Case Report

Successful treatment using targeted therapy, radiotherapy, and intrathecal chemotherapy in a patient with leptomeningeal metastasis with an epidermal growth factor receptor exon 20 insertion mutation: a case report

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Abstract: Leptomeningeal metastasis (LM) is a disastrous complication in lung cancer. LM patients with oncogene-addicted non-small cell lung cancer (NSCLC) have a relatively better prognosis than those with the wild-type counterpart; however, overall post-LM survival is short. Additionally, the high heterogenicity of the LM entity creates a treatment challenge, and to date, no standard strategy has been established. This article describes a female lung adenocarcinoma patient with a resistant epidermal growth factor receptor (EGFR) exon20ins mutation who developed LM only 11 months after radical surgery IIIA (pT1bN2). Intrathecal chemotherapy (ITC), whole-brain radiotherapy (WBRT) with a simultaneous integrated boost (SIB) followed by Osimertinib was initiated. The cerebrospinal fluid (CSF) cytology turned negative. The first remission lasted 6 months, then bone metastases occurred, and the LM progressed. An Ommaya reservoir was implanted. ITC with pemetrexed and anlotinib was administered. A CSF next-generation sequencing (NGS) examination revealed EGFR exon20ins (p. A767_V769 dup 1.5%), which was different from that of the primary tumor (p. V769_D770 ins ASV 17.48%). The CSF cytology then turned negative again; however, the patient succumbed to the disease in December 2020. The patient's post-LM overall survival (OS) time was 13.5 months. This case is novel and of great value. Clinicians should pay special attention to populations at high risk of developing LM. Early detection followed by active intervention, including ITC, RT, and systemic treatment, will result in a better prognosis. The NGS of CSF is fundamental to understanding the genetic profiles of LM and providing effective and precise treatment.

Keywords: Leptomeningeal metastasis (LM); EGFR exon20ins mutation; Osimertinib; radiotherapy; case report

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Introduction

Since the epidermal growth factor receptor (EGFR) exon20ins mutation was first described in non-small cell lung cancer (NSCLC) in 2004 (1,2), over 100 potential mutations have been identified (3). This highly heterogeneous structure displays diverse biological behaviors and different responses to targeted therapy (4). With the exception of A763_Y764insFQEA (1,5), the EGFR exon20ins mutation was viewed as *de novo* resistant to tyrosine kinase inhibitors (TKIs) (4), and conventional chemotherapy (CT) has been the mainstay of its management. Additionally, leptomeningeal metastasis (LM) remains challenging to treat, despite modern strategies that have improved patients' overall survival (OS) time from 1–3

