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CASE REPORT

Redefining Therapeutic Boundaries: PD-1 Blockade Facilitates Surgical Cure in EGFR-TKI Refractory EGFR-Mutant NSCLC with Pleural Metastases

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Abstract: We present a 57-year-old female diagnosed with stage cT3N1M1a (IVA) EGFR L858R-mutant lung adenocarcinoma (PD-L1 TPS 60%). The patient attained sustained disease control with a partial response lasting 22 months on first-line gefitinib. Following progression with persistent EGFR L858R mutation, second-line platinum-pemetrexed-bevacizumab chemotherapy achieved stable disease (SD) in the primary lesion and shrinkage of pleural nodules. Subsequent neoadjuvant therapy with albumin-bound paclitaxel, carboplatin, bevacizumab, and sintilimab induced marked tumor regression, permitting curative-intent R0 resection. Histopathological analysis confirmed ypT0N0, indicating a pathological complete response (pCR). The patient remained recurrence-free 25 months post-surgery. This case illustrates the potential of immunotherapy-based neoadjuvant regimens to convert unresectable PD-L1–high EGFR-mutant lung adenocarcinoma into operable disease and achieve durable pCR.

Keywords: EGFR-mutant lung adenocarcinoma, pathological complete response, immunotherapy conversion, sintilimab, neoadjuvant therapy

Introduction

The management of locally advanced non–small cell lung cancer (NSCLC) with pleural involvement presents considerable therapeutic challenges. The introduction of immune checkpoint inhibitors (ICIs) combined with chemotherapy has transformed the neoadjuvant treatment landscape for resectable NSCLC, achieving pathological complete response (pCR) rates ranging from 24% to 37% in pivotal trials such as CheckMate 816 and NADIM II.[1,2] However, these regimens show limited efficacy in EGFR-mutant tumors, which exhibit inherent primary resistance to PD-1/PD-L1 inhibition, with response rates below 5%.[3] Furthermore, the presence of pleural metastases has traditionally been considered a contraindication to surgical resection. Conversion therapy for initially unresectable disease remains particularly challenging, with pCR rates below 5% even in stage IV NSCLC. Here, we report a rare case in which a pCR was attained through a multimodal strategy incorporating an anti–PD-1 antibody after a suboptimal response to EGFR-TKIs and chemotherapy.

Case Presentation

A 57-year-old non-smoking female presented with a 6.6 cm spiculated mass in the right lower lobe, identified on a chest computed tomography (CT) scan performed in October 2020. The mass exhibited malignant characteristics such as lobulation, pleural indentation, and mediastinal lymph node enlargement. Metastatic pleural nodules are indicated by

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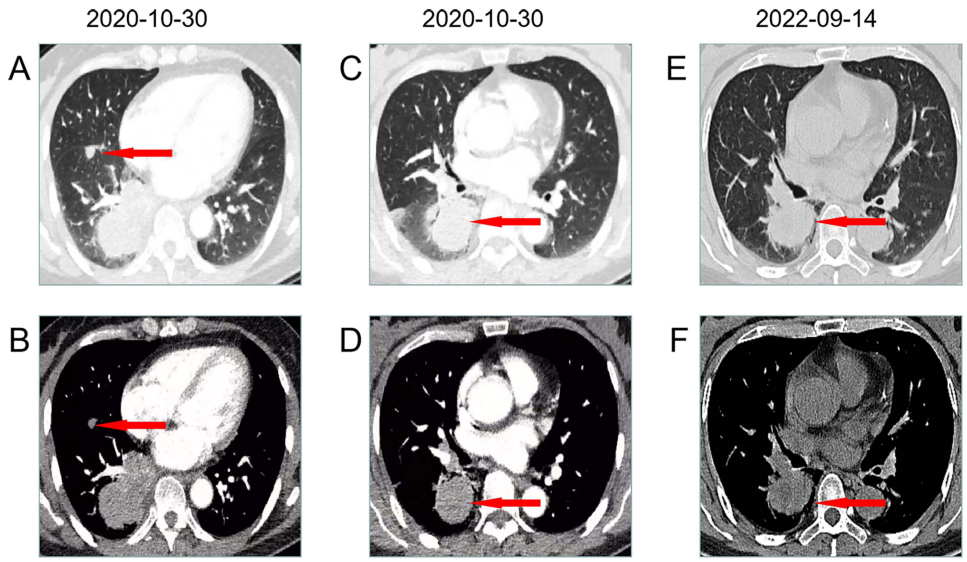

