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CASE REPORT

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First-line osimertinib treatment in a patient with lung adenocarcinoma with coexisting *epidermal growth factor receptor* G719S and de novo T790M mutations

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Abstract

Osimertinib is the standard treatment for non-small cell lung cancer (NSCLC) with an active *epidermal growth factor receptor (EGFR)* mutation and a T790M mutation—present in cases of acquired resistance. However, there have been no reports on the efficacy of osimertinib in patients with *EGFR* G719S and de novo T790M mutations. Here, we present the case of a 71-year-old woman who received first-line osimertinib for lung adenocarcinoma with G719S and de novo T790M mutations. A partial response was observed after osimertinib initiation; however, the disease progressed 5 months after. Next-generation sequencing using a rebiopsy sample from the brain metastases revealed no newly acquired resistance mutations, including *EGFR* C797S. From experience, the efficacy of osimertinib in NSCLC with G719S and T790M compound mutations may be poor. Therefore, optimal treatment for these cases should be determined.

KEYWORDS

de novo T790M, epidermal growth factor receptor, G719S, osimertinib, uncommon mutation

INTRODUCTION

Osimertinib is the standard first-line epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) for treating non-small cell lung cancer (NSCLC) with an active *EGFR* mutation.[1] In addition, osimertinib has been shown to be effective in patients with uncommon *EGFR* mutations.[2]

There has been a report presenting osimertinib as a first-line treatment for NSCLC with *EGFR* common and de novo T790M mutations. This report showed that partial response (PR) was observed in six out of seven cases.[3] There is another report of three osimertinib-treated NSCLC cases with uncommon mutations, G719A and de novo T790M mutations.[4,5]

This is the first report which highlights the efficacy of osimertinib in a patient with NSCLC and uncommon mutations—G719S and de novo T790M mutations.

CASE REPORT

A 71-year-old woman was diagnosed with clinical T1cN3M1c stage IVB lung adenocarcinoma (Fig. 1a); she was diagnosed with coexisting *EGFR* G719S and T790M mutations using a cobas EGFR assay of her mediastinal lymph node. First, she underwent whole-brain radiation therapy (WBRT, 30 Gy/10 Fr) for symptomatic brain metastases (Fig. 2). Osimertinib (80 mg/day) was initiated after WBRT. Head magnetic resonance imaging (MRI) showed

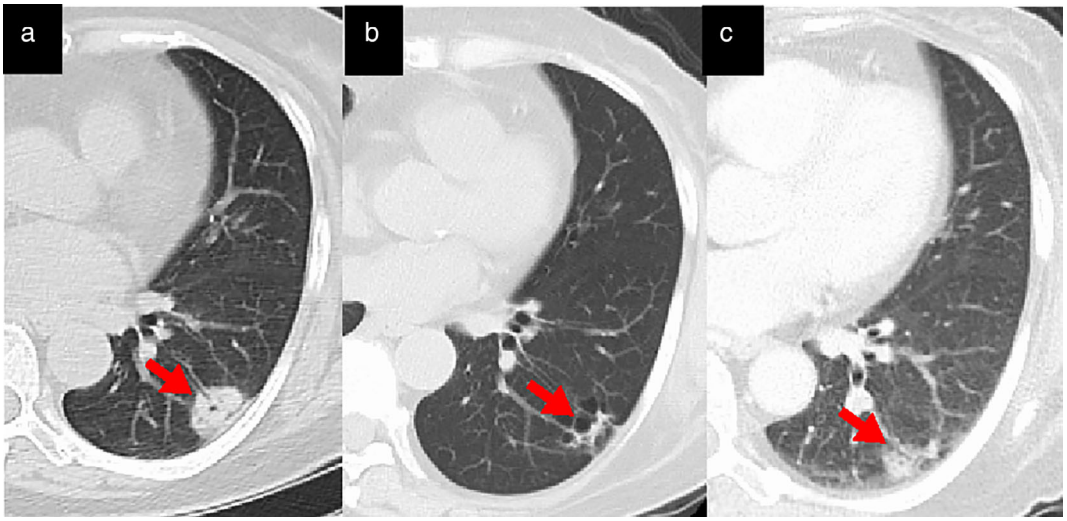

FIGURE 1 Computed tomography of the primary lesion in the lower lobe of the left lung (arrow) (a) at diagnosis, (b) 3 months after initiation of osimertinib, and (c) 5 months after initiation of osimertinib

that the size of the brain metastases decreased and partially disappeared 1 month after osimertinib initiation. Three months later, computed tomography (CT) showed shrinkage of the primary lesion and mediastinal lymph nodes; this was considered as PR. However, 5 months after osimertinib initiation, MRI or CT showed brain metastases, pulmonary lesions, enlarged mediastinal lymph nodes, and disseminated peritoneal lesions (Figs 1, 2).

