CASE REPORT

ALK-Positive Adenocarcinoma After Acquired Resistance to Lorlatinib and Transformation to SCLC: A Case Report

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Received 11 October 2022; revised 13 January 2023; accepted 17 January 2023
Available online - 20 January 2023

ABSTRACT

SCLC transformation is a phenomenon that is rarely described in ALK-rearranged cancers after treatment with ALK tyrosine kinase inhibitors, and it is exceedingly rare after lorlatinib use. We report the first case of a patient with an ALK-EML4 rearrangement who was resistant to lorlatinib simply due to transformation to SCLC and rapidly achieved partial response after traditional etoposide combined with cisplatin therapy. In addition, we provide a fishplot that visualizes tumor evolution on the basis of next-generation sequencing, which may predict small cell transformation and facilitate early treatment.

Keywords: Anasplastic lymphoma kinase; Lung adenocarcinoma; Lorlatinib; Resistance; Small cell lung cancer; Case report

Introduction

ALK gene rearrangements are found in 3% to 5% of patients with NSCLC, and the most common of which is the ALK-EML4 fusion mutation. Lorlatinib is a potent third-generation ALK tyrosine kinase inhibitor (TKI), and it has a high response rate in both first- and second-generation ALK TKI-resistant patients, especially in those with brain metastases. Unfortunately, acquired resistance inevitably occurs after ALK inhibitor use. Studies have found that the resistance mechanisms in ALK-positive NSCLCs comprise ALK gene alterations, such as ALK secondary mutations and gene amplifications, SCLC transformation, and activation of bypass signaling of other oncogenes.[1] SCLC transformations are relatively rare. Whether the pathologic type of the transformation is heterogeneous or gene-driven tumor evolution remains controversial. To date, few studies have reported small cell transformation after resistance to third-generation ALK TKI therapy. Herein, we report a unique case of a patient harboring an ALK-EML4 fusion mutation that transformed the tumor from adenocarcinoma to SCLC after resistance to lorlatinib and its responsiveness to traditional etoposide combined with cisplatin as first-line chemotherapy.

Case Presentation

A 42-year-old woman with no history of smoking but with a family history of endometrial cancer was diagnosed with having stage I NSCLC T1N0M0. In September 2017, the patient underwent thoracoscopic right lung

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Disclosure: The authors declare no conflict of interest.

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Cite this article as: Li H, Song T, Xu X. ALK-positive adenocarcinoma after acquired resistance to lorlatinib and transformation to SCLC: a case report. *JTO Clin Res Rep*. 2023;4:100464.

