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CASE REPORT

Three Novel *EGFR* Mutations (750_758del, I759S, T751_I759delinsS) in One Patient with Metastatic Non-Small Cell Lung Cancer Responding to Osimertinib: A Case Report

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Abstract: Generations of epidermal growth factor receptor tyrosine kinase inhibitors (*EGFR*-TKIs) can significantly improve the outcome of *EGFR*-positive NSCLC patients. However, acquired TKIs-resistant mutations are inevitable. Except the common *EGFR* alterations, more and more rare mutations are revealed by next-generation sequencing (NGS), the clinical significance of which are still unclear. Here, we report an advanced lung adenocarcinoma patient who harbored two novel *EGFR* exon 19 deletions (750_758del and I759S) at the beginning and exhibited a short response to icotinib for 7.0 months. Then, secondary resistance *EGFR* T751_I759delinsS occurred. Chemotherapy combined with bevacizumab and erlotinib was administered in turn but failed. Standard-dose osimertinib (80 mg daily) obtained durable clinical remission for 16 months, and high-dose osimertinib (160 mg daily) further prolonged the survival of 9 months after leptomeningeal metastases (LM) occurring. This study presented the first case of intractable terminal NSCLC in a patient with *EGFR* 750_758del, I759S and T751_I759delinsS mutations, who responded positively to osimertinib and achieved a prolonged OS of 52 months, providing a potential therapeutic option for the patients harboring these particular *EGFR* mutations.

Keywords: non-small cell lung cancer, *EGFR*, 750_758del, I759S, T751_I759delinsS, osimertinib

Introduction

About 48.0% of Asian patients with lung adenocarcinoma have active epidermal growth factor receptor (*EGFR*) mutations, which is higher than the population of Europe.[1] Generations of *EGFR* tyrosine kinase inhibitors (TKIs) can significantly improve the prognosis of patients with *EGFR*-positive NSCLC.[2] It has been reported that common *EGFR* alterations (ie, exon 19 deletion and exon 21 point mutation) approximately account for 85%, which can result in signal activation through modifying the spatial structure of enzyme functional domain.[3] However, an increasing number of rare *EGFR* mutations are revealed by next-generation sequencing (NGS), the clinical significance of which is still unclear and deserves more attention so as to choose the optimal treatment.[4] Herein, we report an advanced lung adenocarcinoma patient who harbored three novel *EGFR* exon 19 deletions (750_758del, I759S and T751_I759delinsS) and presented a durable response to osimertinib after the failure of icotinib and erlotinib treatment.

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Case Presentation

A 55-year-old Asian male with a smoking history was diagnosed with left upper lobe lung cancer by chest computed tomography (CT) in a regular medical examination in November 2015. The postsurgical pathology confirmed the stage IIIA (T3N1M0) lung adenocarcinoma. Adjuvant chemotherapy was applied with 4 cycles of gemcitabine and cisplatin. The disease was stable until July 2016, when positron emission tomography CT (PET-CT) scan revealed multiple enlarged right supraclavicular and mediastinal lymph nodes. Biopsy of the supraclavicular lymph node detected *EGFR* 750_758del and I759S in exon 19 with tumor protein tp53 gene (*TP53*) and AKT serine/threonine kinase 1 (*AKT1*) mutations (Figure 1). Icotinib 125mg three times daily was administrated followed by stereotactic radiotherapy to the mediastinum and supraclavicular (50 Gy in 2 Gy fractions). After 7 months, he experienced disease progression with intrapulmonary metastasis. NGS analysis of plasma samples was performed, and a rare mutation of *EGFR* T751_I759delinsS located in exon 19 was found (Figure 2), accompanied by *TP53* and *AKT1* mutation. Four cycles of pemetrexed, carboplatin and bevacizumab were administered, but multiple vertebral metastases were detected via MRI (Figure 3). So, the treatment with erlotinib (150 mg daily) was started in August 2017. However, brain metastasis was confirmed by MRI in January 2018 (Figure 4A). Repeating NGS with plasma detected *EGFR* T751_I759delinsS along with *TP53* and *AKT1* mutation. The therapy was switched to osimertinib at 80 mg daily, which decreased the levels of multi-tumor markers (Figure 5), and stabilized the lesions of brain (Figure 4B and C) and pulmonary (Figure 6) for 16 months. In June 2019, he showed symptoms of severe headache, nausea, weakness of the lower extremities and back pain, and leptomeningeal metastases (LM) was confirmed by the CSF cytology and MRI (Figure 7). Further NGS analysis of both CSF and plasma demonstrated *EGFR* T751_I759delinsS, *TP53* and *AKT1*. Moreover, ataxia telangiectasia related-3 (*ATR*) mutation was found in the CSF sample. Osimertinib was increased to 160 mg daily, which alleviated neurological symptoms significantly without any notable side effects and maintained the remission for 9 months. The patient passed away in March 2020, with an overall survival (OS) time of 52 months. The patient had no obvious liver, kidney or cardiopulmonary dysfunction while hospitalized. The whole course of treatment was constructed as a timeline (Figure 8).

