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BRIEF REPORT

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Effectiveness of alectinib and osimertinib in a brain metastasized lung adenocarcinoma patient with concurrent *EGFR* mutations and *DCTN1-ALK* fusion

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Abstract

The echinoderm microtubule associated protein-like 4 gene (*EML4*) encodes the predominant anaplastic lymphoma kinase (*ALK*) fusion partner in non-small-cell lung cancer (NSCLC); however, the dynactin subunit 1 (*DCTN1*)-*ALK* rearrangement is extremely rare. The co-occurrence of primary epidermal growth factor receptor (EGFR) T790M mutation with *EGFR* exon 19 deletion (del) in patients with NSCLC is uncommon. Here we report a female lung adenocarcinoma patient with brain metastases and possible coexistence of primary EGFR T790M mutation/*EGFR* exon 19 del/*DCTN1-ALK* translocation. The patient received multiline treatment including chemotherapy, antivascular, and targeted therapies. To overcome developed resistance to chemotherapy or targeted therapy to prolong overall survival, the patient's circulating tumor DNA (ctDNA) was dynamically monitored. The patient responded to successive osimertinib and alectinib treatment, and alectinib achieved a nearly complete response for lung and brain lesions after she acquired osimertinib resistance. Furthermore, we summarize 22 published cases of patients with lung adenocarcinoma with concurrent *EGFR* mutation and *ALK* rearrangement, including details of clinical characteristics, natural history, and pertinent therapy of this uncommon tumor subtype. This literature review shows that EGFR inhibition was an indispensable aspect of the treatment of patients with *EGFR/ALK* co-alterations in the pre-alectinib era and that ALK inhibition with crizotinib did not show more eye-catching therapeutic results. Considering the effectiveness achieved by alectinib, this case study provides a new perspective for the treatment of lung cancer brain metastasis patients with concurrent *EGFR/ALK* mutations.

KEYWORDS
brain metastasis, DCTN1-ALK rearrangement, EGFR T790M mutation, next-generation sequencing, NSCLC

Qiang Yin, Taiyan Guo, Yangyang Zhou contributed equally to this study.

INTRODUCTION

Most epidermal growth factor-receptor (EGFR)-positive patients with non-small-cell lung cancer (NSCLC) will acquire resistance within 1 year after initial EGFR-tyrosine kinase inhibitor (TKI) treatment. Multiple mechanisms are involved in acquired resistance to EGFR-TKIs, including emergence of an EGFR T790M mutation, mutations in *KRAS*, *BRAF* or *PIK3CA*, *MET* amplification, and histological transformation.[1–3] Furthermore, primary resistance to EGFR-TKIs occurs in approximately 5–10% of the Asian population.[4] Anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (ALK-TKIs) are recommended for treating NSCLCs with sensitizing mutations. Here we report a female patient with lung adenocarcinoma harboring an *EGFR* exon 19 deletion (del), a primary EGFR T790M mutation, and a rare *ALK* fusion who achieved a good response to multiline treatment including osimertinib and alectinib. Moreover, we performed a literature review of the rare *DCTN1-ALK* cases and current treatment strategies for patients with the co-alteration of *EGFR* mutation and *ALK* translocation.

CASE PRESENTATION

The patient was a 60-year-old female nonsmoker who presented with a cough and blood-tinged sputum. Chest computed tomography (CT) revealed a space-occupying lesion in the right upper lobe (Figure 1a, 2016 April). A percutaneous lung biopsy performed on the right lung indicated a pathological diagnosis of T3N2M1a (IVA) lung adenocarcinoma, accompanied by multiple metastases in the right pleura, right hilum, and mediastinal lymph node. *EGFR* mutations (exons 18–21) and *EML4-ALK* were undetectable by direct sequencing in 2016. Chemotherapy comprising six cycles of pemetrexed and carboplatin was administered as first-line treatment. The patient experienced stable disease (SD) 8 months later. However, disease progressed after 14 months of chemotherapy. The patient then received docetaxel and carboplatin as second-line treatment. Unfortunately, after 9 months of chemotherapy, tumor progression slowly developed and she presented with hemoptysis as well as brain metastases (Figure 1a, 2018 March). The patient was then switched to antivascular endothelial growth factor receptor 2 (VEGFR2) therapy with apatinib. As we expected, apatinib effectively reduced peritumor edema in the brain 3 months later. However, she discontinued apatinib treatment because of severe adverse reactions. Two months after apatinib was withdrawn, the follow-up images showed that although the primary lung tumor was slightly reduced, new intrapulmonary metastases were present and the intracranial tumor exhibited a significant enhancement ring detected using MRI (Figure 1a, 2018 August).

