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CASE REPORT

Brain Metastatic Tumor Flare After Sunvozertinib Dose Reduction in a Patient with Surgical Resected EGFR ex20ins NSCLC

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Abstract: Therapeutic options for NSCLC with epidermal growth factor receptor exon20 insertions (EGFR ex20ins) are limited. Sunvozertinib is a novel orally EGFR inhibitor that has been approved to treat EGFR ex20ins NSCLC at second line setting. Herein, we reported an unexpected therapeutic outcome of first-line sunvozertinib treatment in a patient with stage IIIB EGFR ex20ins-positive lung adenocarcinoma (T1cN3M0). We found three months of sunvozertinib neoadjuvant treatment led to remarkable shrinkage of the primary tumor and downstaged N3 metastatic disease. A radical resection was scheduled after careful evaluation. Histological assessment of the resected tumor and lymph nodes showed a complete pathologic response. The patient was recommended to continue sunvozertinib as an adjuvant therapy, whereas he developed brain metastasis within three months after surgery. We proposed that the brain metastasis occurred as a result of sunvozertinib dose de-escalation-induced disease flare. Rechallenge with adequate dosage of sunvozertinib led to a rapid shrinkage of the brain metastasis. Our case highlighted the feasibility of sunvozertinib neoadjuvant therapy in EGFR ex20ins-positive NSCLC patient with locally advanced disease. Importantly, adjuvant therapy using an adequate dosage of sunvozertinib is pivotal to prevent disease flare and tumor recurrence.

Keywords: EGFR ex20ins, sunvozertinib, neoadjuvant therapy, downstaging, disease flare

Introduction

Non-small cell lung cancer (NSCLC) patients with canonical activating mutations in epidermal growth factor receptor (EGFR) substantially benefit from EGFR tyrosine kinase inhibitors (TKIs).[1] However, patients with uncommon EGFR mutations, in particular EGFR exon20 insertions (ex20ins), did not respond well due to conformation changes in the EGFR kinase pocket that hindered the binding to TKIs, with an ORR less than 10%.[2] First-line platinum-pemetrexed chemotherapy in EGFR ex20ins NSCLC yielded ORRs ranging from 14% to 25% and a median PFS of six months.[3] While the recently approved EGFR/MET bispecific antibody amivantamab showed limited CNS activity and raised toxicity concerns,[4] effective treatments for patients with EGFR ex20ins NSCLC are urgently needed.

Fortunately, sunvozertinib has been authorized by NMPA and FDA for treating EGFR ex20ins NSCLC who failed on standard chemotherapy.[5] It is an irreversible EGFR TKI that specifically targets EGFR ex20ins, as well as canonical EGFR sensitizing mutations, with weak potency against wild-type EGFR. In addition to EGFR ex20ins, sunvozertinib overcomes steric hindrance via a flexible acrylamide warhead, explaining its activity in TKI-resistant settings.[6]

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Case Presentation

A 66-year-old man without smoking history presented to our institution in May 2024. He had been diagnosed with lung adenocarcinoma based on biopsy of the right lung nodule in a local medical center two weeks earlier (Figure 1A). The cancer cells were poorly differentiated along with complex glandular morphology, and immunologically positive for TTF-1 and Napsin A. The result of PD-L1 status evaluation was negative. Analysis of genetic events by next-generation sequencing (NGS) consisting of 56 cancer-driven genes yielded an EGFR ex20ins mutation (A767_V769 duplication) with 55.91% of tissue abundance. Positron emission tomography CT (PET-CT) examination revealed increased 18F-FDG uptake of the right upper lung nodule with an SUVmax of 8.3 (Figure 1B). The PET-CT scan also showed intensive 18F-FDG metabolism in the ipsilateral supraclavicular lymph nodes (SUVmax = 5.1). Brain magnetic resonance imaging (MRI) was performed and the result was negative for metastasis. Hence, the patient was diagnosed with locally advanced stage IIIB lung adenocarcinoma (T1cN3M0) with EGFR ex20ins and concurrent chemoradiotherapy was recommended by a multi-disciplinary boad. The patient refused chemotherapy and radiotherapy, fearing treatment-related adverse events, and sunvozertinib therapy at a dosage of 200 mg once daily was initiated after careful consideration.