All of the samples were examined using NGS instrument Illumina HiSeq provided by Nanjing Shihe Jiyin Biotech Inc. A total of 139 lung cancer-related genes were detected, including exons, fusion-related introns, specific microsatellite site, and so on. The summary of genetic mutations detected by NGS and the corresponding treatment were shown in Table 1.

Discussion

The treatment of advanced NSCLC is intractable, especially for the patients with central nervous system (CNS) metastases. *EGFR*-TKIs are the first selection for the *EGFR*-mutated patients and have achieved significant survival benefits.[5] However, drug resistance is inevitable, which can be classified into primary resistance and acquired resistance, and has largely restricted the clinical efficacy of TKIs. Acquired resistance always occurs in 9–13 months after the start of TKIs treatment, but the comprehension of primary resistance is limited.[6]

Among the multiple TKIs-resistant mutations, common alterations have been studied well, while the knowledge of uncommon alterations is restricted. For a number of uncommon mutations, first-generation *EGFR*-TKIs have limited efficacy, but second-generation TKI afatinib has been proved to have better activity against these mutations.[4,7] Osimertinib (AZD9291), a third-generation TKI, also can effectively control some of the uncommon mutations,[7] especially for CNS metastases thanks to its excellent blood–brain barrier (BBB) permeability and antitumour activity.[5,8]

In the present case, he harbored *EGFR* 750_758del and I759S mutations at first, and exhibited a short response to icotinib for 7.0 months. After that, secondary resistance *EGFR* T751_I759delinsS occurred without co-existing T790M mutation, and pemetrexed, carboplatin, bevacizumab and erlotinib were administered but all failed. Surprisingly, osimertinib at 80 mg daily obtained durable clinical remission for 16 months, indicating that osimertinib has antitumor activity toward acquired *EGFR* T751_I759delinsS mutation. Moreover, after LM appearing, osimertinib at 160 mg daily further reduced the allele frequency and prolonged the survival of 9 months, owing to that high-dose osimertinib ensured higher local drug level in the CNS and more remarkable curative effect regardless of T790M status.[5,8] In view of the poor prognosis of patients with CNS metastases from NSCLC, a duration of 25 months survival was meaningful.

As far as we know, *EGFR* 750_758del and I759S were reported for the first time, and might be resistant to icotinib. T751_I759delinsS mutation was detected for only