To seek potential therapeutic regimens, next-generation sequence (NGS) analysis of the patient's circulating tumor (ct)DNA was performed. This analysis revealed an *EGFR* exon 19 deletion (level, plasma 0.6%) and a primary *EGFR* T790M mutation (level, plasma 0.1%). The patient then started oral osimertinib and after 8 weeks an SD period was observed for the brain tumor. Imaging scans performed after 6 months showed a partial response (PR) of the lung mass and intracranial tumors (Figure 1a, 2019 February).

After progression-free survival (PFS) for approximately 11 months, although the intracranial tumor continued to exhibit a PR state, the lung lesions progressed, and pleural fluid seemed to accumulate during the 16th month of osimertinib treatment. Four months later, she began to suffer from breath-holding, headaches, dizziness, and speech

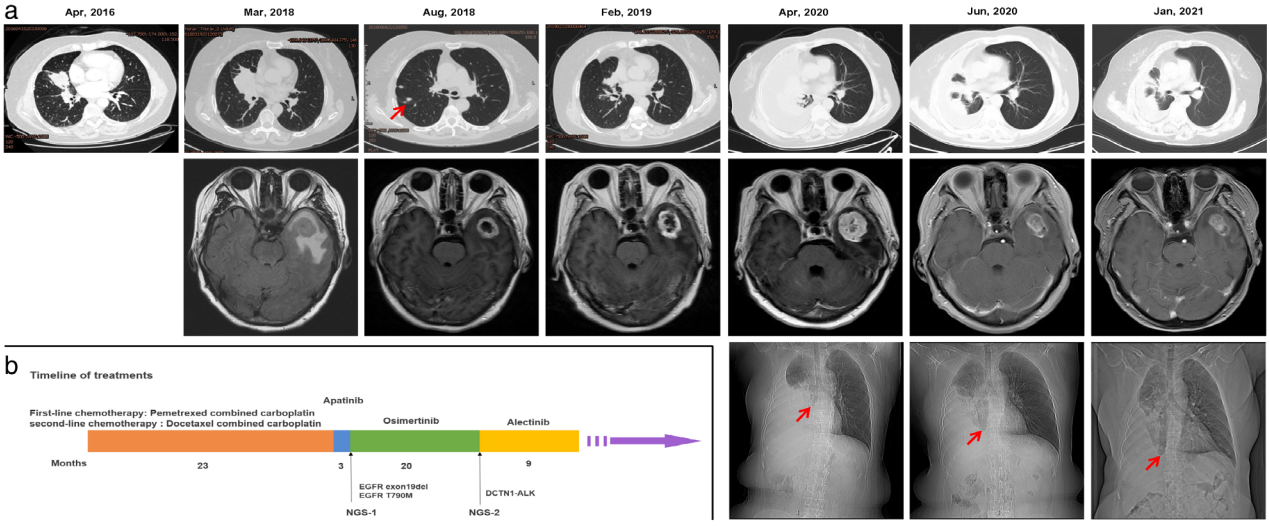

FIGURE 1 The patient's treatment history and chronological imaging follow-up results. (a) Chest CT, brain MRI, and chest X-ray images of the patient before and after treatment. The red arrow in the chest CT of August 2018 indicates new metastases in the lung; the red arrows in the chest x-rays of April 2020, June 2020, and January 2021 indicate the pleural fluid line. (b) Timeline of multiline treatment and summary of the duration of each treatment