Sunvozertinib therapy was effective in our patient according to a repeated chest CT scan one month later. The patient continued to respond to sunvozertinib therapy in our follow-ups, while remarkable lung interstitial infiltration and ground glass opacities suggested the need for significant clinical caution after three months of treatment. In order to examine whether sunvozertinib therapy downstaged the primary tumor stage, PET-CT was performed again in September 2024. The residue 1.7×0.8 cm tumor elicited reduced SUVmax value to 2.11. Intriguingly, 18F-FDG uptake was not detected in the

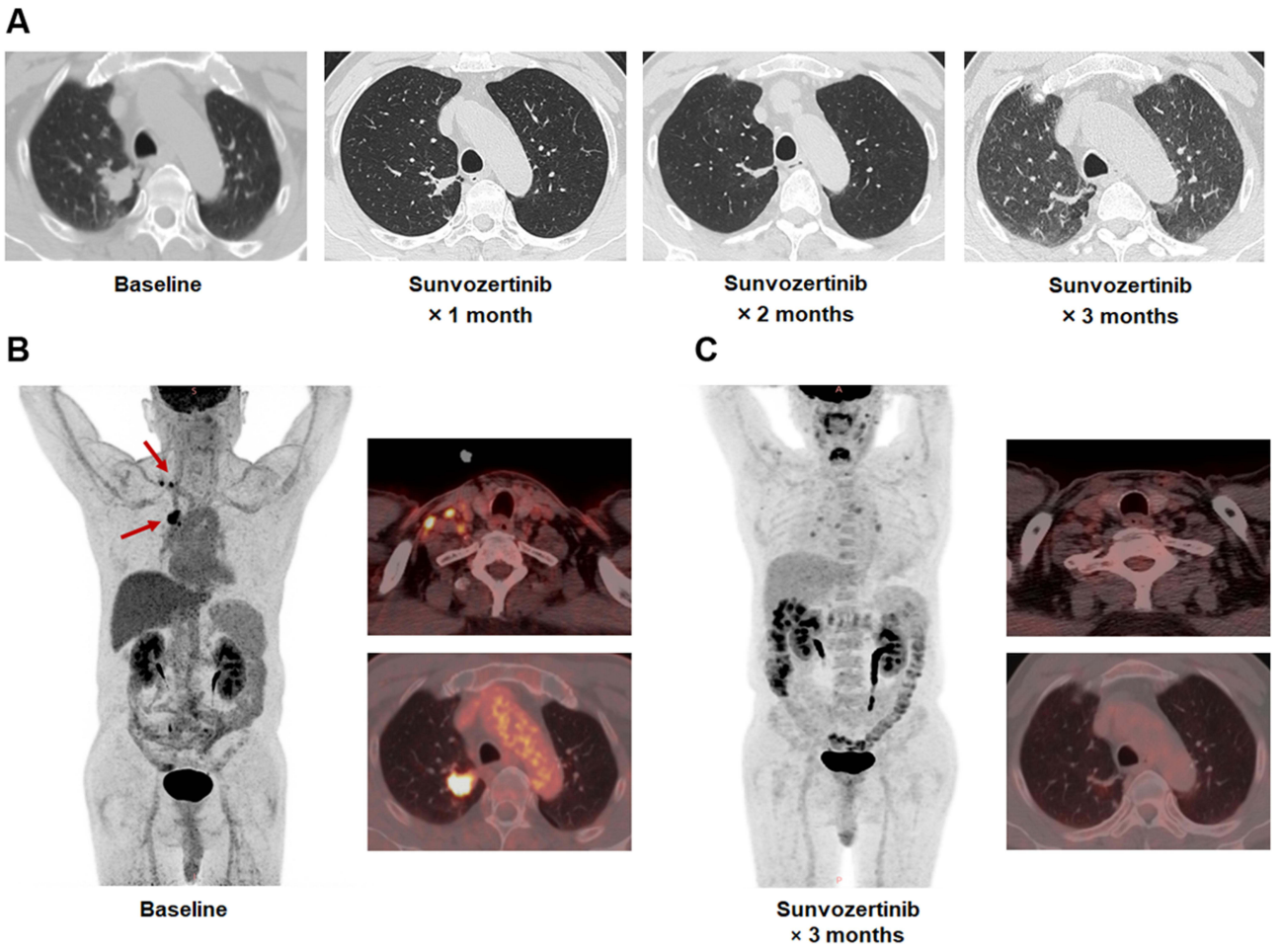

Figure 1 (**A**) Representative chest CT images of right upper lung tumor at diagnosis and after sunvozertinib treatment; (**B** and **C**) baseline PET-CT examination showed 18F-FDG metabolic activity in the right upper lung nodule and supraclavicular lymph nodes (indicated by red arrows). After three months treatment with sunvozertinib, disease remission and tumor downstaging were observed.

