Case Report

A case of different *EGFR* mutations in surgically resected synchronous triple lung cancer

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Abstract: We describe a 77-year-old Japanese woman who presented with three nodule shadows in three different lobes of the right lung, without evidence of lymph node metastasis or distant metastasis. All three tumors were surgically resected. The pathological diagnosis was synchronous multiple primary lung cancer: pT2aN0M0, pStageIB. Based on a differing epidermal growth factor receptor (EGFR) mutation status, no lymph node metastasis, and no distant metastasis, the tumors were characterized as synchronous triple primary rather than intrapulmonary metastases. At eight months after surgery, a new lesion emerged in the right lower lobe. Given that the most advanced tumor had an EGFR del-19 mutation, the patient was orally administered afatinib. Since then, the treatment response of the patient has been assessed as stable disease (SD) for about two years. This is a very rare case of resected triple synchronous primary lung cancer on the same lung side in which the lesions all had a different *EGFR* mutation status, and this report highlights the clinical utility of surgical resection of multifocal lung nodules without lymph node metastasis or distant metastasis in order to optimize therapy for patients with known driver mutations.

Keywords: Triple lung cancer; epidermal growth factor receptor (EGFR); surgery

Submitted Oct 24, 2017. Accepted for publication Mar 07, 2018.
doi: 10.21037/jtd.2018.03.105
View this article at: http://dx.doi.org/10.21037/jtd.2018.03.105

Introduction

With recent advances in diagnostic imaging modalities and the widespread use of chest computed tomography (CT), the frequency of multiple synchronous primary lung cancer including cases with pure ground-glass opacity (GGO) lesions or mixed ground-glass nodules (GGNs) has been increasing (1). It is important to know the driver mutation of each lesion in order to establish an accurate pathologic stage and subsequent treatment strategy.

We herein report the case of a patient with triple synchronous primary lung cancer, all of which were resectable. The analysis of the *EGFR* mutation was useful for developing a treatment strategy when a recurrent lesion emerged.

Case presentation

A 77-year-old female who was a never smoker presented with a mass in the right lower field on chest X-ray. Chest CT showed a mass in the right upper lobe and two ground-glass opacities of 15 and 7 mm in the lower lobe and middle lobe, respectively (*Figure 1A,B,C*). A transbronchial lung biopsy was performed for the mass in the upper lobe, and adenocarcinoma was diagnosed. Positron emission tomography (PET) showed the significant uptake of this mass, with a standardized uptake value (SUV) of 6.07, no uptake of SUV by the other two ground-glass opacities, and no confirmation of distant metastasis. According to the new clinical criteria of the International Association for the Study of Lung Cancer (IASLC) Lung Cancer Staging

