



HER2 exon 20 insertion mutations in lung adenocarcinoma with leptomeningeal metastasis: a case report and response to poziotinib

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Abstract: Leptomeningeal metastasis (LM) is associated with poor prognosis and represents a terminal event of non-small cell lung cancers (NSCLC). In previous studies, most of LM-patients have detected epidermal growth factor receptor (EGFR) mutation and responded to the third generation of EGFR-tyrosine kinase inhibitor (TKI). This study aimed to report a case of ERBB2 (HER2) exon 20 insertion mutations in the cerebrospinal fluid (CSF) of LM-patient which response to poziotinib. At the beginning, postoperative pathology showed a primary invasive adenocarcinoma with no mutations in EGFR and ROS-1. Pemetrexed plus carboplatin combined with bevacizumab was administered as the first-line followed by bevacizumab alone for continuation maintenance therapy. Targeted therapy and immunotherapy were given after the disease progressed in two months. Subsequently, the patient developed mental symptoms and adenocarcinoma cells were found in the CSF. Next-generation sequencing (NGS) results showed HER2 exon 20 insertion mutations in the primary tissue, CSF and plasma samples. Then, poziotinib was administered and the symptoms improved significantly after 3 days and the progress free survival was nearly 2 months. Therefore, we speculate that the CSF concentration and penetration rate of poziotinib may significantly higher than of other TKIs so that it achieves a higher CSF concentration than standard dosing, and successfully controlled LM. It may provide a new therapeutic option for LM-patient and may be especially who are lung adenocarcinoma with HER2 exon 20 insertion.

Keywords: Leptomeningeal metastasis (LM); cerebrospinal fluid; HER2 exon 20 insertion mutations; poziotinib; case report

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Introduction

Leptomeningeal metastasis (LM) is a specific type of neurological metastasis of lung cancer. Meningeal metastasis occurs in 3% to 5% of patients and are associated with a

dismal prognosis (1). Due to the existence of the blood-brain barrier, it is difficult for traditional chemotherapeutic drugs to enter the space between the pia mater and brain parenchyma. Patients with LM usually have a poor

prognosis and the 1-year survival rate is less than 10% (2). However, with the advent of the era of precision therapy, the overall survival of non-small cell lung cancer (NSCLC) patients with targeted gene mutations has been improved. Tyrosine kinase inhibitor (TKI) provides significant clinical benefits for most cancer patients with “classic” sensitized mutations (including deletions in exon 19 and the mutation encoding p.L858R). LM is more common in people with EGFR mutations than wild-type epidermal growth factor receptor (EGFR) mutations in lung adenocarcinoma (3) and about 43–70.5% LM-patient are EGFR-sensitive mutations (4–6). EGFR-TKIs is one of the predictors of good prognosis for LM-patients (7) and can prolong the survival time of LM-patients with EGFR positive (5,6,8). Human epidermal growth factor receptor 2 (HER2/ERBB2) as a target remains poorly described, partly because of its lower incidence occurring in 1.7–3.33% without potent targeted therapies among reported lung cancer biomarkers (9–11). In this study, HER2 exon 20 insertion mutations were found in LM-patient of the lung adenocarcinomas and sensitive to poziotinib. We present the following article in accordance with the CARE reporting checklist (available at <https://apm.amegroups.com/article/view/10.21037/apm-21-213/rc>).

