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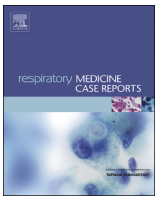

Case Report

Treatment of cavitated non-small cell lung cancer presenting as "Halloween pumpkin" following the consecutive NEOADAURA and ADAURA2 strategy: A case report

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ABSTRACT

Osimertinib is a third-generation tyrosine kinase inhibitor that targets mutant epidermal growth factor receptor (EGFR). The success of FLAURA and ADAURA trials prompted the license of Osimertinib for the treatment of EGFR mutant non-small cell lung cancer (NSCLC) at advanced stage and for patients with stages IB to IIIA disease in post-operative setting. In the present study, we described neoadjuvant use of Osimertinib in an EGFR mutant NSCLC patient with locally metastatic disease (T2aN2M0). Intriguingly, the cavitated NSCLC resembled an impressive"Halloween pumpkin" appearance that dramatically responded to Osimertinib treatment. Downstaging of N2 metastatic disease was reached and surgical resection was scheduled. The post-operative clinical stage was IA3. The patient was recommended to continue Osimertinib adjuvant treatment and our follow-ups showed no signs of disease recurrence. Our case study underscored the feasibility of Osimertinib as a neoadjuvant and adjuvant therapy for patients with locally advanced EGFR mutant NSCLC.

1. Introduction

Activating somatic mutations in epidermal growth factor receptor (EGFR) triggers tumorigenesis in a subgroup of patients with non-small cell lung cancer (NSCLC). These patients are sensitive to small molecule tyrosine kinase inhibitors (TKIs) targeting EGFR [1]. Accumulating evidence has suggested that EGFR TKIs provides substantial clinical benefits over standard platinum-based chemotherapy in EGFR mutant NSCLC at advanced-stage [2,3]. Intriguingly, EGFR TKIs are also considered as a neoadjuvant therapy in locally advanced NSCLC with N2 lymph node metastasis for priming surgical resection [4]. Osimertinib is a third-generation and brain penetrable EGFR TKI that targets activating mutations of EGFR and the T790M resistance mutation [5,6]. The FDA has approved Osimertinib for patients with metastatic EGFR mutant NSCLC and for patients with stages IB to IIIA EGFR mutant NSCLC in adjuvant setting (ADAURA regimen) [7]. However, whether Osimertinib could be used in neoadjuvant setting and in NSCLC with stage IA disease remain to be elusive.

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2. Case report

In December 2022, a 64-year-old man admitted to our hospital with complains of non-productive cough for two weeks. He did not have fever, chest pain, hemoptysis, shortness of breath or dyspnea. His family history included lung cancer in his grandfather and brother. A physical examination did not show signs of abnormality with a saturation of 96 % on ambient air. The patient was a never smoker and had a 5-year history of hypertension. He took nifedipine and metoprolol as medications to control blood pressure. The blood tests, including whole blood cell count, blood biochemistry analysis and coagulation, were within normal limits. The screening across a panel of serology tumor biomarkers, such as carcinoembryonic antigen (1.72 μg/L), neuron specific enolase (13.3 μg/L) and Cyfra21-1 (3.2 ng/mL), did not reveal any abnormalities.