First, we performed radiotherapy to treat the brain metastases and craniotomy for the right parietal lobe lesion. Although her performance score (PS) was three after the treatment for brain tumors, she and her family requested standard treatment for advanced NSCLC. Therefore, we reduced the chemotherapy dose to limit side effects and administered carboplatin (AUC 4) + nab-paclitaxel (80 mg/m^2) + atezolizumab (1200 mg/bodyweight). After the first treatment course, CT showed marked reduction of the lesions. However, her PS dropped to 4; her condition was diagnosed as meningeal carcinomatosis. Next-generation sequencing (NGS) of the brain specimen revealed G719S and T790M mutations, without newly acquired resistance mutations, including *EGFR* C797S.

DISCUSSION

This is the first report to show the efficacy of osimertinib in NSCLC with *EGFR* G719S and de novo T790M mutations. Osimertinib treatment resulted in a shorter PFS in our patient. In the three previously reported NSCLC cases with *EGFR* G719A and de novo T790M mutations, first-line osimertinib yielded an antitumor response (Table 1).[4,5] In our patient, G719S and de novo T790M mutations were observed. A previous in vitro study suggested that osimertinib was less effective in NSCLC with G719S and T790M mutations than NSCLC with common mutations. This study showed that the 50% inhibitory concentration (IC50) value of osimertinib in NSCLC cell lines with G719S and T790M mutations was 97 nM, approximately 30–100 times higher than that for common and T790M mutations.[6] This may explain the poor efficacy of osimertinib in our patient. In another previous case of lung adenocarcinoma with G719S and acquired, but not de novo, T790M mutations, osimertinib was not effective.[6] Therefore, afatinib was considered a potential drug; it had the most potent effect on G719S in the absence of T790M mutations and an IC50 value for T790M + G719S of 34 nM, slightly lower than that of osimertinib.[6] However, T790M is clinically resistant to afatinib.[7] Therefore, osimertinib was selected as first-line treatment in this case.

Osimertinib was also the primary treatment for our patient because it is reportedly very effective for CNS lesions. Osimertinib reportedly has a high response rate of 91% in *EGFR* mutation-positive NSCLC cases.[8] Since osimertinib has a higher CNS penetration ability than afatinib,[9] osimertinib was considered suitable for our patient. Moreover, a previous study showed that osimertinib had better clinical benefits than afatinib in patients with brain metastases.[10]

Tumor shrinkage was observed only few months after treatment initiation in our patient. To detect newly acquired resistant mutations, we performed NGS using Oncomine Dx Target Test Multi-CDx System (Ion Torrent PGM Dx Sequencer; Thermo Fisher Scientific), which is an NGS panel for detecting sequence variations in 46 genes using DNA and RNA in NSCLC. Therefore, whole genome mutations were not detected. However, the NGS revealed that the osimertinib-resistant brain metastases showed no new mutations (including C797S, MET amplification, KRAS, PIK3CA, etc)[11]

We administered the IMpower130 regimen (carboplatin +nab-paclitaxel+atezolizumab) after disease progression occurred, and a marked improvement was observed. A phase