ISSN: 2666-3643

https://doi.org/10.1016/j.jtocrr.2023.100464

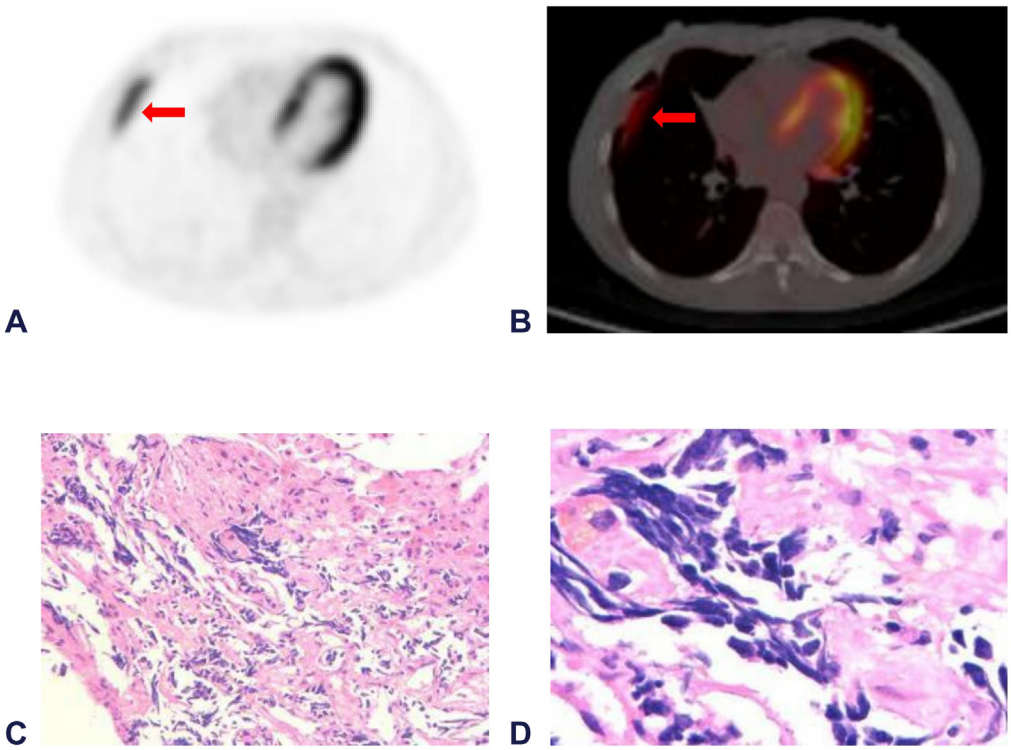
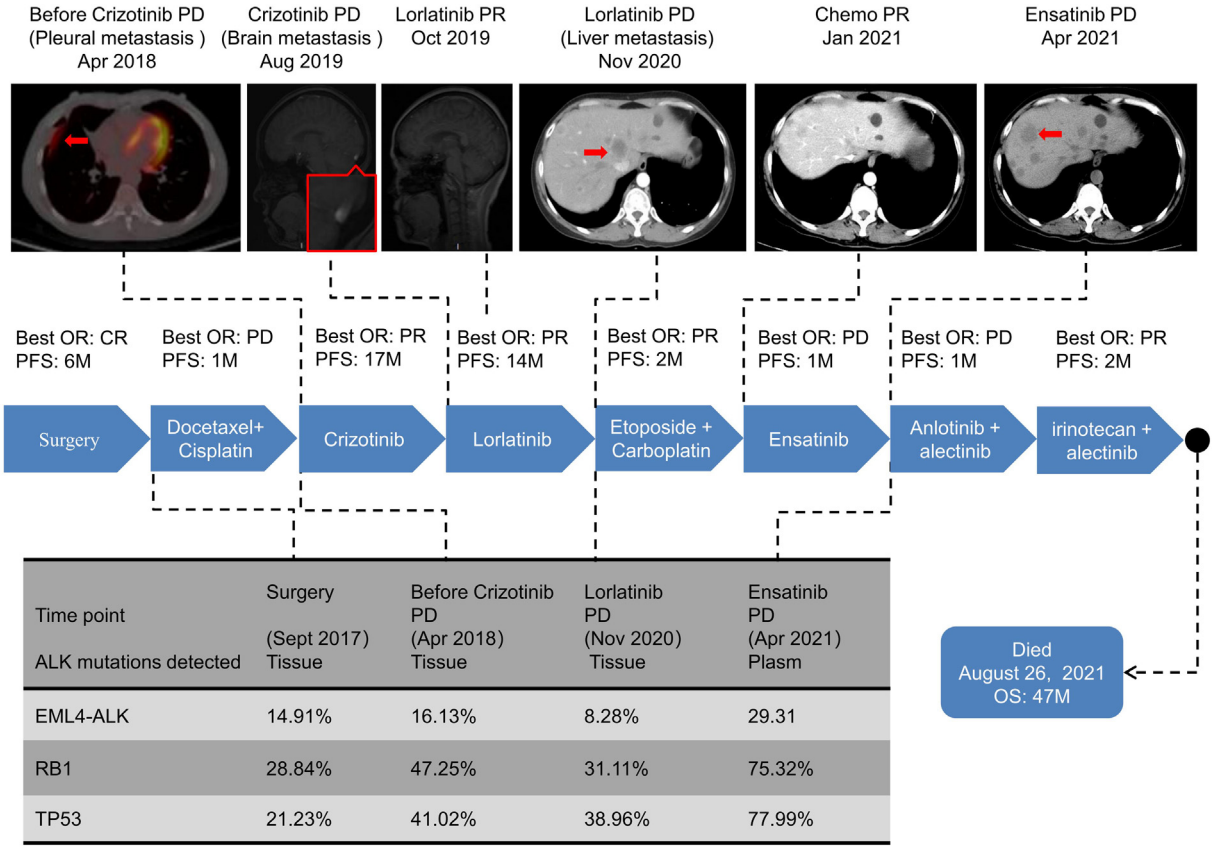