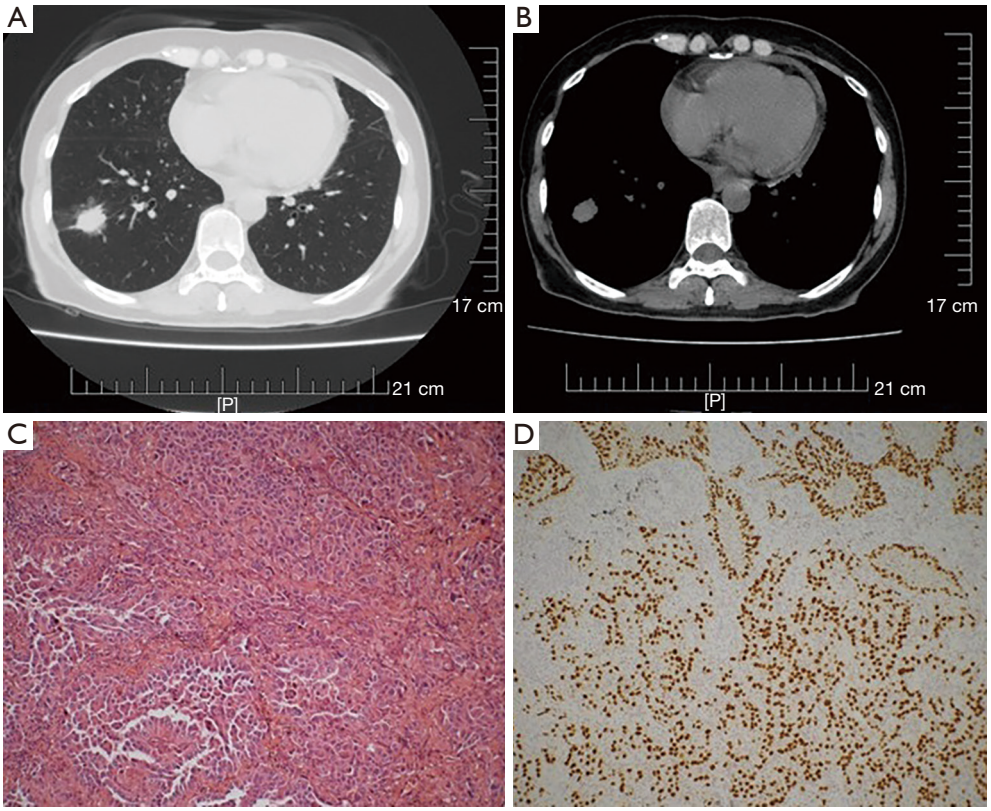

Figure 1 The thoracic CT and pathological results of the primary lung tumor. (A,B) A typical image of the initial thoracic CT (12/04/2018) scan showed an abnormal lump measuring about 1.9 cm ×1.5 cm located in the lower lobe of the right lung (A. lung window; B. mediastinal window). (C,D) Postoperative pathology results showed invasive pulmonary adenocarcinoma (HE staining: C. upper right part-solid type, Lower left part-papillary type, original magnification ×100; D. TTF-1: IHC+, original magnification ×100).

to 3–11 months (6,7). Brastianos *et al.* revealed that in 53% of patients with brain metastasis (BM), a specific genetic alternation developed in the BM was not detected in the matched primary tumor (8). Cerebrospinal fluid (CSF) next-generation sequencing (NGS) also documented different genetic landscapes, such as less T790M and mesenchymal-to-epithelial transition (MET) activation by MET copy number gain (9,10). Thus, CSF NGS provides valuable information for treating these 2 difficult problems clinically. The patient in this case presented with aggressive LM with an EGFR exon20ins mutation. The following case is presented following the CARE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-21-321/rc).

Case presentation

A 56-year-old female non-smoker presented in November 2018 after a lump located in the lower lobe of the right lung (see *Figure 1A*,*1B*) and enlarged mediastinal lymph nodes were found in a routine physical examination. The initial evaluations of the patient's abdomen, bone, and brain were unremarkable. The patient's clinical-stage was IIIA cT1bN2M0. Radical surgery was performed on the patient. The patient's postoperative pathology showed an invasive adenocarcinoma of 1.8×1.8×1.5 cm (solid type: 70%; papillary type: 30%) (see *Figure 1C*,*1D*) with multiple mediastinal lymph node involvement (stations: 2: 2/2; 3: 6/8; 3p: 1/1; 4: 2/2; 7: 3/7). The patient's final pathological stage was III A (T1bN2). The EGFR mutation assessment revealed an EGFR exon 20 insertion mutation without an anaplastic lymphoma kinase (ALK) rearrangement and ROS1 fusion. According to the International Adjuvant Lung Cancer Trial (IALT), cisplatin-based chemotherapy brought both 5-y OS (45% *vs.* 40%, P<0.03) and 5-y DFS (39% *vs.* 34%, P<0.003) benefit comparing with