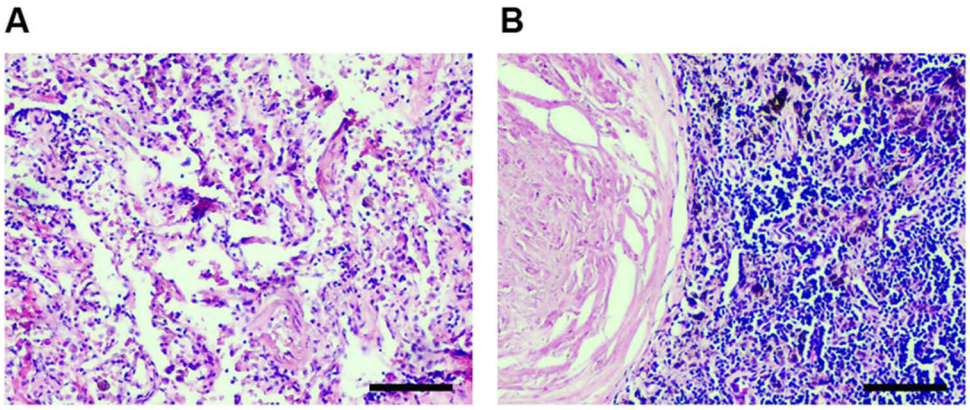

Figure 2 Histological analysis of resected specimen. Hematoxylin and eosin of the resected primary tumor site (**A**) and draining lymph nodes (**B**) revealed fibrosclerotic manifestation and chronic inflammation, without residual and viable tumor cells. Scale bar = 100 μm.

supraclavicular lymph node (Figure 1C). Downstaging of N3 metastatic disease was concluded by experts members of the multi-disciplinary team and surgical resection was approved by the Medical Ethics Committee of Jinling Hospital (2024DZKY-098-01). The patient underwent surgical resection of the right upper lobe, together with dissection of hilar and mediastinal lymph nodes. Histological analysis of the resected specimen showed chronic inflammation and lymphocyte infiltration (Figure 2A). No residual or viable tumor cells were detected in the primary tumor or in the resected lymph nodes (Figure 2B). As a consequence, EGFR ex20ins targeted therapy with sunvozertinib primed radical surgery resection that yielded a complete pathologic response (pCR), albeit surgical removal was not considered at the time of diagnosis. The patient was recommended to continue sunvozertinib 200 mg once daily as postoperative adjuvant therapy.

The patient returned to our hospital for regular postoperative assessment in January 2025. Chest and abdominal CT examination revealed no signs of disease relapse. However, multiple solid nodules in the frontal lobe and cerebellum were noticed in brain MRI T2-FLAIR (Figure 3A). Lumbar puncture was performed and elicited a cerebrospinal fluid pressure of 250 mm H_2O. The cerebrospinal fluid smearing was negative for tumor cells. Thus, a diagnosis of progressive disease due to brain metastasis was reached. It was rather unexpected to see rapid tumor recurrence (< 3 months) in our patient who had already achieved pCR and received adjuvant therapy, even though his brain metastasis was asymptomatic. On detailed interrogation, the patient admitted he had reduced the dosage of sunvozertinib to 100 mg once daily on his own initiative. Sunvozertinib 200 mg was reinitiated and a rapid remission in brain metastatic nodules was observed (Figure 3B).

Discussion

The present study described an interesting case of EGFR ex20ins NSCLC, in which targeted therapy with sunvozertinib downstaged metastatic N3 lymph node and primed surgical resection. It should be noted that sunvozertinib was approved to treat metastatic EGFR ex20ins NSCLC in the second-line setting, and relevant data on neoadjuvant sunvozertinib therapy were lacking. The dosage of sunvozertinib for disease downstaging was 200 mg once daily rather than the standard dosage (300 mg per day). In fact, we prescribed the patient with 300 mg of sunvozertinib at time of diagnosis, while he experienced severe diarrhea that required dosage intervention. Finally, sunvozertinib was maintained at 200 mg once daily. Acting in a neoadjuvant setting, sunvozertinib efficiently alleviated tumor burden and potentially rendered tumor resection. To the best of our knowledge, this is the first case report showing tumor downstaging activity of sunvozertinib in locally advanced EGFR ex20ins NSCLC.

Treating NSCLC with TKIs following prime surgical resection is a feasible approach for patients with locally metastatic diseases. According to the NeoADAURA trial, neoadjuvant therapy with osimertinib (25% MPR rate) or osimertinib plus chemotherapy (26% MPR rate) augmented the incidence of major pathological response (MPR) and prolonged event-free survival (EFS) over chemotherapy alone (2% MPR rate) in stage II–IIIB EGFR mutant NSCLC.[7] A major challenge for TKIs neoadjuvant therapy was the undetermined duration of treatment. In most clinical trials, the treatment duration usually ranged from 42 days to 8 weeks, which resulted in limited MPR ratios.[8] With the extension of neoadjuvant duration, a higher incidence of MPR, or even pCR, may be achieved. Postoperative adjuvant therapy should