Figure 1. Results of positron emission tomography before crizotinib and liver core needle biopsy pathology after 14 months of treatment with lorlatinib. (*A*, *B*) Multiple nodule strip thickening of the right pleura with increased FDG metabolism. (*C*, *D*) H&E-stained section revealing a small amount of heterotypic cell infiltration with crush injury. (*C*) Original magnification, ×100. (*D*) Original magnification, ×400. FDG, fluorodeoxyglucose; H&E, hematoxylin and eosin.

cancer radical resection in another hospital, and postoperative pathologic results revealed well-differentiated invasive adenocarcinoma (mostly vesicular growth, partly papillary), without neuroendocrine expression. Two cycles of first-line chemotherapy (docetaxel and cisplatin) were administered to the patient due to increasing carcinoembryonic antigen values. Nevertheless, positron emission tomography-computed tomography (Fig. 1*A* and *B*) revealed tumor recurrence and right pleural metastasis, and the patient then came to our hospital for further treatment. The diagnosis of adenocarcinoma was confirmed on the basis of the right pleural mass biopsy, and both immunohistochemistry (IHC) and next-generation sequencing revealed an ALK-EML4 mutation. Then, the patient underwent crizotinib-targeted therapy from April 2018 to September 2019, and the best response was partial response (PR). Brain magnetic resonance imaging revealed an abnormal signal nodule in the right occipital lobe. Accordingly, she participated in an oral lorlatinib clinical trial[2] and achieved PR only 2 months after. On November 2020, 14 months after lorlatinib initiation, computed tomography surveillance identified an increase in the number of low-density lesions in the liver. Liver biopsy results revealed a small amount of atypical cell infiltration with crush injury in the liver tissue. The IHC results were as follows: napsin A (−), TTF-1 (+), P40 (−), P63 (−), CK7 (focal+), Sy (+), CD56 (+), CgA (focal weak+), and Ki-67 (+, 90%). On the basis of both the neuroendocrine phenotype and IHC results, lung small cell carcinoma metastasis was considered (Fig. 1*C* and *D*). Hence, the patient received cytotoxic chemotherapy with the EC (etoposide plus carboplatin) regimen, and after two cycles, the response was PR. As the disease progressed again after four cycles and failed to respond to ensatinib treatment for 1 month, the treatment strategy was switched to anlotinib plus alectinib. Because of an increase in liver metastases, irinotecan alone was added in May 2021, and the oral administration of alectinib continued. After 2 months of re-examination, the number and size of the liver lesions were reduced. The patient refused further intravenous chemotherapy and died on August 26, 2021. The timeline of the treatment of the patient was presented in Figure 2

Discussion

There is only one relevant report on the transformation of SCLC after lorlatinib resistance. A 49-year-old man developed the ALK 1196M mutation combined with small cell transformation after first-generation and second-generation ALK TKI treatment. The patient was subsequently treated with vinorelbine and carboplatin. However, his condition deteriorated rapidly, and the