observation in completely resected stage I-III NSCLC (11). Lung Adjuvant Cisplatin Evaluation (LACE) Collaborative Group (a meta-analysis of 4584 patients) also verified a 5-year OS improvement (a 5.4% absolute benefit) following postoperative cisplatin-based CT (12). Further, the TREAT study showed that cisplatin/pemetrexed was a less toxic regimen than cisplatin/vinorelbine and had similar efficacy in completely resected stage IB–III NSCLC patients. Thus, patients could endure more cycles of CT with cisplatin/pemetrexed (13,14). A series of studies have demonstrated that postoperative radiotherapy (RT) improves the survival of stage III–pN2 NSCLC patients (15-17), especially among those with a high metastatic mediastinal lymph node ratio (MLNR) ≥50% (18,19). The patient was at pathological stage III A (pT1bN2). Based on the positivity of the highest resected mediastinal lymph node and a MLNR of 70%, the patient was given postoperative CT and RT. Specifically, the patient underwent 4 cycles of adjuvant CT (PC: Pemetrexed, Carboplatin) followed by thoracic irradiation (50.4 Gy/28 f/44 d, 4/15/2019-5/22/2019) and 2 more cycles of PC CT.

On May 24, 2019, brain magnetic resonance imaging (MRI) with contrast was performed, and metastasis was excluded. In September, the patient suffered from mild headaches and dizziness for a week. On September 18, 2019, another brain MRI with contrast was performed, and 3 metastatic lesions about 0.3–0.4 cm located in the bilateral frontal lobes and the right temporal lobe were found (see *Figure 2A-2C*). Temozolomide (TMZ) was able to cross the blood-brain barrier. A meta-analysis showed that the addition of TMZ to whole-brain radiotherapy (WBRT) resulted in an increased overall response rate (ORR) among NSCLC patients with BM compared to those treated with WBRT alone (11). The tertiary hospital initiated TMZ for 1 cycle (TMZ 200 mg d1–5). However, the patient's brain MRI with the contrast of October 27, 2019, showed an enlargement of the BM above and the onset of the metastatic meningeal lesion (see *Figure 2D-2F*).

The CSF evaluation showed normal biochemical results except for a slightly increased leukocyte count of 11×10^6/L [0–8]; however, malignant cells were found. The NGS of the postoperative tumor tissue revealed an EGFR exon 20 insertion mutation (p. V769_D770 ins ASV: 17.48%), tumor mutational burden (TMB): 3.94 Muts/Mb, microsatellite stable (MSS), TP53 mutation: 4.71%. The PD-L1 expression of the primary tumor had a tumor proportion score (TPS) of 5%.

The patient underwent intrathecal chemotherapy (ITC) with methotrexate (MTX) 6 times (15 mg, 10/31/2019, 11/7/2019, 11/12/2019, 11/19/2019, 11/26/2019, 12/3/2019) and pemetrexed once (10 mg, 12/19/2019), and the CSF tumor cells turned negative (on December 19, 2019). The patient also received WBRT (40 Gy/2 Gy/20 f)and a tumor boost (56 Gy/2.8 Gy/20 f) from October 31, 2019, to November 27, 2019. With the contrast of December 5, 2019, the brain MRI showed a partial response (PR) by the BM and LM lesions (see *Figure 2G-2I*). Osimertinib 80 mg daily was initiated from December 8, 2019.

On June 12, 2020, the patient was referred to our department as she experienced pain and numbness in both lower limbs for 2 weeks. The subsequent lumbosacral spine MRI scan revealed multiple metastases from lumbar 3 to sacral 2 vertebrae, appendages, and bilateral iliac bones. A bone scan also manifested increased radioactivity on the 9th right rib, lumbar 3–5 vertebrae, sacrum, and left iliac bone, which was considered bone metastasis. The brain MRI with a contrast of June 16, 2020, showed lesions in the bilateral frontal lobes, right temporal lobe, and the meninges of the right frontal lobe had disappeared. Anlotinib (10 mg/d) was administered for less than 14 days and then suspended due to nausea. RT to the lumbosacral and pelvic bone metastases was performed with a dose of 50 Gy/2 Gy/25 f from June 23, 2020, to July 30, 2020. Bisphosphate was administered monthly, and the patient's pain was greatly relieved. After that, the patient suffered from vulvar infection, which resolved after anti-inflammatory and symptomatic supportive treatment.