Case presentation

A 55-year-old male with a history of smoking developed chest tightness in March 2016. Chest computed tomography (CT) scan showed nodules in the left lung's lower lobe (*Figure 1A*). Postoperative pathology showed a mass of about $2.1 \times 1.6 \times 1.6 \text{ cm}^3$ of invasive adenocarcinoma (*Figure 1B*) in the lower lobe of the left lung. The immunohistochemical (IHC) analysis revealed positive staining for thyroid transcription factor-1 (TTF-1) and napsin A and negative for p40, CK5/6, VIM, and LCA. Two genes include EGFR and ROS-1, were detected for ARMS method and mutations were not detected. Then he received vinorelbine combined with carboplatin (NC regimen) for four cycles, and the progression-free survival time (PFS) was 10 months. The patient developed disease progression in March 2017. Positron emission computed tomography (PET-CT) showed bilateral pulmonary fibrous hyperplasia, enlarged lymph nodes adjacent to the left pulmonary artery in the mediastinum, and left adrenal metastasis. Pemetrexed plus carboplatin (AC regimen) combined with bevacizumab for four cycles was initiated on March 29, 2017. However, the patient could not tolerate the adverse reactions caused by chemotherapy due to the poor physical

condition. Therefore, pemetrexed was discontinued then followed by 12 cycles of bevacizumab alone for continuation maintenance therapy (CMT). The disease progressed again after 1 year. Chest and upper abdominal CT examination showed an enlargement of mediastinal and left supraclavicular lymph nodes, thickening of the right pleura, and metastasis of the liver left adrenal nodules, and the bone (*Figure 1C*). The patients were treated with anlotinib for 1 month, and then switched to afatinib for 1 month. In August 2018, the patient received immunotherapy with pembrolizumab for one cycle and then changed to anlotinib combined with nivolumab for three cycles. However, the CT of September 27, 2018 showed that although the left pleural multiple plaques with left pleural effusion was not enlarged, the multiple miliary foci of the lung, left hepatic metastatic lesion, and systemic multiple bone metastatic lesions were significantly increased than before medication (*Figure 1D*). Furthermore, the patient developed mental symptoms of depression and intermittent aphasia with short-term speech loss after 1 month. Adenocarcinoma cells (*Figure 1E*) were found in the cerebrospinal fluid obtained by lumbar puncture. Magnetic resonance imaging (MRI) on October 29, 2018 indicated abnormal enhancement on the surface of the left frontal-parietal lobe and metastatic tumors (*Figure 1F*). Targeted next-generation sequencing (NGS) of the primary lung tumor and the cerebrospinal fluid (CSF) are shown in *Table 1* and *Figure 2*. The patient was treated with poziotinib on October 30, 2018. The symptoms improved significantly after 3 days and no serious adverse events were observed during the oral administration of poziotinib. Unfortunately, the disease aggravated again at the end of December 2018. Then, therapy was discontinued and supportive care was given and the patient died on January 17, 2019. This case report was approved by the Medical Ethics Committee of Zhejiang Cancer Hospital (IRB-2019-9).

