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Case Report

Coexistence of A Secondary STRN-ALK EML4-ALK Double-Fusion Variant in A Lung Adenocarcinoma Patient with EGFR Mutation: A Case Report

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Abstract

Anaplastic lymphoma kinase (ALK)-positive disease is characterized by the presence of ALK gene rearrangements that encode driver fusion oncoproteins. Echinoderm microtubule-associated protein-like 4 gene (EML4)-ALK fusion is regarded as the most common type and is reported in 2 to 7% of patients with advanced non–small cell lung cancers (NSCLCs). Striatin (STRN)-ALK is a novel ALK fusion partner in NSCLC and is considered sensitive to targeted therapy. However, there was no study regarding effective therapy for EML4-ALK and STRN-ALK double fusion variants in epidermal growth factor receptor (EGFR)-resistant mutant lung cancer. TP53, RB1, and EGFR exon 21 L858R were found in tumor tissues and plasma from patients with capture-based next-generation sequencing (NGS). After three months of gefitinib treatment, an NGS of plasma circulating tumor DNA (CTDNA) showed that all variants disappeared significantly, and the tumor mass regressed on computed tomography (CT). However, after 10 months, the patient developed drug resistance and the disease progressed with the appearance of new metastatic lesions in the liver and bones. A repeated NGS test revealed EGFR exon20 T790M and the appearance of a novel double-fusion EML4-ALK and STRN-ALK. A combined therapeutic regimen of crizotinib plus osimertinib showed a promising prognosis confirmed with lung CT scans showing stable lesion without any new metastasis. Moreover, a subsequent genotype by NGS also showed the disappearance of STRN-ALK and EGFR exon20 T790M. The therapeutic efficacy of crizotinib plus osimertinib on EML4-ALK and STRN-ALK double-fusion variant in patients with EGFR resistant mutant lung cancer may provide a supportive reference for the patients with such genetic alteration. NGS might contribute to optimizing the selection of patients.

Keywords: STRN-ALK; EML4-ALK; double-fusion; gefitinib; crizotinib; osimertinib

Abbreviations: ALK: Anaplastic Lymphoma Kinase; EML4: Echinoderm Microtubule-Associated Protein-like 4 gene; NSCLC: Non–Small Cell Lung Cancer; STRN: Striatin; EGFR: Epidermal Growth Factor Receptor; NGS: Next-Generation Sequencing; CTDNA: Circulating Tumor DNA CT: Computed Tomography; TKI: Tyrosine Kinase Inhibitors

Introduction

Studies reporting the coexistence of EGFR and anaplastic lymphoma kinase genes (ALK) in a single patient has challenged the previously established theory, which states that EGFR mutation is mutually exclusive to ALK rearrangement. However, such findings reported with double ALK fusion simultaneously in one patient with EGFR mutation is still rare. Herein, we presented a secondary striatin (STRN)-ALK, echinoderm microtubule-associated protein-like 4 gene (EML4)-ALK double-fusion variant in lung adenocarcinoma with EGFR mutations that responded to gefitinib.

