Effective treatment in lung adenocarcinoma patient with brain metastases harboring novel CLHC1/RNT4 intergenic region- ALK fusion
A case report

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Abstract

Rationale: Anaplastic lymphoma kinase (ALK) fusion, an important oncogenic mutation, occurs in 3% to 7% of non-small cell lung cancer (NSCLC) cases, and EML4 is the most common partner gene. With the widespread application of next-generation sequencing (NGS), more gene breakpoint fusions have been discovered and functional fusion transcripts can provide targeted clinical benefits.

Patient concerns and diagnosis: A 40-year-old woman was diagnosed with lung adenocarcinoma with brain metastases. A novel CLHC1/RNT4 intergenic region, ALK (Exon20-29) (abundance 39.97%), was identified using lung puncture tissue by NGS analysis (Simceredx), and results of immunohistochemistry and fluorescence in situ hybridization confirmed ALK fusion.

Interventions and outcomes: The patient was administered oral crizotinib (250 mg bid) combined with endostar (30 mg d1-7) for 12 cycles from June 18, 2020. The patient’s condition was controlled, and the curative effect was evaluated as stable disease (SD). Unfortunately, brain magnetic resonance images showed multiple nodules in the left cerebellar hemisphere, and chest computed tomography showed no significant changes in the progression of the disease. Subsequently, alectinib (600 mg bid) was administered on April 1, 2021. Brain lesions were significantly reduced and partial remission (PR) was achieved. No significant changes were observed in the lung lesions.

Lessons: ALK fusion is a risk factor for brain metastasis (BM) in patients with advanced non-small NSCLC patients. In our case, a novel CLHC1/RNT4 intergenic region, ALK fusion, was identified for the first time in a lung adenocarcinoma patient with BM, who benefited from crizotinib and endostar sequential alectinib. Our case highlights the advantages of NGS for fusion detection and provides promising treatment options for NSCLC patients with BM harboring ALK fusions.

Abbreviations: ALK = anaplastic lymphoma kinase, ALK-TKIs = ALK-tyrosine kinase inhibitors, BM = brain metastasis, CT = computed tomography, LUAD = lung adenocarcinoma, MRI = magnetic resonance images, NGS = next-generation sequencing, NSCLC = non-small cell lung cancer.

Keywords: ALK TKI, brain metastases, lung adenocarcinoma, novel CLHC1/RNT4 intergenic region- ALK fusion

1. Introduction

Anaplastic lymphoma kinase (ALK) fusion, an important oncogenic mutation, occurs in 3% to 7% of non-small cell lung cancers (NSCLC), and EML4 is the most common partner gene.[1] With the widespread application of next-generation sequencing (NGS), more gene breakpoint fusions have been discovered, and functional fusion transcripts can bring targeted clinical benefits.[2] Clinical trials have shown that patients with NSCLC with ALK fusion can obtain significant survival benefits through ALK tyrosine kinase inhibitor (ALK-TKI) treatment. To
date, the FDA has approved 5 ALK-TKIs: crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib. Herein, we first identified a novel CLHC1/RNT4 intergenic region–ALK fusion in a patient with lung adenocarcinoma (LUAD) with brain metastasis (BM), who benefited from crizotinib and endostar sequential alectinib.

2. Case description

A 40-year-old woman was admitted to the hospital on March 7, 2020, with “cough and hemoptysis”. Chest computed tomography (CT) revealed nodules in the upper lobe of the left lung with mediastinal lymph node metastasis (Fig. 1A). Brain magnetic resonance imaging (MRI) revealed BM (Fig. 1F). The neck lymph nodes were enlarged, and pathology of the neck lymph node biopsy showed LUAD. No driver gene mutations were found by ARM-PCR in the patient’s blood in the hospital. Brain radiotherapy (40 Gy/20 f) was performed from April 2, 2020, to May 6, 2020. During brain radiotherapy, cisplatin (40 mg/m², D1-3) and pemetrexed (800 mg/m²/d) were administered for 1 cycle of chemotherapy from April 17, 2020. Unfortunately, her condition worsened, her breathing was difficult, and chest and back pain were present. Positron emission tomography-CT revealed a significant increase in pericardial effusion. The patient received 2 cycles of endostar (30 mg/m²/d, d1-7) combined with cisplatin (40 mg/m², D1-3) and pemetrexed (800 mg/m²/d) on May 8, 2020.

A novel CLHC1/RNT4 intergenic region, ALK (Exon20-29) (abundance 39.97%), was identified using lung puncture tissue by NGS analysis (Simceredx) in June 2020, and the results of immunohistochemistry and fluorescence in situ hybridization confirmed ALK fusion (Fig. 2). The patient then started oral crizotinib (250 mg bid) combined with endostar (30 mg d1-7) for 12 cycles from June 18, 2020. The patient’s condition was controlled and the curative effect was evaluated as stable disease (SD) (Fig. 1C and H). Unfortunately, the patient felt dizzy and unwell in March 2021. Brain MRI showed multiple nodules in the left cerebellar hemisphere (Fig. 1I), and chest CT showed no significant changes (Fig. 1D), revealing the progression of the disease. Alectinib (600 mg twice daily) was administered on April 1, 2021. Brain lesions were significantly reduced, and partial remission (PR) was achieved (Fig. 1J). No significant changes were observed in the lung lesions had no significant change (Fig. 1E). The timeline of treatment and changes in the CT scan and MRI are shown in Figure 1.

3. Discussion

In our case, we identified a novel CLHC1/RNT4 intergenic region–ALK fusion in a LUAD patient with BM, which retained the entire kinase domain (exon 20-29) of ALK (Fig. 2B). Because functional intergenic fusions can bring corresponding clinical benefits, they are receiving increasing attention. Compared with the limited traditional detection methods, the application of NGS has accelerated the discovery of novel ALK fusions, and the requirements for samples have gradually broadened. The novel ALK fusion gene was confirmed as a functional fusion transcript by fluorescence in situ hybridization and immunohistochemistry (Fig. 1L). Lung cancer patients with intergenic ALK fusions respond to ALK-TKIs. ALK fusion is a risk factor for brain patients with advanced NSCLC.
trials of TKI in NSCLC patients with BM have shown a high percentage of objective responses, prolonged PFS, and improved quality of life. Studies have reported that 6 patients with NSCLC and brain metastases received 100% intracranial ORR (4 cases of PR and 2 cases of CR) after receiving osimertinib and bevacizumab combination treatment.[10] The patient in our case with intergenic ALK fusion had a good response to ALK TKI plus endostar.

4. Conclusion

In conclusion, a novel CLHC1/RNT4 intergenic region, ALK fusion, was identified for the first time in a LUAD patient with BM, who benefited from crizotinib and endostar sequential alectinib. Our case highlights the advantages of NGS for fusion detection and provides promising treatment options for NSCLC patients with BM harboring ALK fusions.

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Author contributions

All authors made substantial contributions to the conception of this study. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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