Figure 1 Chest CT imaging features of malignant pulmonary mass. (**A** and **B**) Axial and coronal views demonstrating metastatic pleural nodules (red arrows). (**C** and **D**) Primary lesion in the right lower lobe (red arrows). (**E** and **F**) Representative CT images demonstrating progressive disease (PD) of the primary lung mass after 22 months of gefitinib therapy. Red arrows indicate progression of the primary lesion.

arrows (Figure 1A–B), and the primary lesion in the right lower lobe is shown in Figure 1C–D. A CT-guided biopsy confirmed the diagnosis of moderately differentiated lung adenocarcinoma with an EGFR exon 21 L858R mutation. PD-L1 expression was heterogeneous, with tumor proportion scores (TPS) of 60% (22C3 assay) and 30% (E1L3N assay). Staging identified pleural nodules (cM1a), classifying the disease as stage IVA.

Phase 1: Targeted Therapy

First-line treatment with gefitinib (250 mg/day) was initiated, achieving disease control for 22 months. However, plasma genotyping in July 2022 confirmed persistence of the EGFR L858R mutation (0.1% variant allele frequency, VAF) and emergence of a GNAS R201C mutation (0.2% VAF). Serial CT imaging at 22 months after starting gefitinib revealed disease progression (PD) in the primary lung mass, marked by an increase in lesion size (red arrows, Figure 1E–F), prompting a change in treatment.

Phase 2: Chemoimmunotherapy Conversion

The patient received four cycles of chemotherapy with pemetrexed, carboplatin, and bevacizumab, resulting in stable disease (SD). A PET-CT scan in March 2023 showed metabolic activity in the primary tumor, with a maximum standardized uptake value (SUVmax) of 15.3, and no hypermetabolic lymph nodes. The tumor measured approximately 5.2×3.9 cm (red arrow, Figure 2A–B). The patient then received conversion therapy with nab-paclitaxel (260 mg/m^2), carboplatin (AUC 5), bevacizumab (15 mg/kg), and sintilimab (200 mg). Follow-up imaging four weeks later revealed marked shrinkage of the target lung lesion (red arrow, Figure 2C–D), downstaging the disease to a potentially resectable status.

Phase 3: Surgical Intervention & Outcome

In April 2023, the patient underwent muscle-sparing thoracotomy with right lower lobectomy and systematic mediastinal lymph node dissection. Histopathological examination of the resected specimen showed no residual viable tumor cells (ypT0N0), indicating a pathological complete response (pCR). A chest CT scan 25 months post-surgery showed no recurrence (Figure 2E–F), with no adjuvant therapy administered during this period. The initial right pleural metastatic nodule (Figure 3A, red arrow) showed no significant response after 22 months of gefitinib (Figure 3B, red arrow). However, it exhibited pronounced shrinkage after four cycles of chemotherapy combined with anti-angiogenic therapy

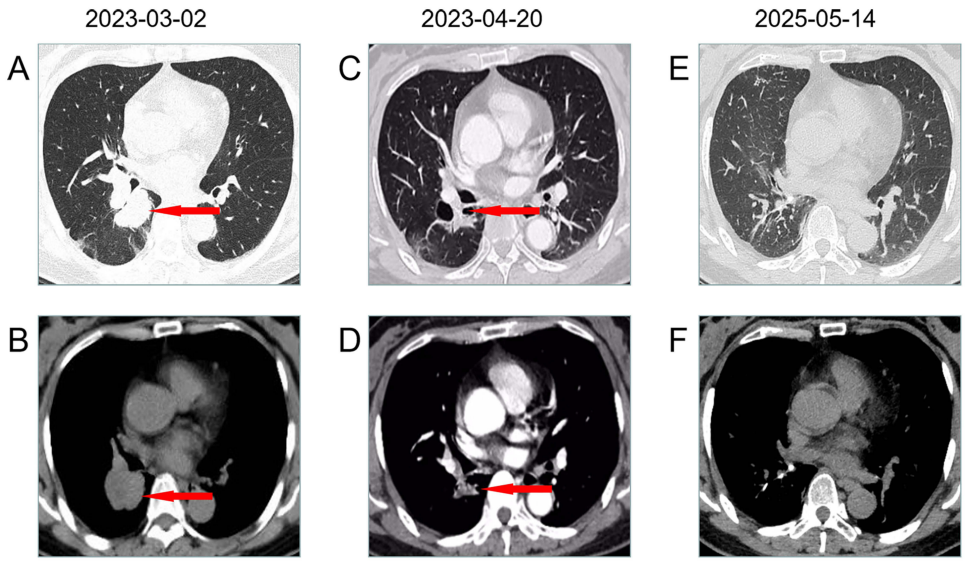

Figure 2 (**A** and **B**) PET-CT following 4 cycles of pemetrexed/carboplatin/bevacizumab: Primary tumor (red arrow, 5.2×3.9 cm). (**C** and **D**) Post-cycle 1 CT after quadruplet therapy (sintilimab 200 mg, nab-paclitaxel 260 mg/m^2, carboplatin AUC 5, bevacizumab 15 mg/kg) demonstrating significant shrinkage of the target lung lesion (red arrow). (**E** and **F**) Follow-up chest CT images (>2 years post-operatively, without adjuvant treatment) showing no evidence of recurrence.
Abbreviations: SD, stable disease; PD, progressive disease.