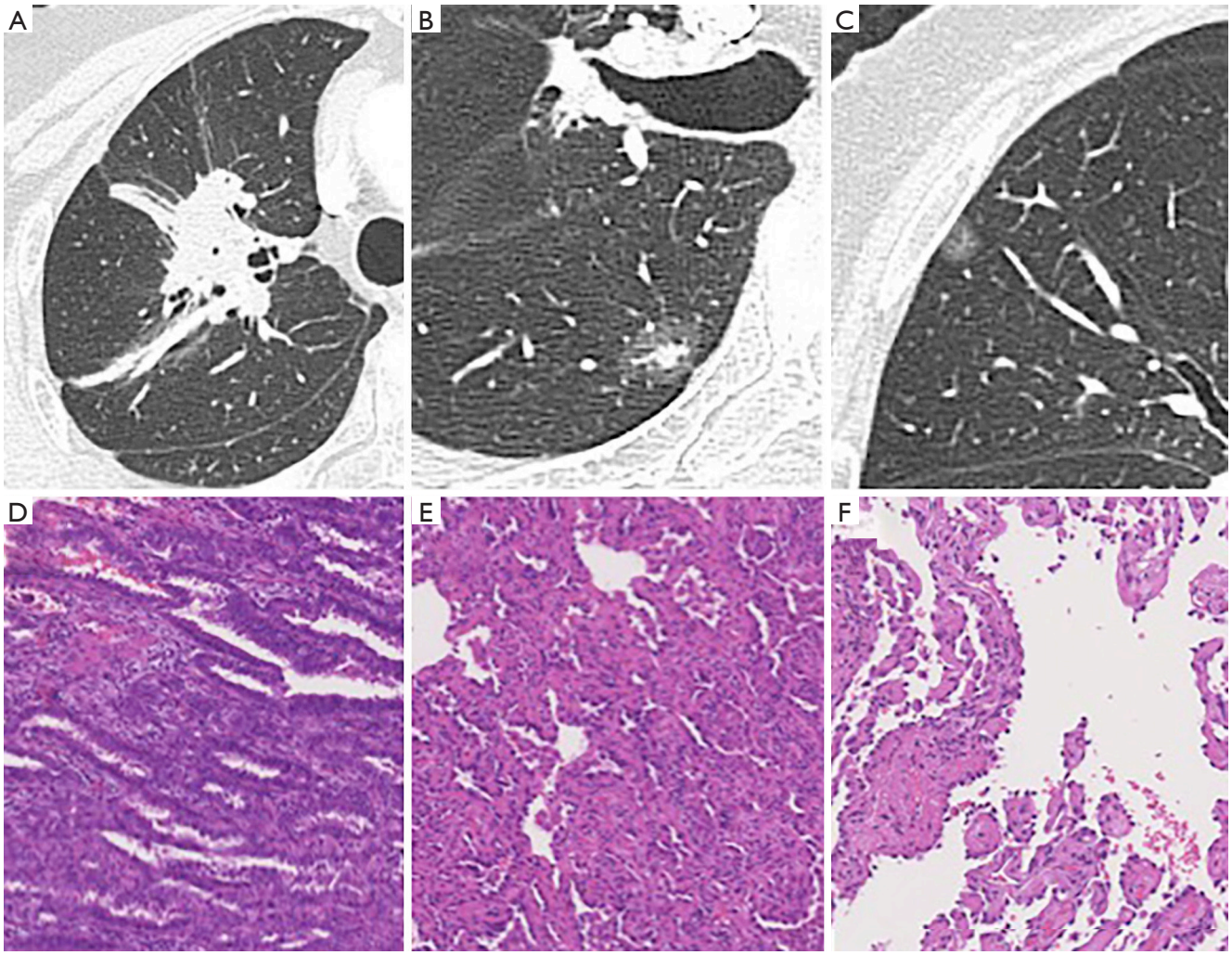

Figure 1 Chest computed tomography (CT) showed separate lesions at the right upper lobe (A), at the lower lobe (S6) (B), and at the middle lobe (C); (D) histology of the right upper lobe tumor (Hematoxylin and eosin; ×200) [Inset, *epidermal growth factor receptor* (*EGFR*) exon 19 deletion]; (E) histology of the right lower lobe tumor (Hematoxylin and eosin; ×200); (F) histology of the right upper lobe tumor (Hematoxylin and eosin; ×200) (Inset, EGFR L858R mutation).

Project (2), the clinical diagnosis was synchronous triple primary lung cancer (pT2aN0M0, pStageIB) because the radiographic appearance and metabolic uptake of the lesions differed and no nodal or systemic metastases were found.

Upper-lobe lobectomy with homolateral mediastinal-hilar lymphadenectomy (ND2a-2), wedge resection of S4, and segmentectomy of S6 were performed. The three lesions were tested for the presence of *EGFR* mutations. Pyrosequencing revealed an *EGFR* exon 19 (E746A750) deletion in the right upper lesion, whereas the lower nodule had an *EGFR* exon 21 (L858R) mutation; the middle nodule was *EGFR* wild-type. We also conducted a genetic analysis of rearrangement of anaplastic lymphoma kinase (*ALK*), ROS1 proto-oncogene receptor tyrosine kinase (*ROS1*), Kirsten rat sarcoma viral homolog gene (*K-RAS*), and rearranged during transfection (*RET*) in the three lesions, and all of the results were negative (*Table 1*). The pathological subtype of each lesion was papillary adenocarcinoma in the right upper lesion, whereas the lower nodule was acinar adenocarcinoma; the middle nodule was adenocarcinoma *in situ*. The pathological diagnosis was also synchronous triple primary lung cancer (pT2aN0M0, pStageIB; *Figure 1D,E,F*) because of the differing *EGFR* mutation status and histological subtype and the absence of nodal or systemic

Table 1 The results of a genetic analysis and subtypes of each of the three lesions

Gene type	RUL	RLL	RML
EGFR	Ex.19 del	Wild type	L858R
K-ras	Wild type	Wild type	Wild type
ALK	Negative	Negative	Negative
RET	Negative	Negative	Negative
ROS1	Negative	Negative	Negative
Subtype	Papillary adenocarcinoma	Acinar adenocarcinoma	Adenocarcinoma *in situ*

RUL, right upper lobe; RUM, right middle lobe; RLL, right lower lobe; *EGFR*, epidermal growth factor receptor; *K-ras*, Kirsten rat sarcoma viral homolog gene; *ALK*, rearrangement of anaplastic lymphoma kinase; *RET*, rearranged during transfection; *ROS1*, ROS1 proto-oncogene receptor tyrosine kinase.

metastases. Considering the patient's age, radiological follow-up was planned without adjuvant therapy.