On August 19, 2020, the patient complained of a headache. A cranial CT scan excluded encephalorrhagia. The CSF evaluation of August 21, 2020, showed adenocarcinoma cells again just as on October 28, 2019, the baseline CSF smear demonstrated malignant cells (see *Figure 3*). The subsequent brain MRI with contrast revealed abnormal thickening and an enhanced cerebellar pial membrane (see *Figure 4*). An intraventricular Ommaya reservoir was implanted, and pemetrexed was administered 6 times (15 mg on 8/28, 9/11, 9/20, 9/27, 10/5, and 10/20) via the Ommaya reservoir, and resulted in negative CSF cytology. Anlotinib (10 mg/d) was administered on August 23, 2020. The CSF NGS examination of October 9, 2020 showed a different EGFR exon20ins (p. A767_V769 dup: 1.5%) and *TP53* mutation (0.3%). The patient succumbed to the disease on December 7, 2020. The patient's OS time after LM diagnosis was 13.5 months (see *Figure 5*).

All the procedures in this study involving the human participant were performed following the ethical standards

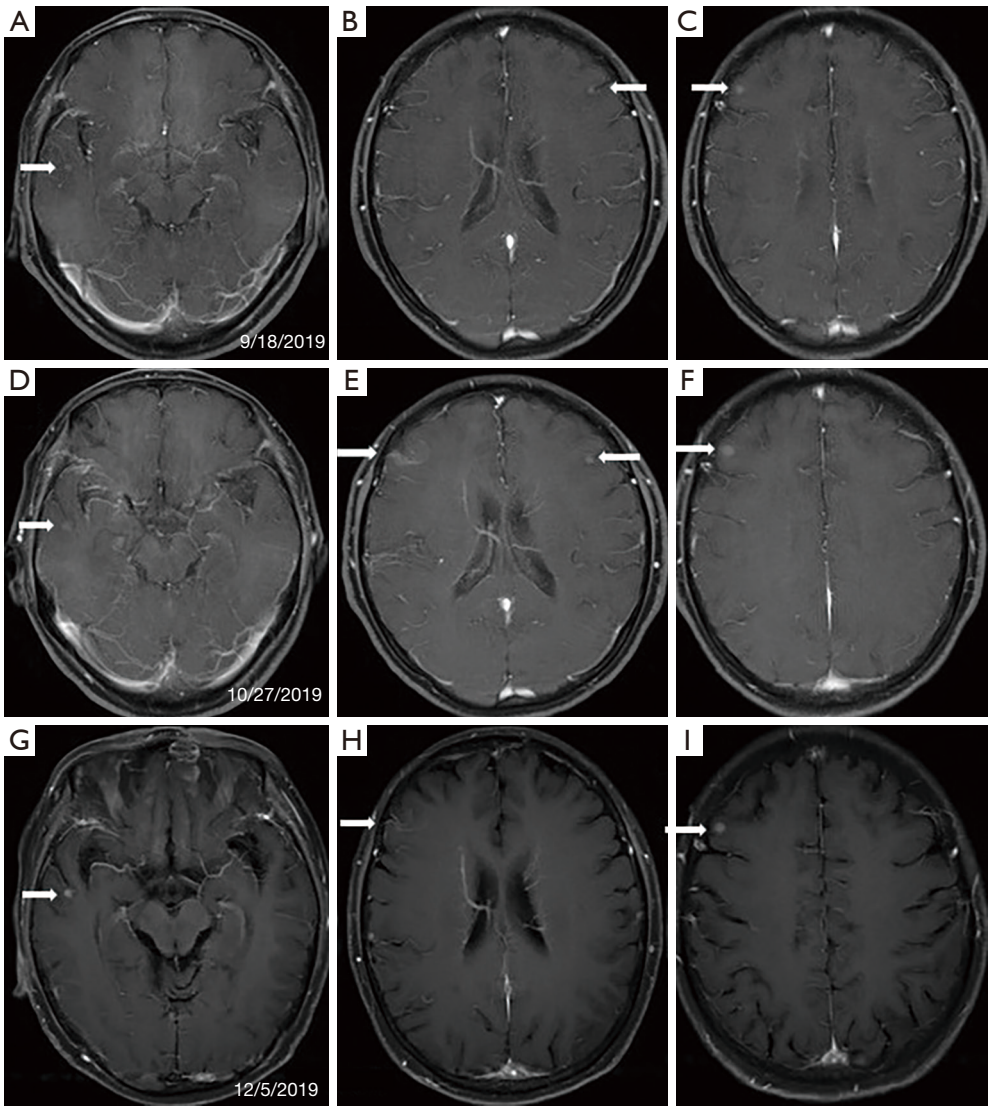

Figure 2 The status of BM and LM lesions before and after WBRT with a SIB. (A-C) Brain MRI with contrast on September 18, 2019, revealed 3 metastatic brain lesions about 0.3–0.4 cm located in the bilateral frontal lobes and the right temporal lobe (as indicated by the white arrows). (D-F) Brain MRI with contrast on October 27, 2019, showed an enlargement of the BM above and the onset of a metastatic meningeal