Case Presentation

A 38-year-old male nonsmoker presented to the hospital with chest pain, dyspnea, and lumbago. A chest computed tomography (CT) scan showed a mass in the left lung, multiple nodules in the right lung with pleural effusion in small quantities (Figure 1A). The brain CT scan was normal. Bone radionuclide CT scan showed multiple bone metastases. Bronchoscopy biopsy revealed atypical cells in the submucosa of the left bronchus. Immunohistochemistry showed positivity for thyroid transcription factor 1, napsin A, and negativity for P40. A capture-based next-generation sequencing (NGS), as well as plasma circulating tumor DNA (ctDNA) detection, were recommended from the bronchoscopy biopsy samples of tumor tissue. TP53, RB1, EGFR exon21L858R were identified in tissue (49.6% abundance, 40.4% abundance and 78.0% abundance) and plasma ctDNA (10.2% abundance, 9.3% abundance and 28.4% abundance) (Table 1). On March 25, 2019, the treatment with gefitinib was initiated (250 mg twice daily). After 3 months of gefitinib therapy, a follow-up CT scan revealed that partial response was achieved with evidence of a significant reduction in tumor size and shrinkage of nodules in the right lung (Figure 1A). Meanwhile, NGS of plasma ctDNA showed the disappearance of all variants (Figure 1B). After 6 months, the disease was evaluated as stabilized and the administration of gefitinib was continued. On April 21, 2020, a CT scan showed that the lung lesion was still stable but with liver metastases and a new appearance of bone metastases. The disease was evaluated as a progressive disease. Simultaneously, NGS assay of patient's plasma ctDNA identified a double ALK fusion: STRN-ALK (S3:A20, 0.70% abundance), EML4-ALK (E2:A20, 0.90% abundance) and new EGFR (exon 20 T790M, 0.80% abundance) in addition to the recurrence of the original TP53, RB1 and EGFR exon 21del (7.0% abundance, 9.4% abundance and 25.9% abundance) (Table 1 and Figure 1C). Based on the above clinical parameters, we prescribed combination therapy with crizotinib and osimertinib. Further lung CT-scan evaluation in June and September 2020 showed that the lesion was confined to its original location without any signs of new metastasis in other areas including liver and bone. (Figure 1A). A repeated NGS assay in September detected TP53, RB1, EGFR exon21, EML4-ALK (22% abundance, 24.8% abundance, 46.2% abundance, and 14% abundance), while the STRN-ALK and EGFR T790M variants were not detected.

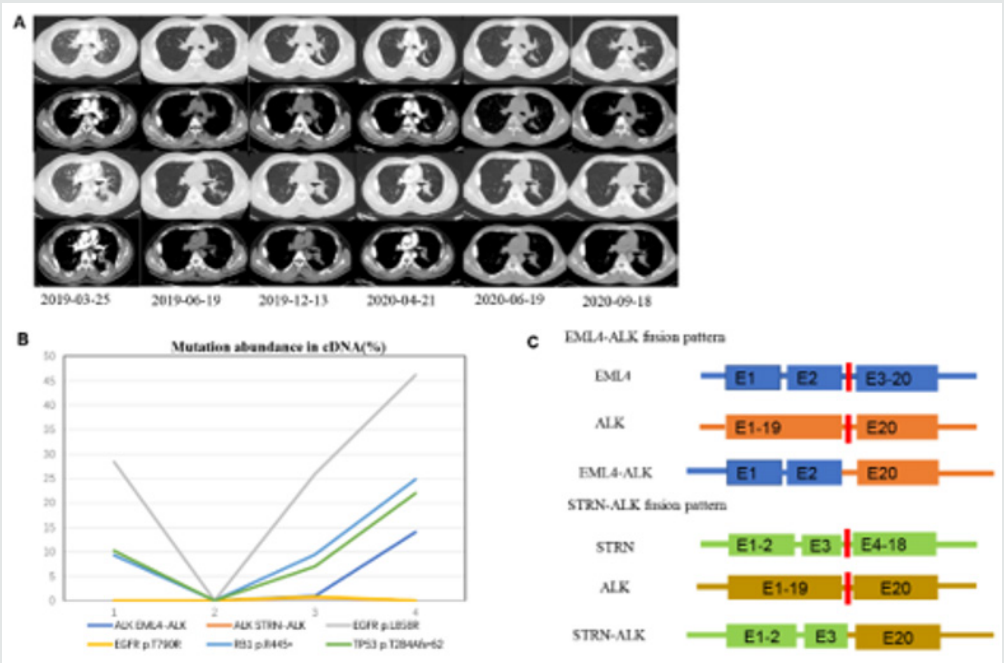

Figure 1: (A) CT images at different phases of treatment. (B) Mutation abundance using the next-generation sequencing (NGS) of circulating tumor DNA (ctDNA). 1, NGS of the patient's plasma ctDNA for the first time on March 25, 2019; 2, NGS of the patient's plasma ctDNA for the second time on June 19, 2019; 3, NGS of the patient's plasma ctDNA for the third time on April 21, 2020; 4, NGS of the patient's plasma ctDNA for the fourth time on September 18, 2020. (C) The fusion pattern of echinoderm microtubule associated protein like 4 gene (EML4)-ALK receptor tyrosine kinase (ALK) and striatin (STRN)–ALK.