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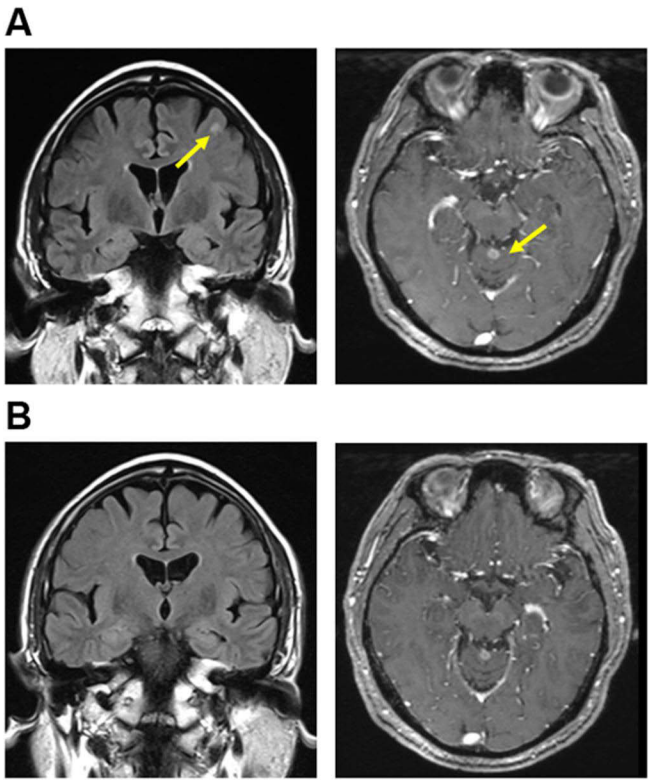

Figure 3 Intracranial response to sunvozertinib upon dose de-escalation-induced metastatic disease flare. (**A**) Intracranial disease progression (indicated by yellow arrows) three months after sunvozertinib dosage reduction (100 mg once daily). (**B**) Partial response of brain metastatic tumor to sunvozertinib at a dosage of 200 mg once daily.

be mandatory for reducing the risk of tumor recurrence. Although our patient also received adjuvant therapy, he reduced sunvozertinib dosage to 100 mg once daily without informing clinicians and developed brain metastasis three months thereafter. Disease progression was very likely attributable to inadequate dose adjustment since the brain nodules responded to sunvozertinib again when dosage was reinitiated at 200 mg. Disease regression to progression switch as a result of sunvozertinib dose reduction is a paradigm of disease flare, a phenomenon defined as sudden and rapid radiological progression. Disease flare usually occurs in cancer patients after TKI discontinuation. When stopping a TKI in EGFR mutant NSCLC, tumor growth is accelerated and leads to disease exacerbation, with an incidence ranging from 4% to 23%. Based on previous studies evaluating therapeutic outcomes of gefitinib and erlotinib in EGFR mutant NSCLC, the median time to flare after stopping a TKI is about eight days.[9] Patients who experience disease flare have shorter post-TKI survival and worse overall survival than non-flare patients.

TKI dose reduction-associated tumor flare was noted in our patient during adjuvant treatment. We did not initiate sunvozertinib dose reduction until disease progression, thus clearer communication with the patient in adjuvant TKIs therapy is required. Switching targeted therapy to cytotoxic chemotherapy after radiological progressive disease is generally adopted for patients who failed on TKIs. However, rechallenge with the prior TKIs or more potent inhibitors after disease flare, rather than chemotherapy, to suppress TKI discontinuation-induced tumor outgrowth has been supported by several clinical experiences.[10] In the present case, sunvozertinib rechallenge was recommended to treat TKI dose de-escalation-induced disease flare. Fortunately, the brain metastatic flares responded again to sunvozertinib upon dose escalation. These results highlight the importance of adequate TKI dosage for adjuvant therapy, as reported in ADAURA (osimertinib 80 mg per day) and ALINA (alectinib 600 mg twice daily) trials.[11,12]

Conclusion

Our case highlighted the feasibility of neoadjuvant therapy with sunvozertinib in locally advanced EGFR ex20ins NSCLC. Exploring curative-intent neoadjuvant therapy with sunvozertinib for potentially resectable EGFR ex20ins

NSCLC warrants multicenter registry studies. Importantly, postoperative treatment using adequate dosage of sunvozertinib is pivotal for preventing disease flare and tumor recurrence. The brain-penetrable potency of sunvozertinib makes it a highly effective treatment for CNS metastatic disease. Taken together, this case supports neoadjuvant sunvozertinib for resectable EGFR ex20ins NSCLC but cautions that inadequate adjuvant dosing may trigger disease flare. Adequate maintenance therapy is critical.

Ethics Statement

This study was reviewed and approved by the Medical Ethics Committee of Jinling Hospital, Affiliated Hospital of Medical School, Nanjing University (2024DZKY-098-01). Institutional approval was not required to publish the case details.

Consent for Publication

Written informed consent was obtained from this patient for the publication of any potentially identifiable images or data included in this article.

Acknowledgment

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Disclosure

The authors report no conflicts of interest in this work.

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