lesion. (G-I) Brain MRI with contrast on December 5, 2019, showed a PR of BM and LM lesions after ITC with MTX 15 mg for 6 times and WBRT with a SIB. BM, brain metastases; LM, leptomeningeal metastasis; WBRT, whole-brain radiotherapy; SIB, simultaneous integrated boost; MRI, magnetic resonance imaging; PR, partial response; ITC, intrathecal chemotherapy; MTX, methotrexate.

of the institutional and/or national research committee(s) and the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's son to publish this manuscript and the accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

LM is generally considered a fatal and disastrous condition in lung cancer. Patients with EGFR-mutated lung cancer have a higher incidence of LM than their EGFR wild-type counterparts (9.4% *vs.* 1.7%) (7). How to screen populations

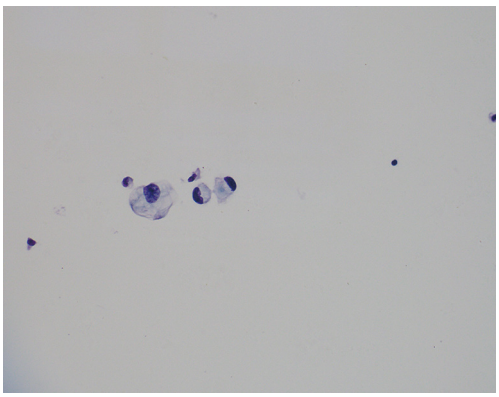

Figure 3 A baseline CSF smear demonstrated malignant cells on October 28, 2019 (Pap staining, ×40). CSF, cerebrospinal fluid.

at high risk of developing LM is critical to clinical decision-making. The precise determination of the related "high-risk" factors will guarantee close follow-up appointments, timely examinations, and the early detection and correct management of this special entity. Boire *et al.* revealed that the complement component 3 (C3) pathway played a key role in LM. Cancer cell-derived C3 disrupted the blood-CSF barrier by activating the C3a receptor located in the epithelium of the choroid plexus (12).

