on the parietal pleura. A biopsy specimen confirmed the diagnosis of lung adenocarcinoma with pleural dissemination and revealed EGFR exon 20-T790M mutation.

Dr. Nobukazu Fujimoto
Department of Medical Oncology, Okayama Rosai Hospital
1-10-25 Chikkomidorimachi,
Minamiku, Okayama 7028055 (Japan)
E-Mail nobufujimot@gmail.com

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Introduction

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) improved the survival of patients with EGFR-mutated non-small cell lung cancer [1–3]. However, most of the patients developed resistance to EGFR-TKIs during treatment. EGFR exon 20-T790M (T790M) mutation develops as one of the mechanisms of acquired resistance in about 50% of patients treated with first-generation EGFR-TKIs [4, 5].

Case Report

A 70-year-old woman underwent right upper lobectomy for adenocarcinoma of the lung (pT1bN2M0 stage IIIA) followed by adjuvant chemotherapy with paclitaxel and carboplatin. Five years after the surgery, lymph node recurrence was detected in the mediastinum (#4R) by fluorodeoxyglucose-positron emission tomography (FDG-PET)/computed tomography (CT). Gefitinib was administered because EGFR exon 19 deletion mutation was detected in the previously resected surgical specimen. Although the lymph node shrank, the patient was switched from gefitinib to afatinib 7 months later because of hepatotoxicity. After 9 months of administration, afatinib was discontinued due to anorexia and skin rush. After another 8 months, multiple brain metastases developed and afatinib was reinstituted. After 8 months of afatinib administration, an FDG-PET/CT scan demonstrated abnormal FDG uptake in the pleura indicating pleural dissemination (Fig. 1a). Pleurocentesis revealed tumor cells in the pleural fluid; however, EGFR mutation testing failed due to inadequate tumor cellularity. Therefore, the patient underwent thoracoscopy under local anesthesia (TULA), which revealed multiple nodules on the parietal pleura (Fig. 1b). A drainage tube was placed into the pleural space via a port site and the tube was removed after pleurodesis with talc. Postoperative bleeding or pneumothorax was not observed.

A biopsy specimen confirmed the diagnosis of lung adenocarcinoma with pleural dissemination and revealed T790M mutation. Osimertinib treatment was started 2 weeks after TULA. Right pleural effusion was decreased, and serum carcinoembryonic antigen levels significantly declined (2,773.5 to 622.6 ng/mL) after 2 months of treatment.

Discussion

The third-generation EGFR-TKI, osimertinib, is recommended for patients who develop T790M mutation [6]. EGFR testing of the resistant tumor to detect T790M mutation is essential for the administration of osimertinib. Kawamura et al. [7] reported the procedures of obtaining tumor tissues for EGFR testing. They reported that among the 75 cases, procedures included 30 thoracocenteses, 24 transbronchial biopsies, 13 CT-guided needle biopsies, and 8 other procedures. None of the patients underwent TULA. Ichihara et al. [8] also reported 55 rebiopsy cases and TULA was also not performed for any patient. To the best of our knowledge, this is the first report of T790M mutation detection by TULA.

It is often difficult to obtain enough tumor tissues for T790M mutation testing because of the peripheral location or small size of the tumor. In the current case, pleurocentesis was first performed to obtain tumor samples in the pleural fluid. However, T790M mutation testing failed because of inadequate tumor cellularity. There was no target region with a large enough size to perform transbronchial or percutaneous needle biopsy, so we selected TULA as the procedure for rebiopsy. TULA has been established as a safe and effective diagnostic procedure for pleural diseases or pleural effusion of unknown etiology [9, 10]. The advantage of this

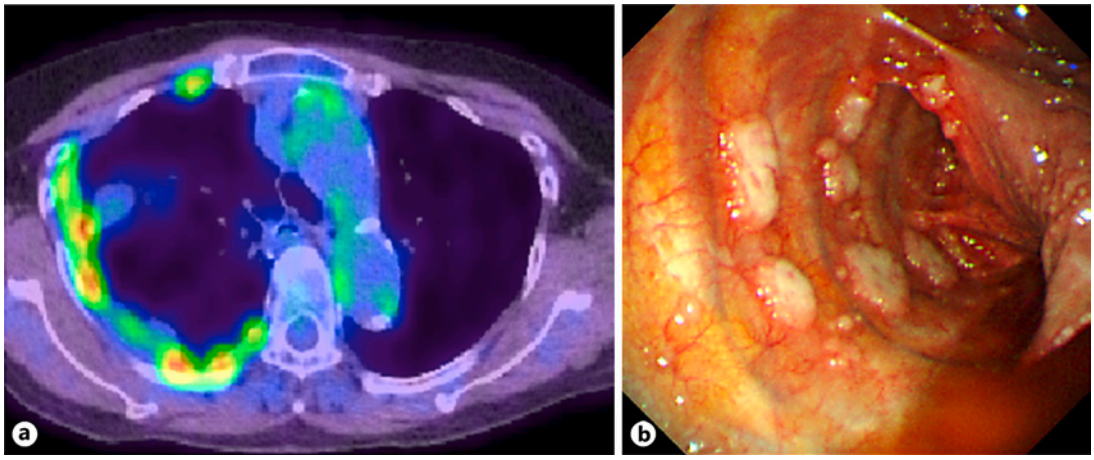

Fig. 1. PET/CT image demonstrating the abnormal uptake of FDG on the right side of the pleura (**a**), and thoracoscopic exploration revealing multiple elevated lesions on the parietal pleura (**b**).

method is the ability to directly visualize the biopsy target. In addition, chest tube placement via a port site can be used for both drainage of the effusion and for pleurodesis. In the current case, pleurodesis was performed with talc through the chest tube after rebiopsy and drainage of the effusion. All of these procedures were completed without complication.

Liquid biopsy attracts a lot of attention as a minimally invasive method for T790M mutation testing, and many findings have been obtained in this field. Currently, liquid biopsy is only recommended by Japanese Lung Cancer Society guidelines in cases for which rebiopsy has failed or is unavailable. In fact, there is a 30% false-negative rate for T790M detection by liquid biopsy [11]. Tumor biopsy and repeated T790M testing should be considered to confirm the presence or absence of T790M mutation using transbronchial biopsy, pericutaneous needle biopsy, or TULA, particularly in cases with pleural effusion and/or pleural dissemination.

Further development of genetic testing for the personalization of chemotherapy will increase the importance of obtaining enough tumor samples. For this purpose, it is extremely important to select the appropriate biopsy target and procedure. TULA may be a useful option as one of the procedures.

Statement of Ethics

The patient gave written informed consent to publish the case.

Disclosure Statement

The authors have no conflicting interests to declare.

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Author Contributions

A. Matsuda designed the study and drafted the article. Y. Fuchimoto, S. Wada, N. Iga, and H. Nishi provided clinical samples and provided scientific advice. Y. Takigawa, S. Mitsumune, T. Tanaka, T. Takeguchi, Y. Miyamoto, and S. Ozaki provided scientific advice. N. Fujimoto supervised the entire project and completed the article.

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