The chest contrast-enhanced CT showed a 32 × 24 mm thick-wall cavitary mass in the dorsal segment of lower lobe of the left lung. Interestingly, this lesion possessed multiple cavities with irregular margin and asymmetric thickening of cavitary wall, resembling a "Halloween pumpkin" appearance with lymphadenopathy of the draining lymph nodes (Fig. 1A). Positron emission tomography revealed marked fluorine-18 deoxyglucose (18F-FDG) uptake of the cavitary mass with a maximum standardized uptake value (SUVmax) of 14.5. The 18F-FDG accumulation was also found in the hilar and mediastinum lymph nodes (SUVmax = 6.25) (Fig. 1B). After evaluation with magnetic resonance imaging, there was no evidence of central nervous system involvement. The mass was diagnosed as adenocarcinoma after lung biopsy. The cancer cells were poorly differentiated with a strong expression of TTF-1 (3+), CK7 (3+) and Ki67 (60 %) (Fig. 2). Immunohistochemistry (IHC) analysis of tumor cell proportion score (TPS) for PD-L1 was 15 %. The DNA-based targeted next-generation sequencing (NGS) of the biopsy sample showed a positive result for EGFR activating mutation (EGFR E746_A750 del), with a tumor mutation burden (TMB) of 5.01 Muts/Mb. Collectively, the patient was diagnosed with EGFR mutant adenocarcinoma of the left lung at the clinical stage of IIIA (T2aN2M0) according to the 8th edition of the TNM classification for lung cancer [8]. Following a discussion with the multidisciplinary broad, neoadjuvant treatment with Osimertinib at 80 mg per day was given for downstaging the N2 metastatic disease (NEOADAURA strategy), which lasted for 2 months. The patient's symptom was markedly relieved after targeted therapy. During treatment with Osimertinib, the patient experienced grade 2 diarrhea that could be well managed by loperamide. Radiographic assessment after Osimertinib treatment showed a partial response (PR), with a remarkable collapse in the size of "Halloween pumpkin" mass (20 × 17 mm) and a resolution of mediastinum lymphadenopathy (Fig. 3).

The patient was re-evaluated for surgical resection. The left lower lobectomy and thoracic lymphadenectomy were done by video-assisted thoracoscopic surgery at the end of February 2023. The postoperative pathological diagnosis was poorly differentiated adenocarcinoma with extensive necrosis. The residue cancer cells spanned an area of 1.5 cm in the greatest dimension, and cells were still positive for TTF-1 (3+), CK7 (3+) and Ki67 (50 %) (Fig. 4). There was no evidence of lymphovascular or visceral pleural invasion, and 0/15 dissected lymph nodes showed tumor involvement. The final postoperative pathological stage was pT1cN0M0, stage IA3. In accordance with the National Comprehensive Cancer Network guidelines (2022 version 3), patients were considered to be at a high risk of disease recurrence when they showed poorly differentiated tumors, thus, the patient was requested to continue adjuvant targeted

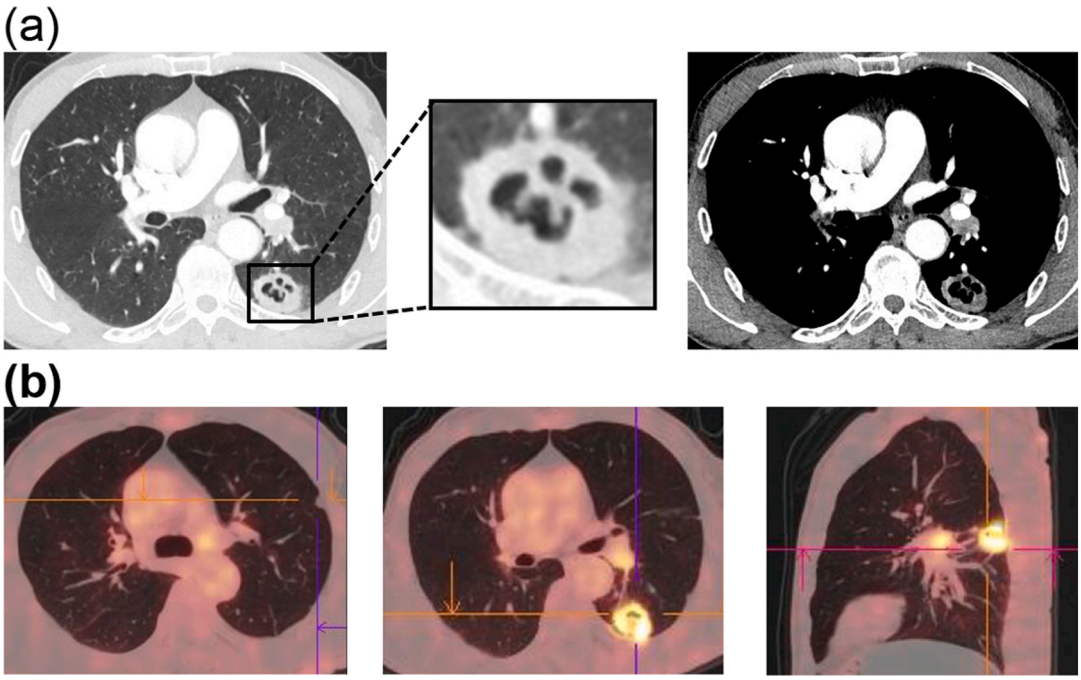

Fig. 1. Radiologic findings of the cavitated "Halloween pumpkin". (A) Chest contrast enhanced CT showed a 32 × 24 mm thick-wall cavitary mass resembling a "Halloween pumpkin" appearance in the lower lobe of the left lung with enlarged hilar lymph nodes. (B) PET-CT scanning revealed hypermetabolism of 18F-FDG of the cavitary mass and the draining hilar and mediastinum lymph nodes.