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

The question of poor prognosis in LM-patients has

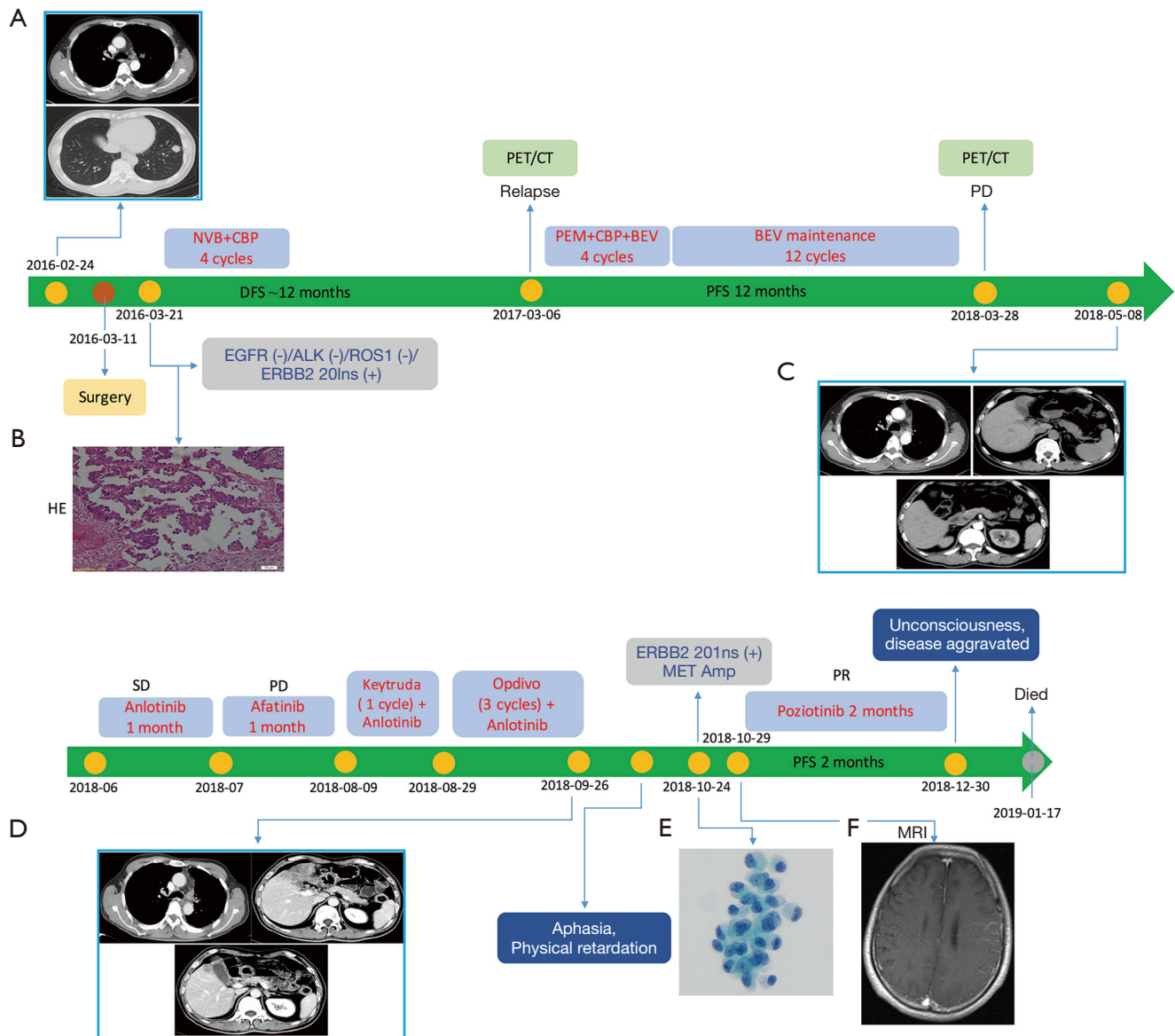


Figure 1 The flow chart of diagnosis and treatment of the patient. Computed tomography (CT) shows a 2.1×1.6×1.6 cm³ mass in the lower lobe of the left lung (A). Hematoxylin-eosin staining for the lung tissue specimen demonstrated adenocarcinoma (B). CT shows the mediastinal and left supraclavicular lymph node enlargement, right pleural thickening, and liver, left adrenal, and bone metastasis (C). CT shows significantly increase in the multiple miliary foci of the lung, left hepatic metastatic lesion, and systemic multiple bone metastasis lesion (D). Adenocarcinoma cell in cerebrospinal fluid (40× objective lens under microscope, Routine Pap staining) (E). MRI shows left frontal and parietal lobe metastases (F). NVB, vinorelbine; CBP, carboplatin; PEM, pemetrexed; BEV, bevacizumab; Ins, insertion; amp, amplification; DFS, disease-free survival; PFS, progression-free survival; PD, progressive disease; PR, partial response; SD, stable disease; MRI, magnetic resonance imaging.

become a major issue. Although many techniques have been developed, the next generation sequencing (NGS) of the cerebrospinal fluid (CSF) plays a significant role in the accurate diagnosis, classification, and follow-up treatment

of LM-patients (12). The cell-free DNA (cfDNA) of CSF has a unique gene mutation map compared with plasma and primary tissue. In our case, many CNVs were detected in the CSF cfDNA, which were not identified in the

