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Early detection of circulating tumor DNA and successful treatment with osimertinib in thr790met-positive leptomeningeal metastatic lung cancer: A case report

Li-Qing Xu, Ying-Jin Wang, Sheng-Li Shen, Yao Wu, Hong-Zhou Duan

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Abstract

BACKGROUND

Patients diagnosed with non-small-cell lung cancer with activated epidermal growth factor receptor mutations are more likely to develop leptomeningeal (LM) metastasis than other types of lung cancers and have a poor prognosis. Early diagnosis and effective treatment of leptomeningeal carcinoma can improve the prognosis.

CASE SUMMARY

A 55-year-old female with a progressive headache and vomiting for one month was admitted to Peking University First Hospital. She was diagnosed with lung adenocarcinoma with osseous metastasis 10 months prior to admittance. epidermal growth factor receptor (EGFR) mutation was detected by genomic examination, so she was first treated with gefitinib for 10 months before acquiring resistance. Cell-free cerebrospinal fluid (CSF) circulating tumor DNA detection by next-generation sequencing was conducted and indicated the EGFR-Thr790Met mutation, while biopsy and cytology from the patient's CSF and the first enhanced cranial magnetic resonance imaging (MRI) showed no positive findings. A month later, the enhanced MRI showed linear leptomeningeal enhancement, and the cytology and biochemical examination in CSF remained negative. Therefore, osimertinib (80 mg/d) was initiated as a second-line treatment, resulting in a good response within a month.

CONCLUSION

This report suggests clinical benefit of osimertinib in LM patients with positive detection of the EGFR-Thr790Met mutation in CSF and proposes that the positive findings of CSF circulating tumor DNA as a liquid biopsy technology based on the detection of cancer-associated gene mutations may appear earlier than the imaging and CSF findings and may thus be helpful for therapy. Moreover, the

routine screening of chest CT with the novel coronavirus may provide unexpected benefits.

Key Words: Non-small cell lung cancer; Epidermal growth factor receptor mutation; Circulating tumor DNA detection; Leptomeningeal carcinomatosis; Osimertinib; Case report

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Core Tip: Examination of circulating tumor DNA in cell-free cerebrospinal fluid (CSF) has been shown to be useful for detecting the genomic mutations of tumors in the central nervous system, and osimertinib is considered to be a recent standardized treatment for epidermal growth factor receptor (EGFR) Thr790Met-mutant non-small-cell lung cancer (NSCLC). Hence, we report a patient with EGFR Thr790Met-mutant NSCLC with meningeal carcinomatosis and resistance to gefitinib and propose that the positive findings of CSF circulating tumor DNA as a liquid biopsy technology based on the detection of cancer-associated gene mutations that may appear earlier than the imaging and CSF findings and thus be helpful for therapy.

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INTRODUCTION

Patients diagnosed with non-small-cell lung cancer (NSCLC) with activated epidermal growth factor receptor (EGFR) mutations are more apt to develop leptomeningeal (LM) metastasis than other types of lung cancers[1]. According to previous studies, patients with NSCLC with LM carcinoma have a poor prognosis[2]. Early diagnosis and effective treatment of LM carcinoma can improve the prognosis. Circulating tumor DNA (ctDNA) is composed of short, double-stranded DNA fragments from tumor cells. Examination of ctDNA in cell-free cerebrospinal fluid (CSF) has been shown to be useful in detecting the genomic mutations of tumors in the central nervous system (CNS) and has also been used to monitor tumor progression and evaluate the response to treatments[3-5]. However, it is unclear whether ctDNA detection in CSF can provide valuable clinical guidance for the treatment of meningeal metastases. Molecular targeted drugs such as EGFR tyrosine kinase inhibitors (TKIs) have been shown to be effective for patients with NSCLC and LM carcinoma who carry target oncogenes[6]. Osimertinib, a third-generation EGFR TKI, is considered to be a recent standardized treatment for EGFR Thr790Met-mutant NSCLC because of its good efficacy in both systemic and CNS metastasis[7]. However, relevant information about the effectiveness of osimertinib in EGFR Thr790Met-mutant meningeal carcinomatosis is limited. Here, we report a case of patient with EGFR Thr790Met-mutant NSCLC with meningeal carcinomatosis, which is resistant to gefitinib.

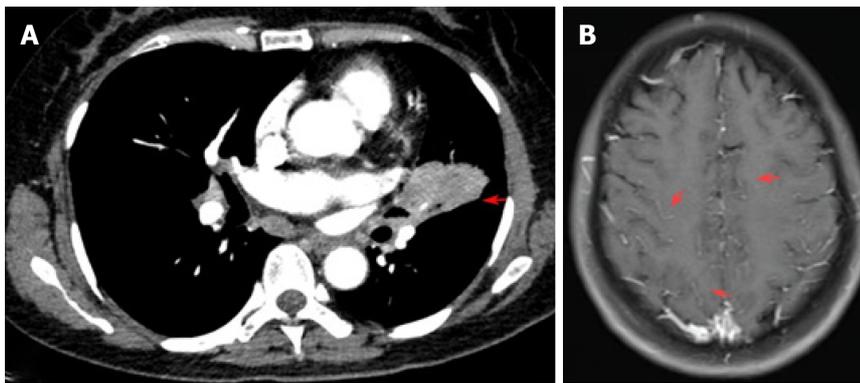
CASE PRESENTATION

Chief complaints

A 55-year-old female experiencing a progressive headache and vomiting for one month was admitted to our hospital.