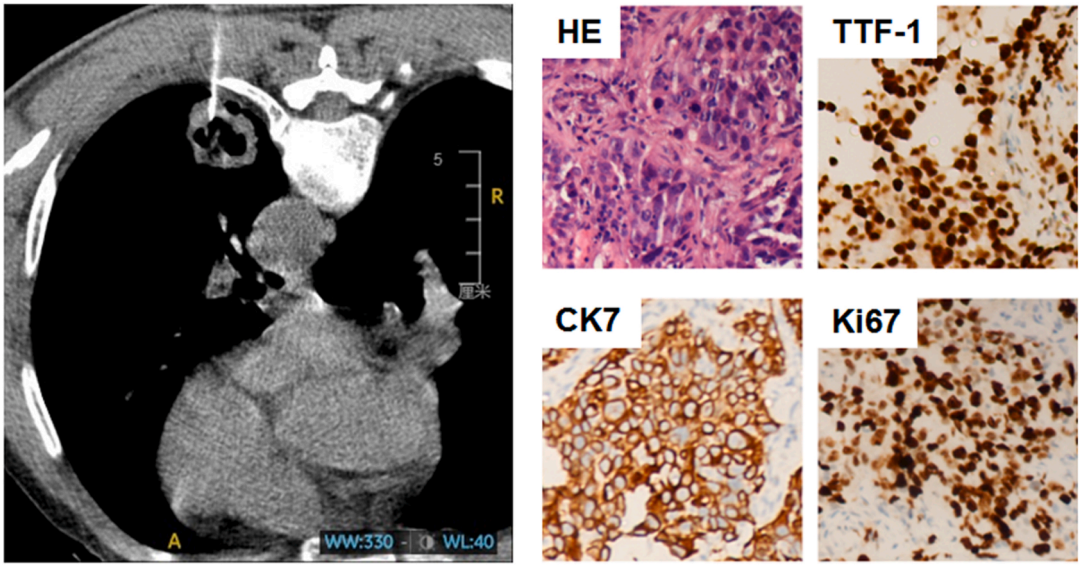

Fig. 2. Representative pathologic images of lung biopsy samples. CT-guided percutaneous biopsy of the cavitated "Halloween pumpkin". Histologic assessment showed poorly differentiated adenocarcinoma cells with a strong expression of TTF-1, CK7 and Ki67.