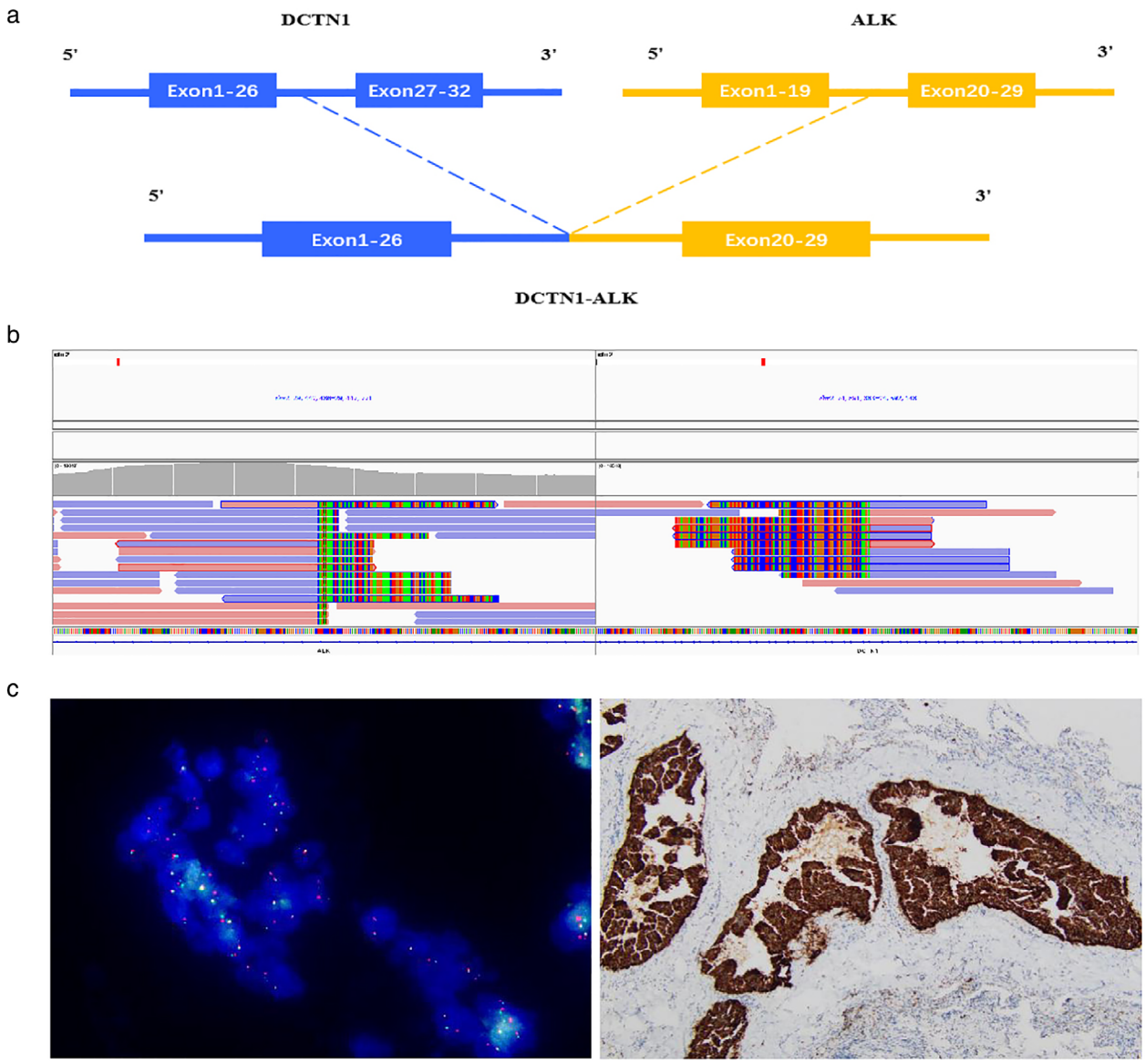

FIGURE 2 Detection of dynactin subunit 1 (DCTN1) and the anaplastic lymphoma kinase fusion (DCTN1-ALK). (a) Detailed fusion site of DCTN1-ALK. (b) NGS results showed a breakpoint of fusion. (c) The DCTN1-ALK fusion was further confirmed by FISH and immunohistochemistry of the primary lung tumor tissue. (Left) A split signal was observed in 68% of cells. (Right) Immunohistochemistry indicated strong ALK expression

problems. Chest CT, chest x-ray, and brain MRI indicated that the patient's disease progressed to a life-threatening state, particularly with severe cerebral edema and midline displacement (Figure 1a, 2020 April). A repeat liquid biopsy was then performed. NGS analysis of ctDNA revealed a rare *ALK* oncogenic fusion involving *DCTN1* exon 26 and *ALK* exon 20 (level, plasma 0.23%), and no detectable T790M mutation.