The EGFR exon20ins mutation accounts for approximately 3.6–13% of all EGFR mutations (4,13-16). EGFR exon20ins mutations have various subtypes, most of which are resistant to first- and second-generation EGFR

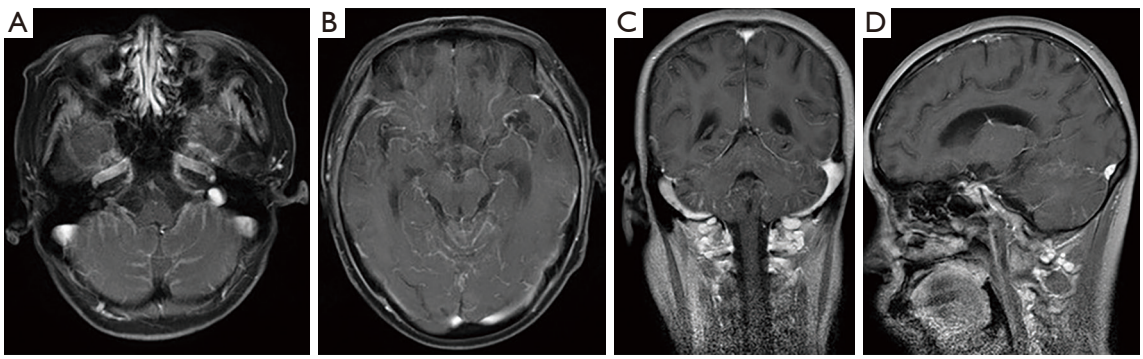

Figure 4 A typical MRI image (8/27/2020) indicated obvious LM progression. (A,B) Transverse view, (C) coronal view, (D) sagittal view. MRI, magnetic resonance imaging; LM, light microscope.

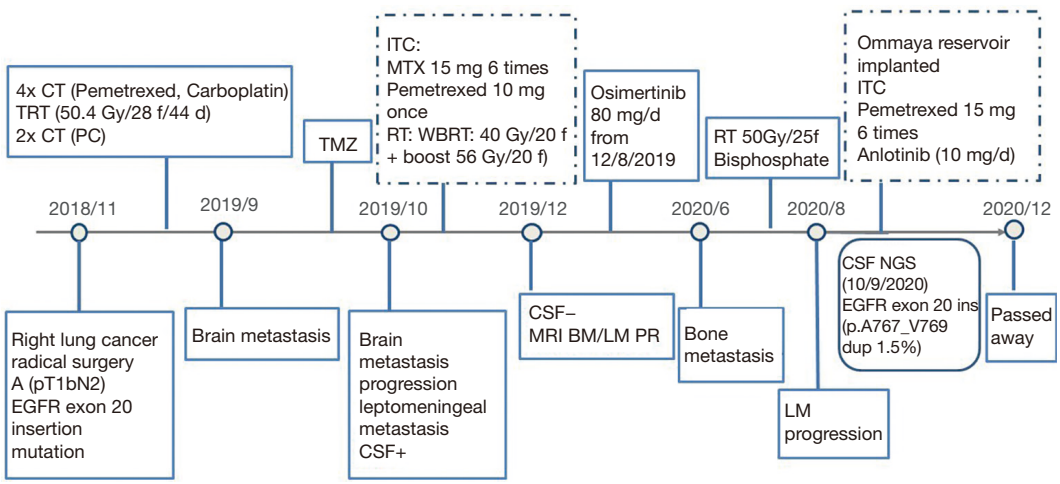

Figure 5 The timeline for the diagnosis, treatment, and outcome for this patient. TRT, thoracic radiotherapy; ITC, intrathecal chemotherapy; MTX, methotrexate; TMZ, temozolomide; RT, radiotherapy; EGFR, epidermal growth factor receptor; CSF, cerebrospinal fluid, MRI, magnetic resonance imaging; BM, brain metastases; LM, leptomeningeal metastasis; PR, partial response; NGS, next-generation sequencing.