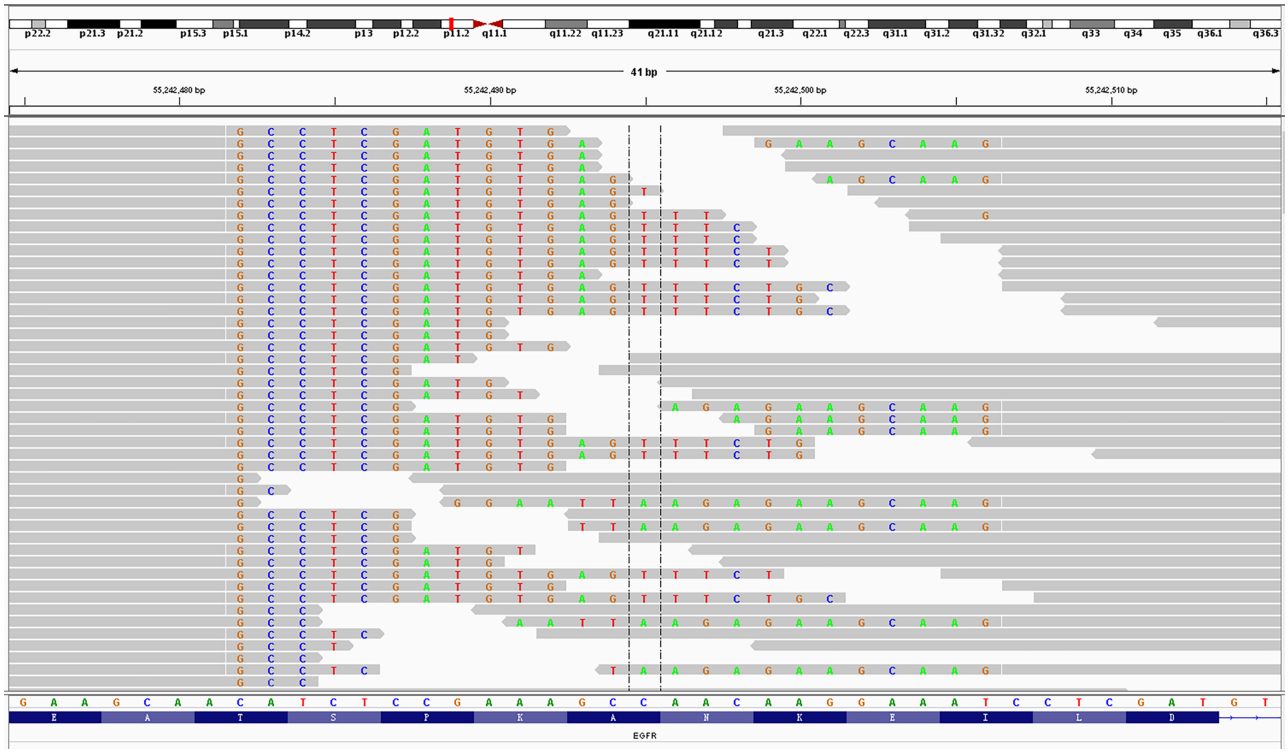

Figure 1 Next-generation sequencing of tissue sample in July 2016.

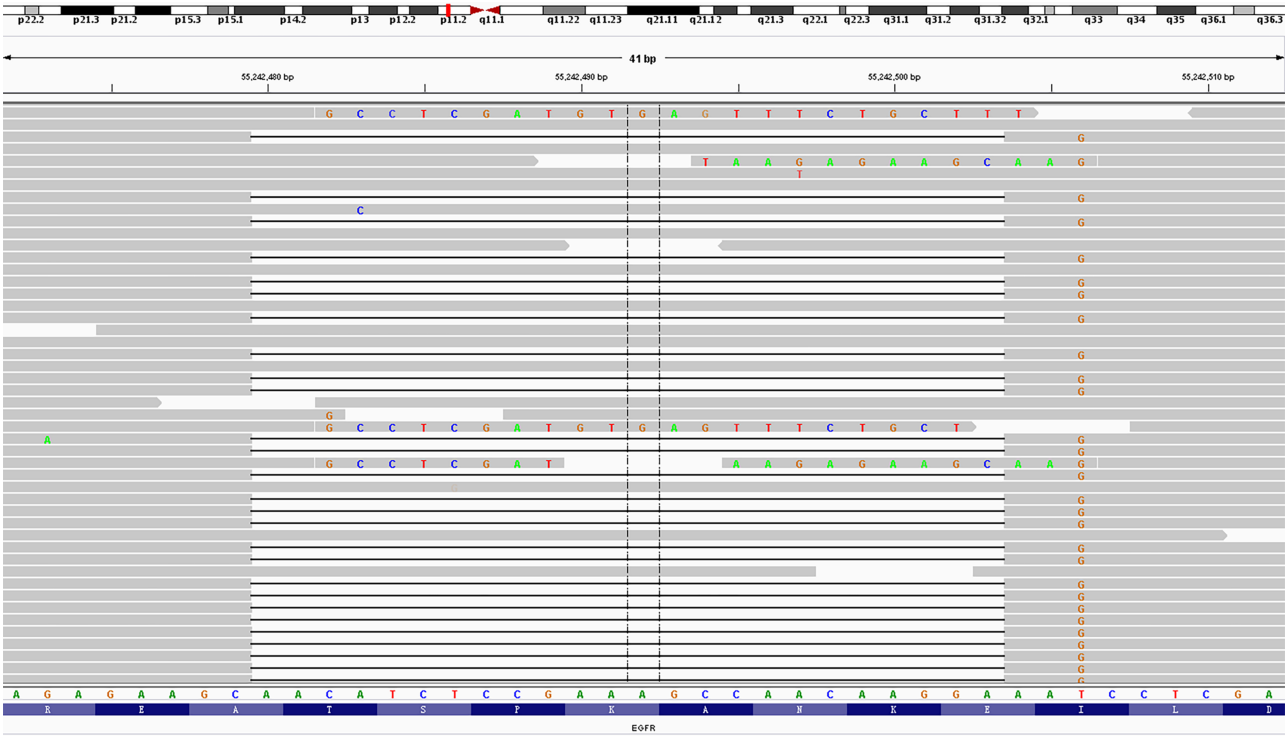

Figure 2 Next-generation sequencing of plasma sample in February 2017.