Time point ALK mutations detected	Surgery (Sept 2017) Tissue	Before Crizotinib PD (Apr 2018) Tissue	Lorlatinib PD (Nov 2020) Tissue	Ensatinib PD (Apr 2021) Plasm
EML4-ALK	14.91%	16.13%	8.28%	29.31
RB1	28.84%	47.25%	31.11%	75.32%
TP53	21.23%	41.02%	38.96%	77.99%

Figure 2. The timeline for the clinical course of the patient from diagnosis to death is found along with radiographic images and gene detection results. Apr, April; Aug, August; CR, complete response; Jan, January; M, month; Nov, November; Oct, October; OR, overall response; OS, overall survival; PD, progression of disease; PFS, progression-free survival; PR, partial response.

curative effect was not satisfactory.[3] Here, we report a case of lorlatinib-induced SCLC transformation after crizotinib treatment. The gene detection of the patient was ALK-EML4 throughout, without any other ALK mutations. This better reflects that small cell transformation is an independent mechanism of lorlatinib resistance. Although the pathogenesis of the transformation to SCLC remains unclear, studies have shown that TP53-deficient and RB1-deficient cells promote lineage plasticity and metastasis of neuroendocrine tumors.[4] The small cell transformation in the patient may be associated with RB1 and TP53 gene mutations. According to the fishplot (Fig. 3), a simple and intuitive graph of tumor gene evolution, mutations in RB1 and TP53 may exist at the time of initial diagnosis, and their levels are closely correlated with tumor progression. Consequently, attention should be given to RB1 and TP53 mutation levels in the early stage of NSCLC, which can be predictive of SCLC transformation and thus monitor tumor progression.

So far, there is no standard treatment strategy for patients with ALK-positive SCLC transformation after ALK TKI treatment. On the basis of epigenetic evidence, the molecular phenotypic characteristics and clinical course of EGFR mutant–resistant transformed SCLC are more similar to classic SCLC than NSCLC.[5] Accordingly, the treatment strategy of classical SCLC should be considered for patients with transformed SCLC. A similar treatment regimen should be considered for patients with ALK-mutated transformed SCLC. Etoposide plus platinum is the first-line regimen for SCLC and is also widely used for transformed SCLC. Most cases of SCLC transformation exhibit neuroendocrine differentiation and increased chemosensitivity to etoposide and platinum, translating into a good response to initial chemotherapy.[6] The current patient might be sensitive to EC chemotherapy and achieved PR in two cycles. Nevertheless, because the disease progressed after four cycles, a refractory response to treatment for SCLC should be taken into consideration. In conclusion, etoposide plus platinum-based chemotherapy can be preferentially used to control the disease in the short term in ALK-positive patients after confirmed small cell transformation.

In addition, immunotherapy combined with chemotherapy may be a promising treatment option for

