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CASE REPORT

Tyrosine kinase inhibitor acquired resistance mechanism alternates between EGFR and ALK in a lung adenocarcinoma patient

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Abstract

Drive gene mutation positive non-small cell lung cancer achieves reliable clinical responses to subsequent target therapy. However, most patients will inevitably develop disease progression with multiple treatment failure. Next generation sequencing can identify clear resistance mechanisms. We report a case of a late stage, non-smoking, male non-small cell lung cancer patient that developed dual mutations and our attempts to determine the novel resistance mechanism. After systematic chemotherapy, he was administered multiple target therapy according to different genotypes. Larger panel gene detection was adapted after the failure of different treatments to investigate the resistance mechanism. Re-biopsy and large panel NGS revealed an *EGFR* mutant lung adenocarcinoma with alternating changes in acquired resistance between *EGFR* and *ALK*. The total survival time was 73 months. The genotypes and treatments in this patient provide new insight of target therapy resistance mechanisms. Re-biopsy and large panel gene detection should be performed for each driver gene mutation to provide precision treatment strategies.

Introduction

Lung cancer remains the leading cause of cancer-related death worldwide.[1] With improvements in gene testing, many driver mutations, including *EGFR*,[2] *ALK*,[3] *ROS1*[4] and *MET*[5] are now assessed as targetable genes and patients have achieved remarkable responses from targeted treatment. T790M detection has been approved as the first choice for lung adenocarcinoma after progression with first-line EGFR-tyrosine kinase inhibitors (TKIs).[6] However, next generation sequencing (NGS) in clinical practice can clearly detect resistant mechanisms and thus assist to provide precision treatment strategies. Herein, we present a case of a lung adenocarcinoma patient who displayed alternative drug resistance between *EGFR* mutation and *ALK* rearrangement. The patient benefited from treatment for the newly occurring driver gene mutations, which can only be detected by NGS from liquid biopsy.

Case presentation

A 43-year-old non-smoking man presented at the hospital after experiencing a cough and sputum for one month. Computed tomography (CT) showed a primary tumor located at the lower lobe of the right lung with lymph node metastases in the right hilar and mediastinum. Post-surgery, the patient was diagnosed with adenocarcinoma stage pT1N2M0 IIIA and NGS (168 genes; Burning Rock, Guangzhou, China) of resected tissue and immunohistochemistry (D5F3, Ventana Medical Systems Inc., Roche, Tucson, AZ, USA) detected *EGFR* exon 19 deletion (19del) but was negative for *ALK*. The patient agreed to four cycles of adjuvant chemotherapy. However, metastases in the right hilar,

mediastinum, and right adrenal gland were detected 20 months later by positron emission tomography (PET)-CT. Treatment with gefitinib was initiated and a partial response (PR) was obtained. After 24 months, gefitinib combined with whole brain radiotherapy (40Gy/F) was administered for isolated metastases in the brain and the disease was controlled for the next five months. A CT scan then showed increased metastasis in the right middle lobe nodule, multiple lymph nodes, multiple bilateral pulmonary nodules, and the liver. A bronchial re-biopsy confirmed that the pathological diagnosis remained adenocarcinoma. NGS of the right middle lobe nodule recurrence showed the existence of *EGFR* 19 del along with *EML4-ALK* rearrangement as drug resistance (Fig 1a,b). A new therapeutic strategy including both gefitinib and crizotinib treatment was initiated and a response was obtained. The patient developed a grade II rash. CT revealed new liver metastases and a new nodule in the left adrenal gland. NGS-based liquid biopsy showed the coexistence of *EGFR* 19del and exon 20 T790M (T790M) mutations, but no *ALK* rearrangement. Treatment was modified to osimertinib plus crizotinib and PR was obtained. The patient again developed a grade II rash. After five months, with new metastases in the liver and left adrenal gland, the patient was evaluated with PD (Fig 1c). Liquid biopsy by NGS revealed *EGFR* 19del, *ALK* rearrangement, and three newly occurring point mutations, including *ALK* p.G1128A, *ALK* p.C1156Y, and *ALK* p.F1174L, but no T790M mutation (Fig 1b). The treatment was modified once again to osimertinib combined with brigatinib and PR was obtained with the genotype of *EGFR* 19del and T790M (Fig 1b,c). The adverse events were grade II rash and diarrhea. After 13 months, new metastases in the liver and left adrenal gland were observed on CT and the patient was evaluated with PD. Liquid biopsy by NGS revealed the genotype was *EGFR* 19del, T790M, *EML4-ALK*, *ALK* p.F1174L, and a newly occurring *ALK* p.G1202R (Fig 1b). The patient died two months later after being treated with best supportive care. The mutation burden, the relative tumor burden, as well as tumor evolution showed dynamic changes following the transformative treatments (Fig 2).