History of present illness

55-year-old female experiencing a progressive headache and vomiting for one month was admitted to our hospital. She was diagnosed with lung adenocarcinoma (Figure 1A) with osseous metastasis 10 mo prior to admittance. EGFR mutation was detected upon genomic examination, so she was first treated with gefitinib for 10 mo before acquiring resistance. A previous enhanced cerebral magnetic resonance imaging (MRI) and PET-CT one month prior showed that there was no obvious abnormality in the CNS. Lumbar puncture showed an increased intracranial pressure (+ACY-gt+ADs-330 mmH₂O) without positive cytology and biochemical examination findings in the CSF. However, further CSF ctDNA detection by next-generation sequencing showed an EGFR-Thr790Met mutation. After the patient was admitted, a second enhanced MRI was performed and showed comprehensive linear leptomeningeal enhancement in the cerebral sulcus (Figure 1B). A second cytology and biochemical examination of the



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Figure 1 Chest computed tomography. A: Chest computed tomography image at admission shows a lesion in the lingual segment of the upper lobe of the left lung (arrows); B: A follow-up cerebral contrast-enhanced magnetic resonance imaging shows diffuse and linear enhancement along the surface of the cerebrum (arrows).

CSF remained negative.

History of past illness

The patient had no special history of past illness other than a hysterectomy procedure for fibroids 10 years prior.

Personal and family history

The patient had no special history of past illness other than a hysterectomy procedure for fibroids 10 years prior.

Physical examination

Neurological and pulmonary examination of the patient showed no obvious abnormalities.

Laboratory examinations

Lumbar puncture showed an increased intracranial pressure (> 330 mmH₂O) without positive cytology and biochemical examination findings in CSF. However, further CSF ctDNA detection by next-generation sequencing showed an EGFR-Thr790Met mutation, and the variation frequency was 11.7%.

Imaging examinations

(1) Chest CT image at admission shows a lesion in the lingual segment of the upper lobe of the left lung (arrows); and (2) A follow-up cerebral contrast-enhanced MRI shows diffuse and linear enhancement along the surface of the cerebrum (arrows).

FINAL DIAGNOSIS

Based on these findings, a diagnosis of LM carcinomatosis of EGFR-Thr790Met-positive lung adenocarcinoma (cT3N3M1b: stage IVA) was established.

TREATMENT

Neither surgery nor chemotherapy was applied to the patient due to osseous metastasis. In addition, surgery could not achieve a radical cure. Hence, osimertinib (80 mg/d) was given as a second-line treatment.

OUTCOME AND FOLLOW-UP

The patient showed a good response within a month. What's more, the patient's headache and symptoms of intracranial hypertension disappeared rapidly after 3 days of osimertinib treatment. After discharge, osimertinib (80 mg/d) was continued, and the patient was closely followed-up. There were no obvious toxic or adverse side effects except for diarrhea and leukopenia. The lung lesion continued to

shrink by the 6-month follow-up CT, and the intracranial pressure returned to normal without the patient experiencing a headache.

DISCUSSION

Patients with NSCLC and LM carcinoma have a poor prognosis. Early diagnosis and an appropriate treatment regimen are important to improve the prognosis. The analysis of ctDNA in CSF can be used to detect nervous system tumors and their drug resistance mechanism[8]. According to previous studies, EGFR-TKIs are effective in patients diagnosed with NSCLC and LM carcinoma with positive EGFR mutations[9]. Osimertinib has been reported to be more effective due to its better blood-brain barrier permeability[7]. This report shows a great clinical benefit of osimertinib in LM patients with positive detection of the EGFR-Thr790Met mutation in their CSF. Interestingly, the cytology in CSF and neuroimaging were all negative at the beginning, and when the patient's imaging turned positive, the result of CSF cytology examination was still negative one month after the EGFR-Thr790Met mutation was detected in CSF. Hence, we propose that the positive findings of CSF ctDNA as a liquid biopsy technology based on the detection of cancer-associated gene mutations may appear earlier than the imaging findings and the CSF findings and could thus be more helpful for therapy. Moreover, the character of this report is that headache is the chief complaint of the patient with lung cancer. The patient's initial outpatient cranial MRI and lumbar puncture showed no abnormalities in CSF biochemistry and cytology, except for elevated intracranial pressure. The patient's lung lesion was found due to the routine screening of chest CT with novel coronavirus. Just as the old saying goes, 'there is no great loss without some small gain'.

CONCLUSION

This report shows a great clinical benefit of osimertinib in LM patients with positive detection of the EGFR-Thr790Met mutation in CSF and proposes that the positive findings of CSF circulating tumor DNA as a liquid biopsy technology based on the detection of cancer-associated gene mutations may appear earlier than the imaging findings, and the CSF findings and could thus be helpful for therapy. Moreover, the routine screening of chest CT with the novel coronavirus may provide unexpected results.

FOOTNOTES

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