Table 1 NGS results of different times and locations during the disease course of the patient

Gene name	Mutation type	Variation	Tissue (2018-04)	CSF (2018-10)	Plasma (2018-10)
			VAF/Change-fold	VAF/Change-fold	VAF/Change-fold
<i>ERBB2</i>	Inframe_insertion	c.2313_2324dupGCATACGTGATG (p.Y772_A775dup)	16.9%	44.1%	22.8%
<i>TP53</i>	Frameshift	c.310_311insGAAAACCTACC (p.Q104fs*23)	16.2%	97.6%	46.1%
<i>TP53</i>	Missense	c.A299C (p.Q100P)	19.9%	97.6%	46.1%
<i>TP53</i>	CNV	One copy loss	WT	0.6-fold	WT
<i>MET</i>	CNV	Amplification	WT	2.3-fold	1.4-fold
<i>EGFR</i>	CNV	Amplification	WT	2.0-fold	1.6-fold
<i>HGF</i>	CNV	Amplification	WT	2.1-fold	WT
<i>CDK4</i>	CNV	Amplification	WT	2.0-fold	WT
<i>RB1</i>	CNV	One copy loss	WT	0.5-fold	WT

NGS, next-generation sequencing; CNV, copy number variation; WT, wild type.

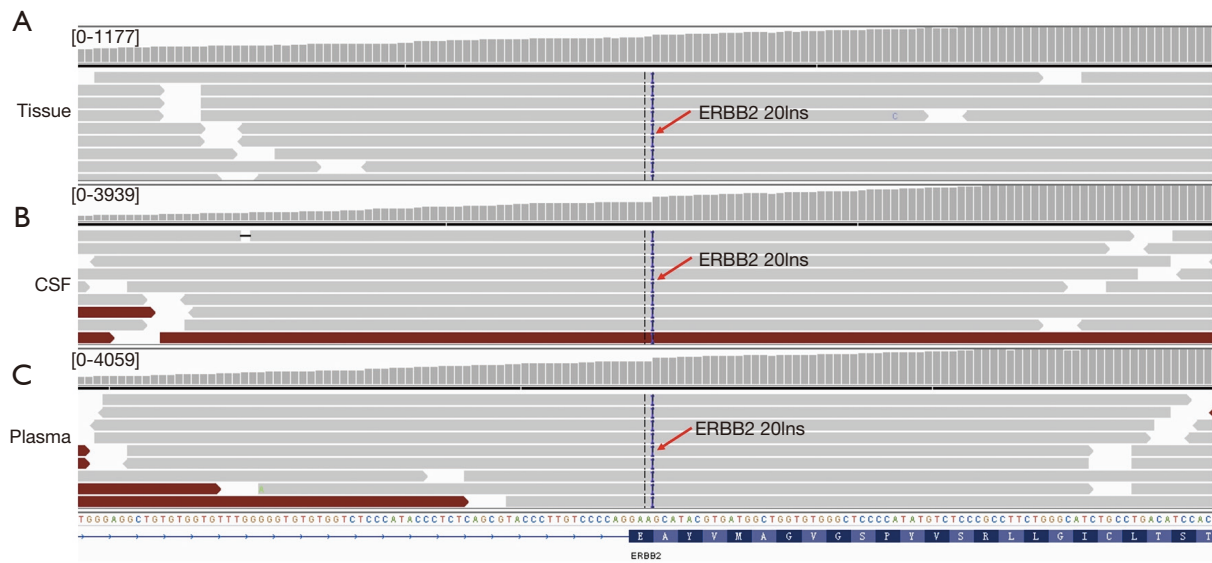


Figure 2 Visualization of ERBB2 20Ins in the case using the Integrative Genomics Viewer (IGV). IGV display of ERBB2 20Ins in the primary tissue, cerebrospinal fluid, and plasma samples. IGV display of ERBB2 20Ins in the primary tissue (A). IGV display of ERBB2 20Ins in the cerebrospinal fluid (B). IGV display of ERBB2 20Ins in the plasma samples (C).