Discussion

Lung cancer patients with oncogenic driver gene mutations can achieve better prognosis from target TKIs than traditional chemotherapy.[7,8] However, patients will inevitably develop disease progression, with complex resistance mechanisms including T790M, transformation to small cell

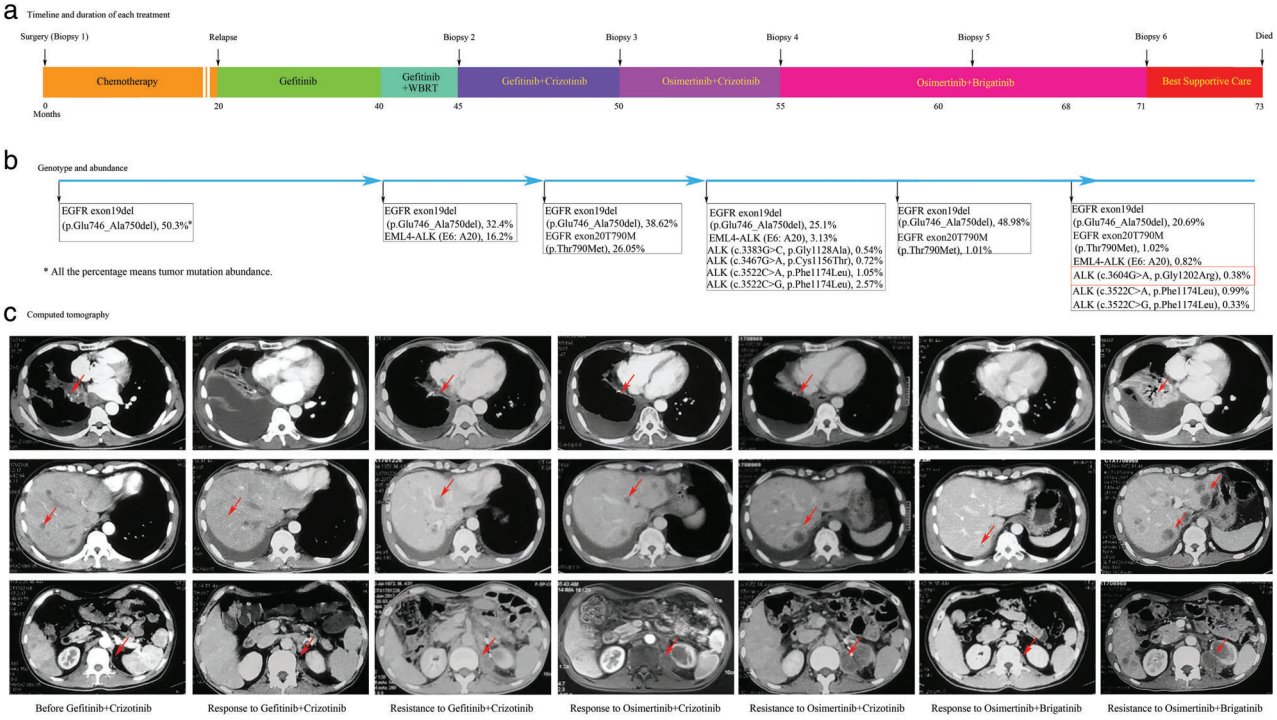

Figure 1 Genotype and duration time of each treatment. (**a**) The various treatments of the lung as well as the duration of each treatment. (**b**) The phenotypes and the abundance of mutation detected by next generation sequencing under the various treatments. (**c**) Computed tomography images of the patient's metastatic liver, lung, and adrenal gland disease before he received gefitinib (G) + crizotinib (C), response to G + C, resistant to G + C, response to osimertinib (O) + C, resistant to O + C, response to O + brigatinib (B), respectively (G, 250 mg oral once daily; C, 250 mg oral twice daily; O, 80 mg oral once daily; B, 180 mg oral once daily). The red arrows show pulmonary nodules and metastasis. WBRT, whole brain radiotherapy.