TKIs (14) (except the EGFR A763_Y764insFQEA). According to a report by Fang *et al.*, A767_V769dup is the most common EGFR exon20ins type and comprises 32.1% (17/53) of all EGFR exon20ins (17). Additionally, EGFR exon20ins appear to be exclusive with other important driver genes, including *ALK*, *BRAF*, *RET*, and *ERBB2* (17). *TP53* is a common co-mutation (49.1%) (17). In our patient, the NGS of the primary tumor revealed an EGFR exon20ins mutation (p. V769_D770 ins ASV: 17.48%) with a *TP53* mutation (4.71%). The CSF NGS showed different EGFR exon20ins (p. A767_V769 dup: 1.5%) and *TP53* mutations (0.3%).

CSF NGS is fundamental in diagnosis, gene landscaping, determining treatment options, and evaluating responses. The circulating tumor cells (CTC) in CSF have a sensitivity of 94%, which is higher than that of cytology, which has a sensitivity of 76% (18). Thus, CSF CTC can be used to identify patients with LM more accurately (18).

Liu *et al.* described a stage IV NSCLC patient with BM with EGFR exon21 L858R, who developed LM after the first-line treatment of icotinib. Osimertinib was then initiated for acquired T790M. However, after 9 months of Osimertinib treatment, the LM had progressed. Further, the CSF NGS revealed an L718Q mutation. The switch to afatinib correspondingly controlled the disease for 4 months (19). In our patient, the CNS NGS revealed a different EGFR exon20ins variant (p. A767_V769 dup: 1.5%) from that of the primary tumor (p. V769_D770 ins ASV: 17.48%). This emphasizes the importance of liquid biopsies of CSF NGS for the precise management of LM, as tumor cells mutate genetically to adapt to new microenvironments. The management of the EGFRexon20ins mutation is challenging, and to date, no standard has been established. van Veggel *et al.* found that the intensification of the EGFR blockade by afatinib and cetuximab in 4 patients harboring the EGFRexon20ins mutation achieved a PR in 3 patients and a stable disease (SD) response in 1 patient, and a median progression-free survival (PFS) time of 5.4 months. However, the common side effects, such as skin toxicity and diarrhea, caused by both afatinib and cetuximab add up, and a dose reduction was required in 2 patients (20).

The third-generation EGFR TKI-Osimertinib has shown certain efficacy concerning the EGFRexon20ins mutation in preclinical models (21). According to a retrospective study of 6 patients with EGFR exon20ins mutations, the administration of 80 mg of Osimertinib daily achieved a PR in 4 patients (p. A767_V769dup: 3.48%; p. S768_D770dup: 1.75%; p. D770_N771insG: 24%; p. A763_Y764 ins FQEA: 0.2% with T790 M: 0.3%) and a SD response in 2 patients (p. N771_P772insL: 47%; p. S768_D770dup: 3%) with a median PFS time of 6.2 months (17). Floc'h *et al.* established CRISPR-Cas 9 engineered cell lines with common EGFR exon20ins mutations (D770_N771InsSVD or V769_D770InsASV) and verified the efficacy of Osimertinib *in vitro* and *in vivo* xenograft models (3). Poziotinib, a potent inhibitor of the EGFR and HER2 exon 20 mutation, had an ORR of 64% (22). The Hsp90 inhibitor Luminespib can degrade EGFR exon 20 mutations (23) and showed a 17% ORR in a phase II trial of NSCLC patients carrying the EGFR ins20 (24). TAS6417/CLN-081 had better efficacy for EGFR exon20ins mutations than Poziotinib (25). Based on the availability of agents, our patient was treated with Osimertinib combined with ITC, RT, and anti-angiogenesis drugs and achieved a 13.5-month OS.