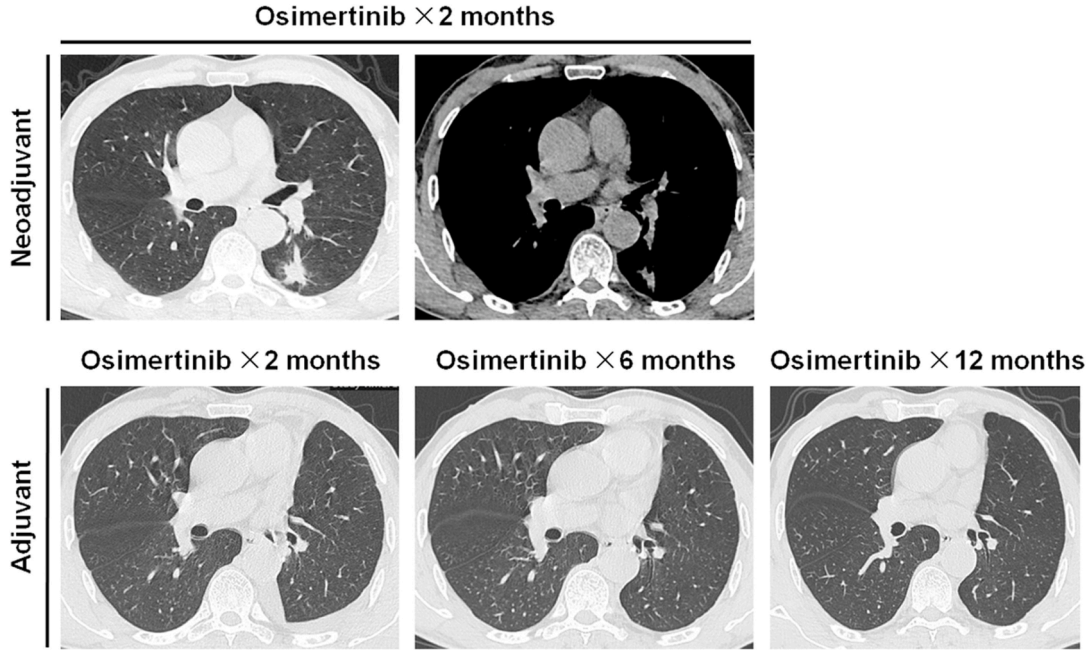

Fig. 3. Radiologic evaluation of Osimertinib neoadjuvant and adjuvant therapies. The patient with EGFR mutant stage IIIA (T2aN2M0) NSCLC was treated with Osimertinib neoadjuvant therapy for 2 months. Repeated chest CT examination suggested a significant PR of the primary tumor and downstaging of metastatic lymph nodes (upper panel). Surgical resection was performed and the post-operative clinical stage was IA3 (pT1cN0M0). Targeted therapy with Osimertinib was continued in adjuvant setting and chest CT evaluation in our follow-ups indicated no evidence of disease recurrence.

therapy with Osimertinib 80 mg once daily (ADAURA2 strategy) followed by regular interview. The surveillance imaging with chest CT at 2 months,6 months and 12 months after surgery was stable without signs of recurrent malignancy (Fig. 3).

3. Discussion

Lung cavity is a common radiologic presentation in both benign and malignant settings. Cavitary lesions are reported in tuberculosis, granulomatosis, pneumonia, fungal infection and NSCLC [9,10]. The key reliable radiologic feature that helps to distinguish benign and malignant diseases is the thickness of the cavity wall. In a retrospective analysis of patients with lung cavities, 94 % (30/32) of cavities with maximal wall thickness less than 4 mm were benign [11]. In contrast, thick-wall cavity with a maximum wall thick-

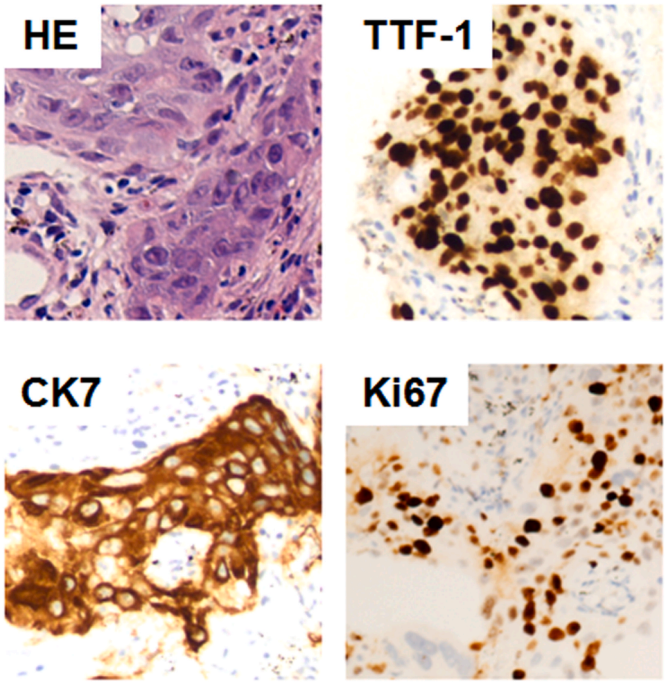

Fig. 4. Pathologic assessment of the resected tumor. The cavitated "Halloween pumpkin" and metastatic lymph node after 2 months of Osimertinib neoadjuvant targeted therapy were surgical resected and subjected to pathologic evaluation. The residue tumor cells elicited as poorly differentiated adenocarcinoma with positive expression for TTF-1 (3+), CK7 (3+) and Ki67 (50 %). None of the dissected lymph nodes showed tumor involvement.

ness over 15 mm on chest X ray (CXR) indicated malignancy in more than 90 % cases. It was also noted that malignant cavities were more likely to have an irregular internal wall and have an indentation of the outer wall as compared with benign cavities [12,13].