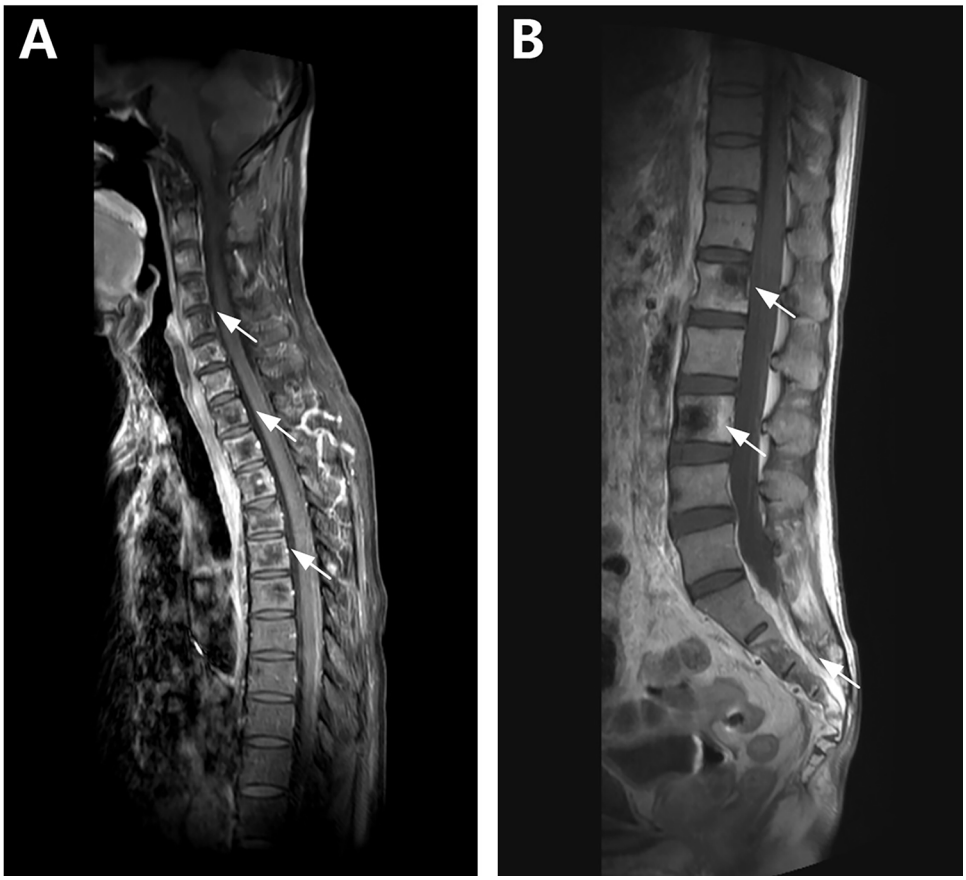

Figure 3 Sagittal T1-weighted (T1w) spinal MRI showed multiple vertebral metastases in August 2017.
Notes: (**A**) C2-7 and T1-6 (white arrows). (**B**) L1, L3 and S2-4 (white arrows).