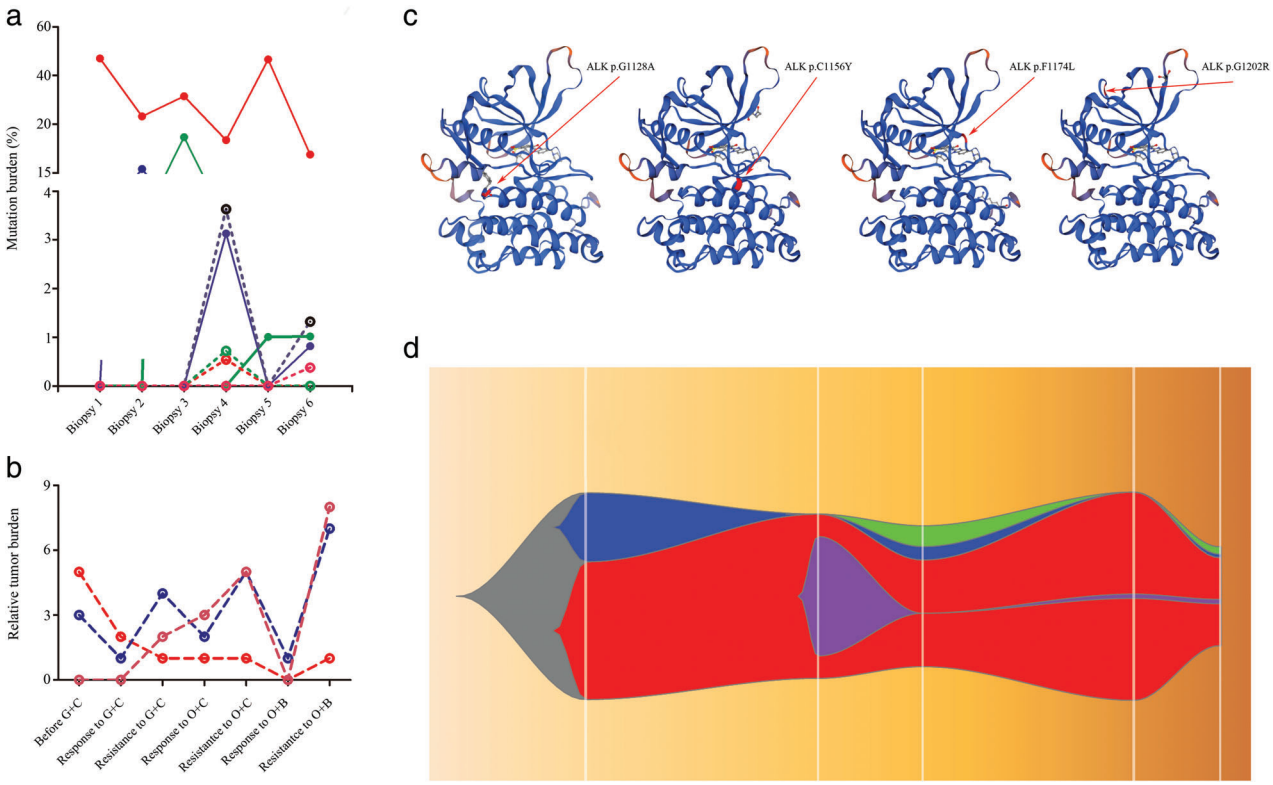

Figure 2 The evolution of the patient's tumor. (**a**) The dynamic change in mutation abundance with each *EGFR* and *ALK* mutation. (**b**) The relative tumor burden of the patient under various treatments (each diameter of sum lesions including the lung, liver, and adrenal gland was calculated separately to draw the tumor burden curve). (**c**) The structure analyzed by Swiss-Model for newly occurring *ALK* point mutations, including p.G1128A, *ALK* p.C1156Y, *ALK* p.P1174L and *ALK* p.G1202R, respectively. (**d**) Tumor evolution between treatments of gefitinib (G) + crizotinib (C) and osimertinib (O) + brigatinib (B). The model is based on an analysis of next generation sequencing (NGS) of pretreatment and resistant biopsy samples. A founder *EGFR* exon19del subclone was detectable in the pretreatment tumor specimen after surgery. With G therapy, this subclone expanded to 60% of the tumor cell population with *EGFR* exon19del and 40% of the tumor cell population with *ALK* fusion, which led to the patient's disease progression. G + C was effective against the G-resistant tumor, but the T790M subclone developed as an acquired mechanism. The three point-mutant subclones (G1128A, C1156Y, and F1174L) were insensitive to O + C, but *EGFR* exon19del was still the dominant subclone in the progressive tumor. The new *ALK* point mutation (G1202R) identified by NGS showed resistance to O + B. All of the measurable lesions and mutation abundance were calculated using R software to draw the tumor evolution). (—●—) *EGFR* exon 19del, (—●—) *EGFR* exon 20 T790M, (—●—) *ALK* p.F1174L, (-·○·-) ALK p.G1128A, (-·○·-) *ALK* p.C1156Y, (-·○·-) *ALK* p.F1174L and (-·○·-) *ALK* p.G1202R; (-·○·-) Lung, (-·○·-) Liver, and (-·○·-) Adrenal gland; (——) *EGFR* 19del, (——) *EML4-ALK*, (——) *EGFR* T790M, and (——) *ALK* resistance