The patient was therefore treated with alectinib, and her symptoms significantly improved after 1 month with almost no noticeable side effects. Follow-up images in June 2020 showed marked pulmonary improvement, resolution of pleural effusion, dramatically decreased brain tumor volume, and significant amelioration of cerebral edema, as well as relief from midline displacement (Figure 1a, 2020 June). The patient was evaluated with a PR, nearly complete response (CR), as revealed by chest CT, chest x-ray, and brain MRI 6 months later (Figure 1a, 2021 January). The timeline of the overall treatment process is summarized in Figure 1b. Detection of the *DCTN1-ALK* fusion, including detailed breakpoint identification of the 2020 ctDNA NGS analysis and fluorescence in situ hybridization (FISH) plus immunohistochemistry (IHC) result of the 2016 primary lung tumor tissue, is illustrated in Figure 2. Long-term follow-up of this patient and the evaluation of the efficacy of alectinib will be continued, and we will pay close attention to whether she develops alectinib resistance in the future.

TABLE 1 Clinical treatment outcomes of NSCLC with concurrent *EGFR* mutation and *ALK* rearrangement

Case/reference	Age/ sex	Histology	*EGFR* and *ALK* alterations	Targeted agents (treatment lines)	*EGFR* TIKs treatment PFS (months)	*EGFR* TIKs treatment AEs	*ALK* TIKs treatment PFS (months)	*ALK* TIKs treatment AEs	Total PFS (months)
1/Tanaka et al.[13]	39/M	Ad	*EGFR* L858R/ *EML4-ALK*	Erlotinib (first)	1	NA	NA	NA	1
2/Xu et al.[14]	71/F	Ad	*EGFR* exon19del/ *EML4-ALK*	Gefitinib (first)	8	NA	NA	NA	8
3/Yang et al.[16]	44/F	Ad	*EGFR* exon19del/ *EML4-ALK*	Gefitinib (first)	9	NA	NA	NA	9
4/Yang et al.[16]	56/F	Ad	*EGFR* L858R/ *EML4-ALK*	Gefitinib (first)	11.2	NA	NA	NA	11.2
5/Yang et al.[16]	59/M	Ad	*EGFR* L858R/ *EML4-ALK*	Erlotinib (first)	13	NA	NA	NA	13
6/Yang et al.[16]	70/M	Ad	*EGFR* L858R/ *EML4-ALK*	Erlotinib (first)	27.4	NA	NA	NA	27.4
7/Yang et al.[16]	40/M	Ad	*EGFR* exon19del/ *EML4-ALK*	Erlotinib (first)	17.5	NA	NA	NA	17.5
8/Yang et al.[16]	60/F	Ad	*EGFR* exon19del/ *EML4-ALK*	Afatinib (first)	7	NA	NA	NA	7
9/Yang et al.[16]	66/F	Ad	*EGFR* L858R/ *EML4-ALK*	Gefitinib (first)	24.5	NA	NA	NA	24.5
10/Kuo et al.[18]	72/F	Ad	*EGFR* exon19del/ *EML4-ALK*	Gefitinib (first)	7	NA	NA	NA	7
11/Shin et al.[19]	77/F	Ad	*EGFR* L858R/ *EML4-ALK*	Osimertinib (first)	5.1	NA	NA	NA	5.1
12/Popat et al.[23]	65/F	Ad	*EGFR* exon19del/ *EML4-ALK*	Erlotinib (first)	25	NA	NA	NA	25
13/Santelmo et al.[24]	52/F	Ad	*EGFR* exon19del/ *EML4-ALK*	Gefitinib (first)	7	NA	NA	NA	7
14/Yang et al.[16]	54/F	Ad	*EGFR* exon19del/ *EML4-ALK*	Erlotinib (first) Crizotinib (second)	12	NA	2.7	NA	14.7
15/Yang et al.[16]	45/F	Ad	*EGFR* exon19del/ *EML4-ALK*	ND (first) Crizotinib (second)	NA	NA	15.1	NA	15.1
16/Baldi et al.[17]	68/M	Ad	*EGFR* L858R/ *EML4-ALK*	Erlotinib (second) Crizotinib (third)	7	skin toxicity	11	Visual toxicity	18
17/Chen et al.[22]	56/M	Ad	*EGFR* exon19del/ *EML4-ALK*	Erlotinib (second) Crizotinib (third)	8	rash	∼1.5		∼9.5
18/Shin et al.[19]	57/F	Ad	*EGFR* L858R/ *EML4-ALK*	Gefitinib (first) Crizotinib (second) Osimertinib (third)	7.7; 9.5	NA	0.75	NA	17.95
19/Shin et al.[19]	32/M	Ad	*EGFR* L858R/ *EML4-ALK*	Osimertinib (first) Crizotinib (second)	0.75	chest pain; fever	1	NA	1.75