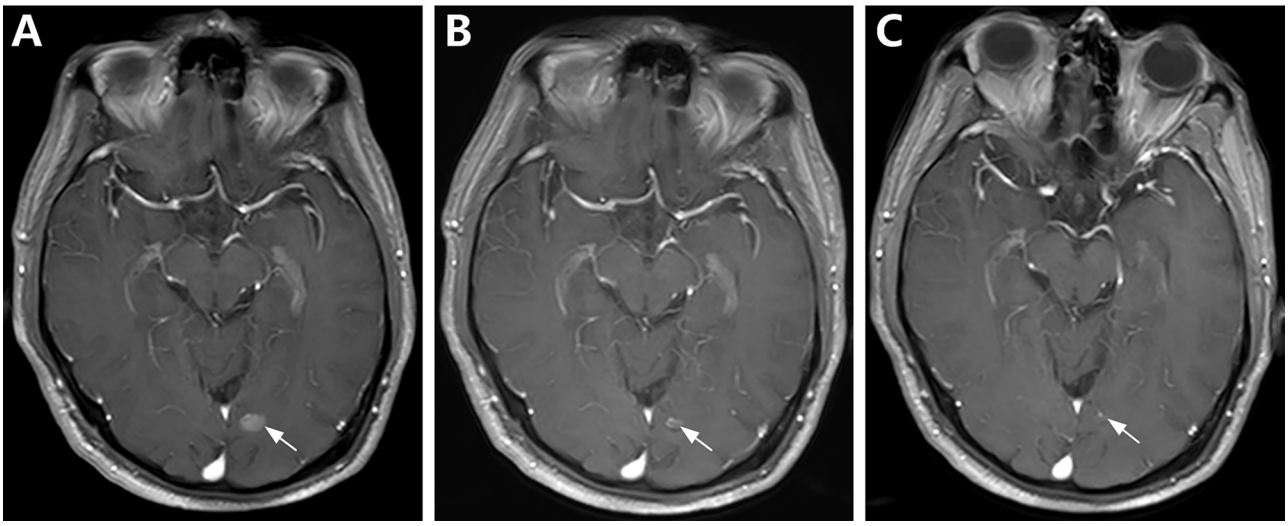

Figure 4 Axial T1w C+ craniocerebral MRI.
Notes: (**A**) Baseline MRI in January 2018 showed a patchy enhancement (white arrow). (**B**) Repeat MRI in May 2018 showed a shrunken lesion (white arrow). (**C**) Repeat MRI in January 2019 showed a reduced lesion (white arrow).

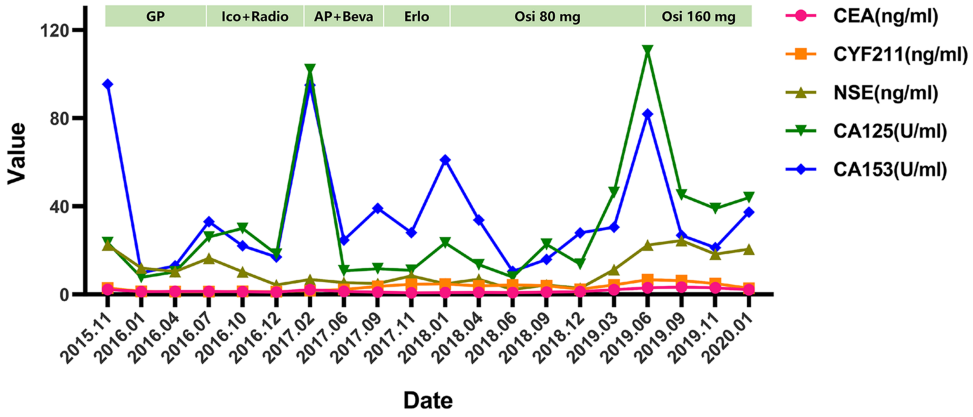

Figure 5 Changes of the concentrations of CEA, CYF211, NSE, CA125, CA153 in peripheral blood and the corresponding treatment.
Abbreviations: GP, gemcitabine and cisplatin; Ico, icotinib; Radio, radiotherapy; AP, pemetrexed and carboplatin; Beva, bevacizumab; Erlo, erlotinib; Osi, osimertinib.

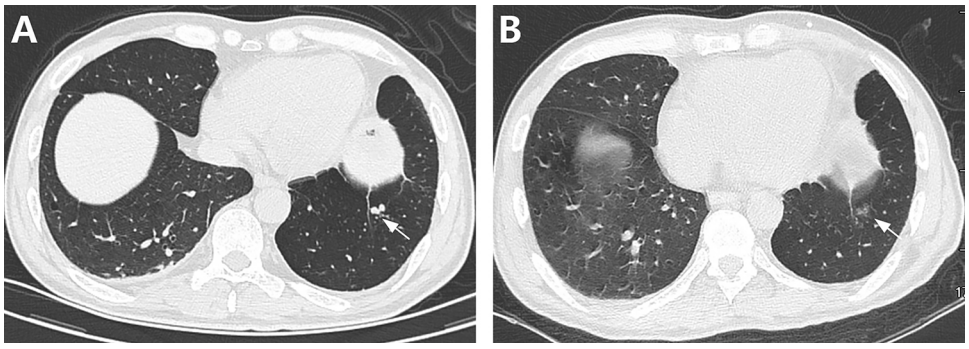

Figure 6 Chest CT showed stable lesions in the inferior lobe of left lung.
Notes: (**A**) In February 2017 (white arrow). (**B**) In January 2019 (white arrow).