Eight months later, a new nodule appeared in the right lower lobe. It was difficult to make a pathological diagnosis because of its anatomical position; however, it was considered to be recurrence of the right upper lobe cancer because that lesion had been the most advanced of the three, and the new lesion showed a similar radiographic appearance. The patient was orally administered afatinib at 30 mg/day because of an *EGFR* mutation with exon 19 (E746A750) deletion. Based on the Response Evaluation Criteria in Solid Tumors (RECIST), the treatment response of the patient was assessed as stable disease (SD) for about two years with good tolerance.

Discussion

The present report describes a case of triple synchronous primary lung cancer in which all of the lesions were resectable and each showed a different status of *EGFR* mutation. Some studies have reported cases of multiple synchronous lung cancer possessing different driver mutations in each lesion (3-5). However, most of those cases were double primary cancer, and resected triple synchronous primary lung cancer with different *EGFR* mutations is rare (just 1 case in 59; 1.7%). To our knowledge, there has only been one other case report describing different *EGFR* mutations in surgical resected synchronous triple lung cancer (6). Thus, this is the second case report of resected triple synchronous primary lung cancer in which the lesions all had a different *EGFR* mutation status. Furthermore, this is the first case in which all lesions were on the same side. Of note, the analysis of the *EGFR* mutation was useful for establishing a treatment strategy when a recurrent lesion emerged.

The Martini and Melamed criteria have long been used to diagnose multifocal lung cancer clinically (7). Although the criteria are based on tumor locations and histological findings, in clinical practice, some cases, such as those with multifocal GGNs, do not meet the criteria. In recent years, great advances have been made in distinguishing multifocal lung cancer using gene profile analyses, such as comparative genomic hybridization or next-generation sequencing (8,9); however, there is no gold-standard method, and the available methods are too complex to feasibly integrate into routine clinical practice. We therefore adhered to the clinical and pathological criteria of the IASLC Lung Cancer Staging Project (2). In the present case, each lesion had a different radiographic appearance, different pathological subtype, and different *EGFR* mutation status. Based on these findings, this case was diagnosed as multiple primary lung cancer under the criteria of the IASLC Lung Cancer Staging Project.

The *EGFR* mutation status were useful not only for distinguishing the multifocal lesions but also for deciding on the therapy to use for post-operative recurrence. The treatment strategy for postoperative recurrence in our case was determined based on the *EGFR* exon 19 (E746A750) deletion noted in the most advanced of the three primary lesions. The patient was therefore orally administered afatinib, a second-generation EGFR-TKI (tyrosine kinase inhibitor) approved for the treatment of lung adenocarcinoma with *EGFR* mutations. LUX-LUNG 3 and LUX-LUNG 6 studies revealed an overall survival benefit for afatinib compared with chemotherapy in patients with *EGFR* del-19 mutations (10-12). Since then, the treatment response of the patient has been assessed as SD for about two years.

Suda *et al.* reported that the expression of *EGFR* mutant protein and *EGFR* gene copy number do not change as a consequence of tumor progression, based on biopsy specimens from metastases as a surrogate for primary tumor (13). However, as described above, the heterogeneity in the *EGFR* mutation status is increased in patients with multiple primary lung cancer (3-5). Chen *et al.* reported that the *EGFR* mutation discordance rates in paired multiple pulmonary nodules was 24.4% (5). Current practice guidelines suggest a biopsy only be taken of one lesion for the histological diagnosis and molecular analysis; however, our findings suggest that complete resection of all lesions may be the better option in cases of synchronous multifocal lung cancer, not only for achieving a cure but also for optimizing therapy for patients with known activating *EGFR* mutations. If complete resection of all lesions is impossible, especially in cases of pulmonary metastasis, surgical resection or a biopsy of only the most advanced of the lesions in patients with multifocal lung cancer may prove useful for deciding on the treatment strategy.

Conclusions

We herein report the case of a patient with triple synchronous primary lung cancer wherein all of the lesions were resectable and each had a different mutation of *EGFR*. For cases with a low possibility of intrapulmonary metastasis clinically, surgical resection may be a useful therapy, and a genetic marker analysis may help accurately determine the pathologic stage and subsequent treatment strategy.

Acknowledgements

We thank Brian T. Quinn for his critical comments on the manuscript.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Informed Consent: Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

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Cite this article as: Haratake N, Takenoyama M, Edagawa M, Shimamatsu S, Toyozawa R, Nosaki K, Hirai F, Yamaguchi M, Taguchi K, Seto T, Ichinose Y. A case of different *EGFR* mutations in surgically resected synchronous triple lung cancer. J Thorac Dis 2018;10(4):E255-E259. doi: 10.21037/jtd.2018.03.105