Table 1: Changes in liquid biopsy.

Gene	c.HGVS	p.HGVS	Functional Region	20190325	20190619	20200412	20200918
TP53	c.848-849dupgGC	p.T284Afs*62	EX8	10.20%	ND	7.0% 22%	22%
RB1	c.1333C>T	p.R445*	EX14	9.30%	ND	9.4% 24.8%	24.8%
EGFR	c.2369C>T	p.T790M	EX20	ND	ND	0.80% ND	ND
EGFR	c.2573T>G	p.L858R	EX21	28.40%	ND	25.9% 46.2%	46.2%
STRN-ALK		Fusion	EX3:EX20	ND	ND	0.70% ND	ND
EML4-ALK		Fusion	EX2:EX20	ND	ND	0.90% 14%	1%

ND: Not Detected; c.HGVS: Description of Coding DNA (c.) HGVS: variants by Human Genome Variation Society; p.HGVS, description of protein (p.) variants by HGVS. *describe a stop codon.

Discussion

The most common fusion partner in ALK-rearranged NSCLC is EML4 [1], while the STRN-ALK fusion occurs very rarely. Up till now, only five cases of STRN-ALK fusion in lung cancer have been reported. Functionally, Variant 5 (exon 2 of EML4 was connected to exon 20 of ALK) which is peculiar with its coiled-domain play a critical role in the dimerization and activation of EML4-ALK subtypes and in binding EML4-ALK to certain subcellular components [2]. Proportionately, the fusion product of EML4 with ALK kinase domains varies with the extent of fusion [3]. To the best of our knowledge, this is the first study to report the STRN-ALK, EML4-ALK double fusion, and the coexistence of double fusion and EGFR mutation in a lung adenocarcinoma patient. Secondary resistance of EGFR exon20 T790M is most commonly found in first-line EGFR-tyrosine kinase inhibitors (TKI), but it responds well to osimertinib [4]. STRN and ALK are situated on the same short arm of chromosome 2 as EML4 [5]. Recently, STRN-ALK fusion protein has been identified as a potential therapeutic target in many cancer types, including those of few highly aggressive cancers of the thyroid, colorectal and renal cell carcinomas, in addition to cancers of the liver and lungs. Moreover, these carcinomas show similar invasive features with extra-organ and lymph node metastasis [6-8]. It was reported that the thyroid and colorectal cancer patients responded significantly well to crizotinib. STRN-ALK–transfected rat thyroid cells were sensitive to crizotinib based on an in vitro experiment, but the sensitivity to alectinib or other ALK inhibitors was unclear [9]. It was reported that an NSCLC patient harboring STRN-ALK fusion without ALK-resistant mutation showed resistance to alectinib therapy and died 6 months after the initial diagnosis [5]. It was regarded that STRN-ALK fusion was sensitive to crozotinib with exceptionally long survival but was unresponsive to alectinib [4]. However, there is no data on the sensitivity of EML4-ALK and STRN-ALK mutations in EGFR-resistant mutant NSCLCs to the combination therapy of crizotinib and osimertinib. Recently, the use of crizotinib to inhibit ALK has become the standard therapeutic strategy in advanced ALK-rearrangement NSCLC, but ALK fusion forms vary widely in their curative effect and duration of response. Even with the specific EML4-ALK fusion variant, it will show different sensitivity to crizotinib in vitro [1]. Although the exact function remains unclear, EMLs are considered to represent a type of inhibitor modulating the microtubule function in association with its ability to restrain the cellular proliferation and mitosis [3].

Conclusion

As for the existing patient, we hypothesized that STRN-ALK fusion was the main cause of extrapulmonary metastasis in lung cancer. We speculated that gefitinib can be an ideal alternative therapeutic target to supplant Osimertinib in patients with the non-existence of EGFR exon 20 T790M reported with drug resistance. Besides, our case study also demonstrated that plasma CTDNA analysis can be effectively applied to detect the variant type and to further predict and complement the efficacy of TKI in NSCLC based on the link between variant and clinical outcome. Collectively, our data may provide supporting evidence and guidance for implementing an effective therapeutic strategy for similar cases.

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