lung cancer, bypass activation, and downstream signal activation.[9] A study reported that *ALK* point mutations are the response of acquired resistance to crizotinib.[10] Functional oncogenic mutations *EGFR* and *ALK* are mutually exclusive.[11] However, the drug resistant mechanism in patients with double or multiple mutations is unclear.[12] In this patient, a newly occurring *EML4-ALK* fusion developed after gefitinib resistance, and the drug resistance mechanism during the subsequent course of disease exhibited alternate changes between *EGFR* and *ALK*. Possible explanations include the heterogeneity of the original tumor and evolution under the stress of multiple TKIs.[13]

ALK p.G1202R and p.F1174L are common resistance mutations in crizotinib-treated NSCLC patients.[14] Brigatinib has been reported to be effective in patients with *ALK* p.F1174L and p.G1202R.[15] However, in our case, after *ALK* p.F1174L and *ALK* p. G1202R developed with an existing *ALK* p.F1174L mutation, the patient presented acquired resistance to osimertinib and brigatinib. This may be associated with the joint function of four different point mutations and the complex tumor environment of two different oncogenic mutations.[16]

Re-biopsy and gene detection is considered standard procedure for patients in whom target treatment has failed. Previous research has tended to focus only on changes in signaling pathways. However, TKI resistance mechanisms are exhibited not only by changes to signaling pathways but also by new gene mutations. In this patient, a newly occurring *ALK* fusion was identified as a resistance mechanism to gefitinib and *ALK* point mutations as resistance mechanisms to osimertinib. Large panel gene detection of lesions or blood at disease

progression is important to assist in deciding subsequent therapeutic strategies.

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Disclosure

No authors report any conflict of interest.

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