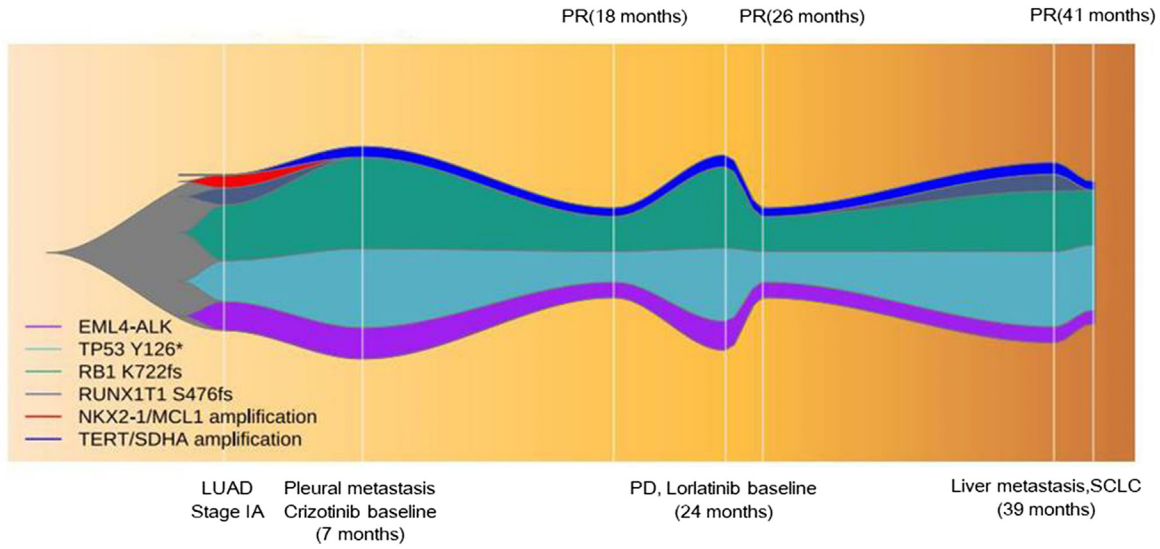


Figure 3. Visualizing tumor gene evolution of the patient with the fishplot. LUAD, lung adenocarcinoma; PD, progression of disease; PR, partial response.

transformed SCLC, given that immune checkpoint inhibitors can improve the prognosis of patients with SCLC and NSCLC.[7] IMpower133 and CASPIAN trials revealed that for patients with extensive-stage SCLC, adding immunotherapy to chemotherapy yielded significant overall survival and progression-free survival benefits.[8,9] Nevertheless, a retrospective study involving 67 patients with EGFR mutations revealed that patients with transformed SCLC responded poorly to immune checkpoint inhibitors.[10] In addition, a 62-year-old man with ALK rearrangement lung adenocarcinoma underwent three regimens (nivolumab, irinotecan, and amrubicin) after SCLC transformation, which also revealed poor efficacy.[11] Hence, further studies are recommended to determine whether immunotherapy combined with chemotherapy holds great promise for patients with transformed SCLC.

The antiangiogenic drug anlotinib, usually in combination with chemotherapy or ALK TKIs, is another option for treatment. Although there was little benefit observed for this patient, research has revealed that patients with transformed SCLC treated with anlotinib have significantly prolonged overall survival compared with those who did not receive anlotinib treatment.[12]

Sequential treatment with cytotoxic agents and alectinib manifested that readministration of ALK TKIs after chemotherapy failure remains effective in transformed SCLCs.[13] Irinotecan and platinum are also first-line treatment strategies for SCLC. Fujita et al.[14] reported a case of transformed ALK-mutated SCLC treated with irinotecan-alectinib therapy, with sustained PR in the primary lesion and maintained PR in the other lesions. Our patient received a combined treatment of irinotecan and alectinib. After 2 months, the liver metastases indicated an ideal curative effect. For some cases[15] of ALK-rearranged small cell transformation, readministration of ALK TKIs is recommended, but further investigations will be needed to confirm its efficacy. Currently, most studies on transformed SCLC have been case reports and small sample retrospective studies. In the future, prospective and large retrospective studies should be conducted to identify the clinical characteristics and improve the prognosis of patients with transformed SCLC, as there is a dearth of medical literature in this unique circumstance.

Conclusion

This case reveals that the EC regimen and irinotecan and alectinib are suggested for transformed SCLC. Nevertheless, treatment strategies should be identified on the basis of the patient's specific condition. Biopsy is the definitive standard for transformed SCLC. It is necessary to perform rebiopsy on patients with drug-resistant ALK mutations to clarify the pathology and gene mutation results, so as to carry out precise individualized treatment.

CRediT Authorship Contribution Statement

Huihui Li: Conceptualization, Data curation, Formal analysis, Visualization, Software, Roles/writing—original draft.

Tianqi Song: Investigation, Data curation, Formal analysis, Methodology, Visualization, Software, Validation.

Xiaoling Xu: Funding acquisition, Project administration, Resources, Supervision, Writing—review and editing.

Acknowledgments

The authors obtained informed consent from the patient's family for publication of the clinical data.

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