(Continues)

TABLE 1 (Continued)

Case/reference	Age/sex	Histology	*EGFR* and *ALK* alterations	Targeted agents (treatment lines)	*EGFR* TIKs treatment PFS (months)	*EGFR* TIKs treatment AEs	*ALK* TIKs treatment PFS (months)	*ALK* TIKs treatment AEs	Total PFS (months)
20/Lee et al.[20]	73/M	Ad	*EGFR* exon19del/*EML4-ALK*	Gefitinib (first) Crizotinib (second) Osimertinib (third)	0.5	NA	9	NA	9.5
21/Liu et al.[21]	NA/NA	NA	*EGFR* exon19del/T790M/*CEBPZ-ALK*	Erlotinib (first) Osimertinib (second) Crizotinib (third)	NA	NA	NA	NA	13.2
22/Liu et al.[21]	NA/NA	NA	*EGFR* exon19del/*EML4-ALK*	Erlotinib (first) Osimertinib (second) Osimertinib +Crizotinib (third)	NA	NA	NA	NA	18.6

Abbreviations: Ad, adenocarcinoma; NA, not available; ND, not done; PFS, progression-free survival.

DISCUSSION

The EGFR T790M mutation, which is one of the common mechanisms of acquired resistance to EGFR inhibitors, is detected in 50–60% of EGFR-TKI therapy-resistant cases.[5,6] Recently, primary EGFR T790M mutation was identified by routine molecular testing in a minor subgroup of TKI-naive NSCLC patients.[7,8] Generally, there are differences in clinical and molecular characteristics between primary and acquired T790M mutations.[9] However, studies are inconsistent because of their different sample sizes. The primary EGFR T790M mutation always coexists with L858R, whereas the acquired T790M is more likely to coexist with EGFR exon 19 del.[9] Both primary and acquired EGFR T790M mutations respond well to osimertinib. Patients with an acquired T790M mutation experience longer overall survival during the entire course of clinical treatment. However, patients with a primary T790M mutation may experience greater benefits from osimertinib.[10]

Previous studies showed that ALK rearrangements and EGFR mutations were mutually exclusive.[11,12] Nevertheless, some recent studies have shown that *EGFR* mutations may coexist with *ALK* fusions in patients with lung adenocarcinoma.[13–17] With the popularization and advancement of NGS technology, there will be more and more reports about EGFR/ALK co-mutations.

For therapy of patients with concurrent acquisition of *EGFR* mutations and *ALK* rearrangements, Kuo et al. described a favorable response to gefitinib of a patient with lung adenocarcinoma with *EML4-ALK/EGFR* co-alterations.[18,19] However, Lee et al. reported the opposite, in which the patient did not respond to EGFR-TKI treatment but responded to crizotinib.[20] Another study suggested that dual-TKI treatment (EGFR-TKI plus ALK-TKI) may be more effective than single TKI (EGFR-TKI or ALK-TKI) for *EML4-ALK/EGFR* co-altered patients.[21]

We reviewed 22 NSCLC cases with the *EGFR* and *EML4-ALK* mutations and the clinical outcomes of EGFR TKIs and ALK TKIs (Table 1).[13,14,16–19,21–24] Although the total PFS achieved using dual-TKI/triple-TKI treatment seemed longer than single-TKI treatment for these co-altered patients, the difference was not statistically significant ($p = 0.85$). Yang et al. reported that the diverse response to EGFR-TKIs, ALK-TKIs, or both, may be associated with diverse phospho-ALK and phospho-EGFR levels.[16] Unfortunately, the ALK inhibitor used in the 22 EGFR/ALK co-altered cases was crizotinib, not alectinib, partially explained by later marketing approval and application of alectinib.

In our case, possibly due to the limitation of the relatively low sequencing depth achieved by the local molecular testing center (in 2018), *ALK* fusion was not discovered along with EGFR mutation. Thus, the patient was not administered dual-TKI treatment. Whether dual-TKI therapy is the best strategy for these co-altered patients, or if alectinib is better administered before an EGFR inhibitor, remains to be determined. Furthermore, long-term follow-up of this patient is in

progress, and we will pay close attention to whether alectinib resistance develops.

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CONFLICT OF INTEREST

The authors declare that there are no potential conflicts of interest.

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