In the management of LM, local RT aims to control bulky or nodular lesions, correct CSF flow, helping ITC to exert the effect (9). Presently, there is no consensus about the role of WBRT in LM (9), especially in the oncogene-addicted population with CNS-potent target agents. In their report, Li *et al.* found that the addition of WBRT failed to add any survival benefits to LM patients harboring EGFR common mutations who received TKI alone (7). Yan *et al.* found no difference in intracranial ORR and DCR between a WBRT and non-WBRT group in 51 EGFR-mutated LM NSCLC patients (19del: 20; 21 L858R: 31) (26). Morris *et al.* reviewed 125 NSCLC patients who developed LM (9: known EGFR mutation) but found no survival difference between WBRT (n=46) and non-WBRT patients (n=59; P=0.84) (27). Conversely, Liao *et al.* revealed that WBRT was an independent factor for a better prognosis among LM patients (28). Wu *et al.* performed a single institutional analysis of 420 patients who had received first-generation EGFR TKI over 6 months and found that 29 of the 420 patients suffered from LM after a median duration of 16.5 months. Multivariate analysis indicated that WBRT was associated with improved OS (P=0.048) (29). Given the rapid progression of LM and the unavailability of other target agents, including Poziotinib, TAK788, WBRT (40 Gy/20 f) with a simultaneous integrated boost (SIB) (56 Gy/20 f) followed by Osimertinib was initiated. Radical local treatment (WBRT with a SIB) controlled the LM to a certain extent. Concurrent ITC with 15 mg of MTX (6 times) and 10 mg Pemetrexed (once) led to CSF cytological negativity.

The intraventricular Ommaya reservoir provides better CT agent distribution and is safer and more convenient

than a conventional lumbar puncture (30). ITC with pemetrexed exerted a certain efficacy in NSCLC patients with LM, especially those resistant to TKIs (31). Miao *et al.* reported that intrathecal pemetrexed–based multimodal treatment provided reasonable control of refractory LM with tolerable toxicity (32). Anlotinib, as a novel multitarget TKI for tumor proliferative signal and anti-angiogenesis (VEGFR, PDGFR, FGFR, c-Kit) (33), might help to reverse treatment resistance partially. In a further analysis of ALTER0303 (34), anlotinib was shown to prolong the time to brain progression significantly. In the refractory LM setting, 15 mg of pemetrexed (6 times) was delivered by the intraventricular Ommaya reservoir with 10 mg of Anlotinib and 80 mg of Osimertinib (daily) turned the patient's CSF cytology negative again and further extended the patient's OS by 4 months.

The role of the immune checkpoint inhibitor (ICI) in LM has not yet been established. Only a few cases have reported on patients' responses to ICI in the LM setting (35). The NGS of the primary tumor showed MSS status, low TMB, and PD-L1 expression concerning our patient. Anti-inflammatory treatment was given to control the patient's vulvar infection. It is unlikely that the patient would have benefited from ICI.

Conclusions

In this article, we presented the case of a patient with refractory LM NSCLC harboring the EGFR exon20ins mutation. NGS of both the primary tumor and CSF enabled a systemic therapy to be tailored for the patient, and the multimodalities conferred a post-LM OS of 13.5 months. The findings, in this case, are noteworthy for clinicians. Further attention needs to be paid to populations at high risk of developing LM. It is strongly recommended that patients suffering from BM, especially those with indicative radiologic signs of LM, such as linear or nodular leptomeningeal enhancement, BM near the leptomeninges, brain ventricle or in the sulcus, undergo a liquid biopsy of CSF for early diagnosis, genetic profile identification, and a corresponding systemic therapy for LM. Additionally, multidisciplinary modality is vital for a better prognosis. MTX/pemetrexed delivered by the Ommaya reservoir, local RT, CSF NGS guided target therapy, and even ICI can prolong patients' survival significantly.

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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-21-321/rc

Peer Review File: Available at https://apm.amegroups.com/article/view/10.21037/apm-21-321/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-21-321/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work, including ensuring that all questions related to the accuracy or integrity of any part of the work have been appropriately investigated and resolved. All the procedures in this study involving the human participant were performed following the ethical standards of the institutional and/or national research committee(s) and the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's son to publish this manuscript and the accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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