In the present study, the asymmetric thick-wall cavities with irregular inner contours and margins resembled a unique "Halloween pumpkin" appearance in the left lung. Malignant cavities were highly suspected and confirmed by lung biopsy. The cavitated tumor was proven potentially resectable EGFR mutant adenocarcinoma at stage IIIA with N2 lymph node metastasis. Although concurrent chemoradiotherapy with or without anti-PD-L1 consolidation therapy is the standard of care for unresectable stage III NSCLC, there is still a big gap in urgent clinical needs for this group of patients. For example, patients with EGFR mutant NSCLC did not benefit from this treatment and experienced a higher frequency of treatment-related toxicity [14,15]. Despite EGFR TKIs have not been approved for unresectable EGFR mutant stage III NSCLC, there are preliminary studies showing robust efficacy of targeted therapy in both EGFR mutant early-stage resectable NSCLC and EGFR mutant stage III unresectable NSCLC [16]. After a careful discussion with the multidisciplinary broad, we reached an agreement of using Osimertinib for downstaging N2 metastatic disease in our patient. The ongoing NEOADAURA trial (NCT04351555) aims to assess the efficacy of neoadjuvant Osimertinib versus chemotherapy in patients with stage II-IIIB EGFR mutant NSCLC. The NEOADAURA study is expected to support neoadjuvant therapy with Osimertinib in patients with potentially resectable EGFR mutant NSCLC.

The post-operation stage in our patient was IA3. Although the management of NSCLC patients with stage I disease is predominantly follow up after complete tumor resection, however, poorly differentiation of tumor cells has been identified as an independent risk factor of disease recurrence [17]. The phase III ADAURA study has demonstrated that Osimertinib adjuvant therapy reduced the risk of disease recurrence in patients with stage IB, II and IIIA NSCLC. The potential significance of adjuvant Osimertinib treatment in stage IA EGFR mutant NSCLC following complete tumor resection is being evaluated in the ongoing ADAURA2 study (NCT05120349) [18]. These lines of evidence thus prompt us to recommend adjuvant Osimertinib treatment in our patient and he is fine without signs of recurrence.

This case report is a paradigm of biomarker-guided precision oncology for patients with NSCLC. The EGFR mutant cavitated "Halloween pumpkin" was successfully treated with sequential Osimertinib neoadjuvant therapy, surgical resection and Osimertinib adjuvant therapy. Although there is a number of attempts about using EGFR TKIs as neoadjuvant therapy for the purposes of disease downstaging, it should be noted that these reports are predominantly based on single patient's experience, which limits the generalizability of the findings. Moreover, the duration of neoadjuvant EGFR TKIs therapy is quite heterogeneous among different studies, mostly ranging from 42 days to 8 weeks. The treatment duration of 2 months in this case may not be optimal and could vary for different patients. As such, the precise duration for neoadjuvant therapy is still under clinical investigation. Future studies should carefully address these questions to refine treatment protocols for locally advanced EGFR mutant NSCLC.

4. Conclusion

Osimertinib shows remarkable clinical benefits not only for advanced-stage EGFR mutant NSCLC but also as a neoadjuvant therapy for downstaging locally metastatic disease. Additionally, Osimertinib adjuvant therapy should be considered for post-operative stage IA disease to reduce the risk of recurrence.

Ethics approval

This study was approved by the Medical Ethics Committee of Jinling Hospital, Affiliated Hospital of Medical School, Nanjing University. Written informed consent was obtained from the patient.

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CRediT authorship contribution statement

Lingyun Wei: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Nan Yang:** Methodology, Formal analysis, Data curation. **Chuan Gao:** Methodology, Formal analysis, Data curation. **Weinan Li:** Methodology, Formal analysis. **Mingxiang Ye:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

We declare no conflicts of interests.

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