primary tissue or plasma, which was consistent with the previous study (13). MET amplification and TP53 deletion was also detected indicating that there may be a more complex mechanism of CSF resistance in LM-patients. The evolution of CNVs may be caused by the genomic instability processes at the chromosomal and mutational levels and even key mutations that predominate in LM-

patients (14).

Immunotherapy has been shown to improve survival in patients with NSCLC. Check point inhibitors, nivolumab and pembrolizumab, are recommended as a second line for advanced or metastatic NSCLC. However, there is a great deal of evidence that the patients with EGFR oncogene mutations benefits less from immunotherapy (15-18).

In addition to EGFR mutations, ERBB2 activation mutations play a previously unknown role in promoting drug resistance to ICI therapy (19). Patients with EGFR disease and ERBB2 activation mutation who received immunotherapy were negatively correlated with survival time, and their median PFS was lower than that of patients with wild-type gene (log rank $P=0.0023$) (20). Li *et al.* (21) reported that none of the seven patients with HER2 mutant NSCLC achieved a response to prior PD-1 inhibitors, which was similar to our patient.

Targeted therapies are highlighted in this small cohort of patients with HER2 exon 20 insertion mutations. The symptoms of LM were relieved rapidly after 3 days of administration of poziotinib and the PFS was nearly 2 months. The patient might derive more clinical benefit if he was treated at an earlier point of the disease course with a better performance status suggesting its specific clinical effect on LM-patients with ERBB2 20 exon insertion. Thus, poziotinib has a unique clinical effect on LM patients with ERBB2 exon 20 insertion. What's more, poziotinib is a potent tyrosine kinase inhibitor (TKI) of EGFR and HER2 exon 20 insertion mutants (22,23). In a phase II trial of poziotinib, the objective response rate (ORR) of 11 NSCLC patients with EGFR exon 20 mutations was 64% and the median progression-free survival (PFS) duration had not been reached at 6.6 months. These results contrast with ORRs of <10% and PFS durations of <2 months observed when such patients have received approved EGFR TKIs (24). In a phase II study of poziotinib (25), the disease control rate (DCR) was 68.7% and the mPFS was 4.2 months of 115 NSCLC patients with EGFR20 exon insertion mutation. More importantly, the ORR was 8.3% in patients with brain metastasis and 15.5% in patients without brain metastasis.

Nevertheless, there is no report and relevant clinical data analysis about LM-patient with Her2 mutant treated with poziotinib. Previous studies have shown that erlotinib can be more effective for LM than gefitinib due to its higher CSF concentration (26) and the clinical symptoms was obviously improved by using high- dose erlotinib pulse therapy (27,28). Thus, the therapeutic effect can be expected if sufficient TKIs concentration can be achieved in CSF. The CSF concentration and penetration rate of poziotinib may significantly higher than of other TKIs so that it achieves a higher CSF concentration than standard dosing, and successfully controlled LM. However, the CSF concentrations of poziotinib and other TKIs have never been directly compared.

To conclude, this is the first report of a LM-patient who harbored HER2 exon 20 insertion mutations and response to poziotinib. Poziotinib may provide a new therapeutic option for LM-patient and may be especially who are lung adenocarcinoma with HER2 exon 20 insertion. The specific mechanisms keep unclear and large prospective studies should be performed.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at <https://apm.amegroups.com/article/view/10.21037/apm-21-213/rc>

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at: <https://apm.amegroups.com/article/view/10.21037/apm-21-213/coif>). All authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This case report was approved by the Medical Ethics Committee of Zhejiang Cancer Hospital (IRB-2019-9). All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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