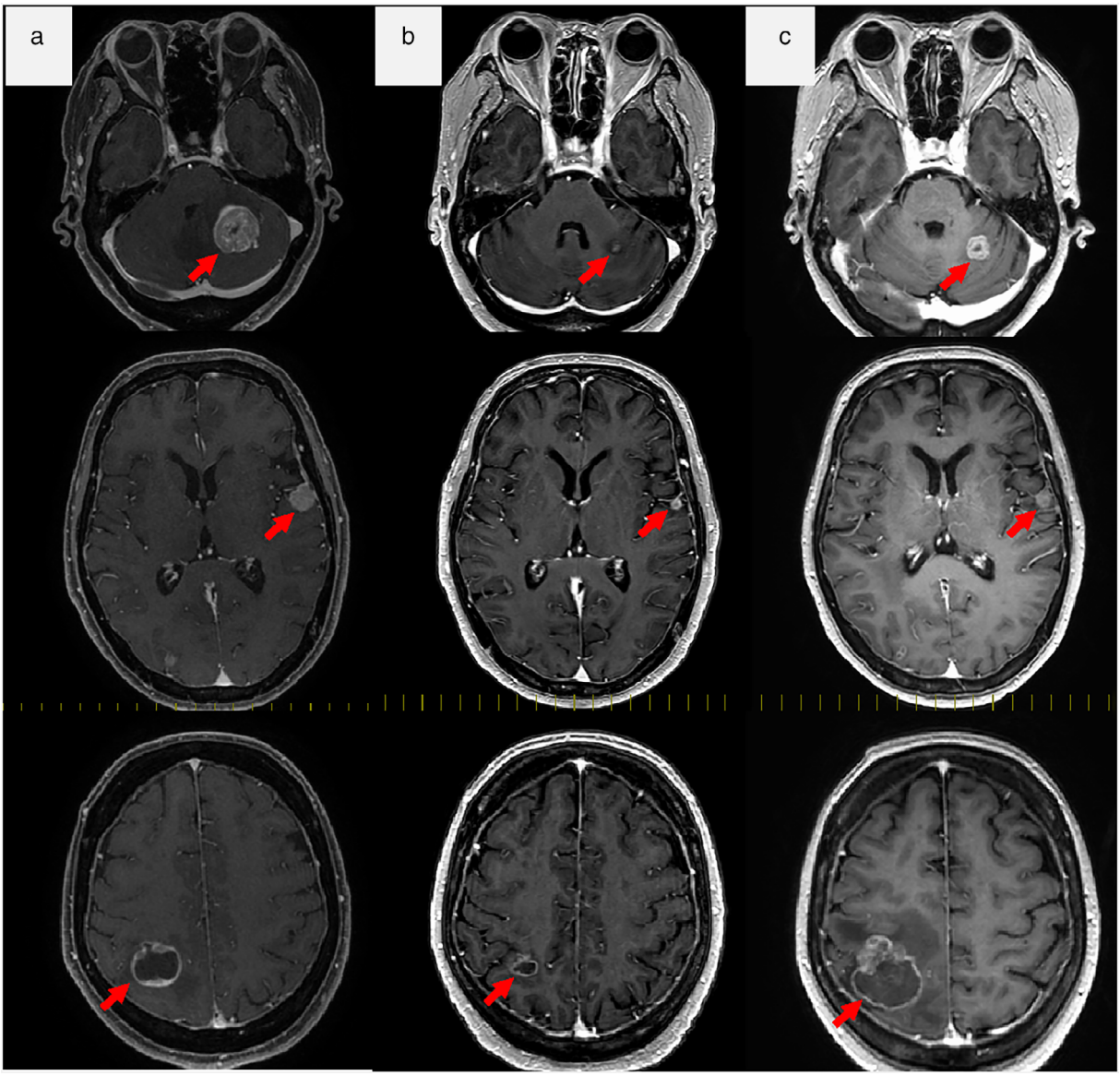

FIGURE 2 Enhanced head magnetic resonance imaging showing brain metastases (arrows) (a) at diagnosis, (b) 1 month after initiation of osimertinib, and (c) 5 months after initiation of osimertinib

TABLE 1 Cases of de novo T790M + G719X mutation-positive lung cancers treated with osimertinib

	Age	Gender	*EGFR* mutations	Stage	Metastatic lesion	Best overall response	Progression-free survival (m)	Overall survival (m)
Ikari et al.[5]	70	Male	G719A + denovoT790M	IVA	Pleura	Partial response	>4	>4
Ancevski Hunter et al.[4]	33	Female	G719A + denovoT790M	IVB	Liver	Partial response	>5	>5
Ancevski Hunter et al.[4]	51	Female	G719A + denovoT790M	IVB	Brain	Stable disease	15	>15
Current case	71	Female	G719S + denovoT790M	IVB	Brain	Partial response	5	8

III study (IMpower150 study) showed that progression-free survival was higher in the atezolizumab+bevacizumab+carboplatin+paclitaxel (ABCP) group than in the bevacizumab+carboplatin+paclitaxel group for patients with EGFR or ALK genetic alternations.[12] Therefore, the ABCP regimen was considered suitable for the patient. However, bevacizumab was considered to inhibit wound healing post-surgical resection of the brain metastases. Subsequently, we excluded pemetrexed-containing regimens due to her decreased renal function. In addition, a previous retrospective study investigated the efficacy

of immune checkpoint inhibitors (ICIs) in NSCLC with uncommon *EGFR* mutations after acquisition of resistance to EGFR-TKIs. This study showed that patients with uncommon mutations had a higher response rate to ICIs than those with common mutations (hazard ratio 0.047, 95% CI: 0.04–0.557, $p = 0.015$).[13] Based on these, we used the IMpower130 regimen for our patient.

To conclude, the efficacy of osimertinib in NSCLC with G719S and T790M mutations may be poor. Therefore, we should investigate the optimal treatment for these cases in future.

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CONFLICT OF INTEREST

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