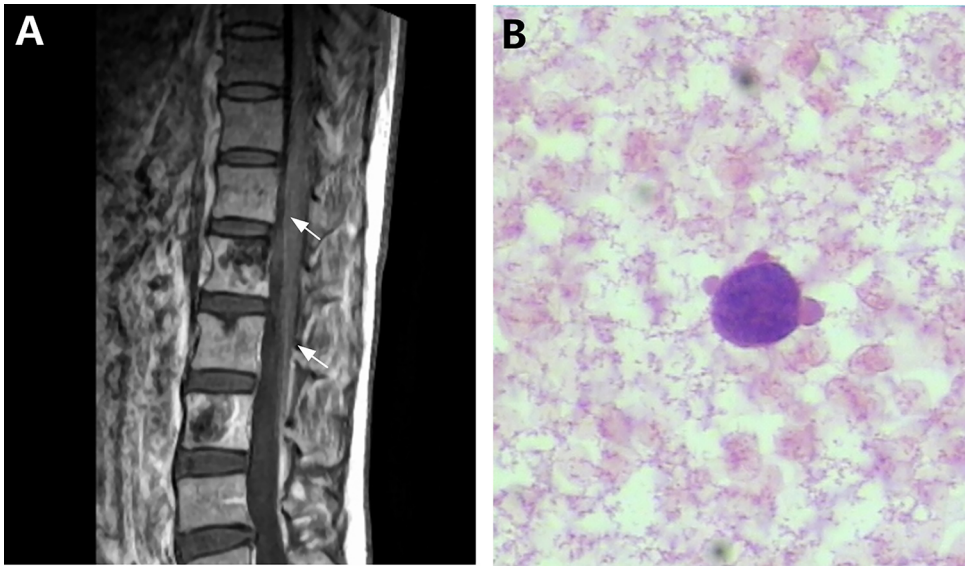

Figure 7 Leptomeningeal metastases (LM) was confirmed in June 2019.
Notes: (**A**) MRI showed enhancement of the spinal pia mater (white arrows). (**B**) CSF smear found tumor cell (hematoxylin and eosin staining).

once in the previous studies, but unfortunately without the detailed information about the therapy.[9] Our study showed that *EGFR* T751_I759delinsS mutation had better response to osimertinib compared to erlotinib, providing an important reference to the choice of medication. Due to the lack of NGS analysis of resected tumor sample and repeated

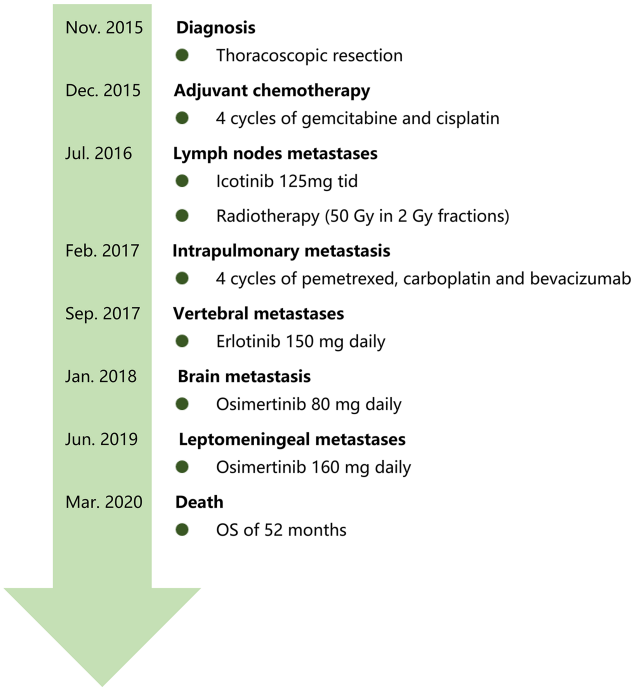

Figure 8 Treatment timeline.

tests of tissue samples after disease progression in this case, the above conclusions are limited and need more clinical cases and further researches to be determined.

The co-occurring *TP53* mutation has been identified as a negative prognostic factor and indicates shorter progression-free survival (PFS) and OS. It could be due to *TP53* mutation is involved in primary resistance to first- and second-generation TKIs in *EGFR*-positive NSCLC patients.[10,11] In addition, the clinical outcome of patients treated with osimertinib could be affected by the *TP53* gene mutation, exon 8 of which has the worse prognosis than other types.[11] *TP53* mutation of this case was located in exon 5, and its frequency showed a descending trend during the therapeutic process, which might contribute to his longer survival.

Another accompanying mutation, *AKT1* is known to promote the invasion and metastasis of NSCLC cell. Activated *AKT1* is overexpressed in NSCLC, and its inhibitors, such as A-674563, could be effective to reduce NSCLC cell survival.[12] However, Rao et al found that inhibition of *AKT1* is associated with the increased migration and invasion of *EGFR*+ NSCLC cells by regulating the *AKT1*- Myristoylated alanine-rich C-kinase substrate (MARCKS)-LAMC2 feedback loop.[13] This study showed a conflicting role of *AKT1* on metastatic NSCLC processes. Therefore, the accurate efficacy of *AKT1* could not be evaluated in this report.

Table 1 Summary of Genetic Mutations Detected by Next-Generation Sequencing and the Corresponding Treatment

Date	Sample	Gene	Mutation	Exon/ Intron	Allele Frequency	Corresponding Treatment
2016–07	Tissue	*EGFR*	p.750_758del	EX19	43.0%	Icotinib 125mg tid and radiotherapy of lymph nodes
		EGFR	p.I759S	EX19	43.0%	
		TP53	p.C176F (c.527G>T)	EX5	58.0%	
		AKT1	p.M178V (c.532A>G)	EX7	29.0%	
2017–02	Plasma	*EGFR*	P.T751_I759delinsS (c.2252_2276delinsS)	EX19	38.2%	4 cycles of pemetrexed, carboplatin and bevacizumab
		TP53	p.C176F (c.527G>T)	EX5	41.2%	
		AKT1	p.M178V (c.532A>G)	EX7	39.0%	
2018–01	Plasma	*EGFR*	P.T751_I759delinsS (c.2252_2276delinsS)	EX19	11.0%	Osimertinib 80 mg daily
		TP53	p.C176F (c.527G>T)	EX5	12.0%	
		AKT1	p.M178V (c.532A>G)	EX7	10.6%	
2019–06	Plasma	*EGFR*	P.T751_I759delinsS (c.2252_2276delinsS)	EX19	6.6%	Osimertinib 160 mg daily
		TP53	p.C176F (c.527G>T)	EX5	3.7%	
		AKT1	p.M178V (c.532A>G)	EX7	3.8%	
	CSF	*EGFR*	P.T751_I759delinsS (c.2252_2276delinsS)	EX19	3.3%	
		TP53	p.C176F (c.527G>T)	EX5	0.8%	
		AKT1	p.M178V (c.532A>G)	EX7	2.5%	
		ATR	p.Q1732L (c.5195A>T)	EX29	1.0%	

Moreover, *ATR* mutation was identified by NGS analysis of CSF after a period of osimertinib, which is a regulator involved in necessary DNA damage response. Research has shown that the selective *ATR* inhibitor, M6620, has preclinical antitumor activity and can increase the susceptibility of NSCLC cells to the chemotherapy of gemcitabine.[14] Another study demonstrated that the inhibition of *ATR* could reverse the drug resistance of NSCLC cells caused by cisplatin or cisplatin plus gemcitabine via obstructing the repair of DNA interstrand crosslinks (ICLs) and double-strand breaks (DSBs).[15] In the present case, no *ATR* inhibitor was implemented due to unknown effects on the patients with rare *EGFR* mutation.

In conclusion, this study presented the first case of intractable terminal NSCLC patient with *EGFR* 750_758del, I759S and T751_I759delinsS mutations, who responded well to osimertinib and achieved a prolonged OS, providing a feasible treatment option for such a patient. The underlying mechanisms need to be further investigated.

Statement of Ethics

Written informed consent was obtained from his next-of-kin following his death regarding the publication of the case details and associated images. This is a retrospective case report and institutional approval was not needed.

Acknowledgments

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Disclosure

The authors report no conflicts of interest in this work.

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