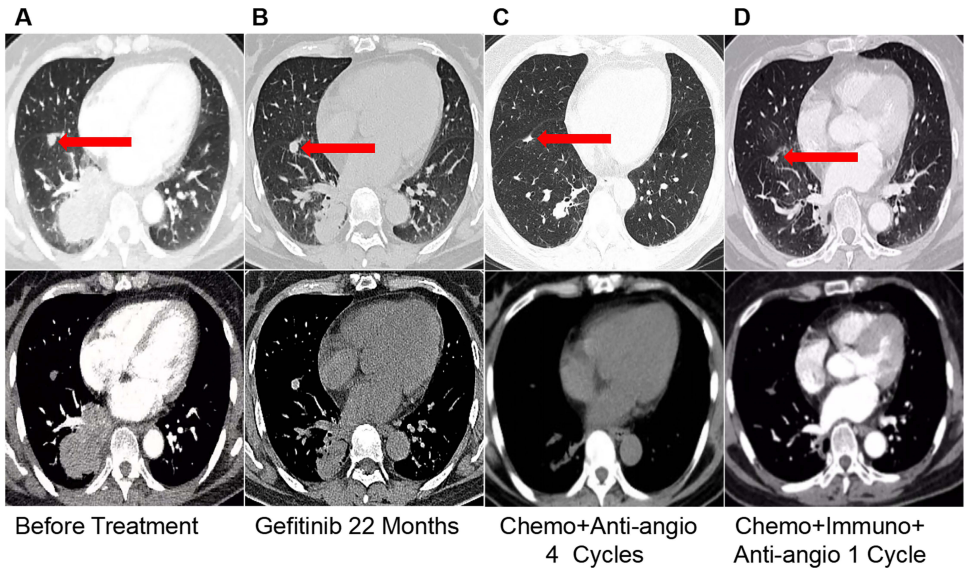

Figure 3 Evolution of pleural metastatic nodules: initial nodule (**A**) as indicated by the red arrow. After 22 months of gefitinib therapy (**B**), (red arrow); after four cycles of chemotherapy+anti-angiogenic therapy (**C**), (red arrow);After one cycle of immunotherapy+chemotherapy+anti-angiogenic therapy (**D**), (red arrow).

(Figure 3C, red arrow). After subsequent immunotherapy, the nodule remained stable without further significant change (Figure 3D, red arrow).

Discussion

Emerging evidence from recent case reports indicates that patients with traditionally unresectable stage IIIB NSCLC, who harbor both high PD-L1 expression and specific driver mutations, may derive considerable benefit from combined targeted therapy and immunotherapy. Such regimens have enabled tumor downstaging, successful R0 resection, and pCR. In one report by Zhang et al, a patient with an ERBB2 mutation achieved surgical conversion and pCR following treatment with T-DXd plus a PD-1 inhibitor.[4] Similarly, Cheng et al documented pCR in a case with a BRAF

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V600E mutation using neoadjuvant dabrafenib and trametinib combined with a PD-1 inhibitor.[5] In contrast, the present case involves stage IV NSCLC, initially characterized by an EGFR mutation and high PD-L1 expression, which, after multiple lines of therapy, underwent successful conversion therapy, R0 resection, and attained pCR. This outcome is particularly remarkable in advanced driver-mutant lung cancer and offers valuable clinical insights for managing similarly challenging cases.

Although high PD-L1 expression (≥50%) in EGFR-mutant NSCLC is typically associated with poor prognosis and primary resistance to TKIs,[6] the patient described in this report, who had high PD-L1 expression and an EGFR mutation, initially exhibited a favorable response to EGFR-TKIs. However, as discussed in a previous review,[7] the tumor immune microenvironment (TIME) in EGFR-mutant lung cancer following targeted therapy is often characterized by an immunosuppressive state. This includes the enrichment of regulatory T cells (Tregs), functional exhaustion of cytotoxic T cells, and polarization of tumor-associated macrophages (TAMs) toward a pro-tumor M2 phenotype. These factors contribute to an "immune-excluded" or "immune-desert" type of "cold" tumor microenvironment, where the immune system fails to effectively recognize and eliminate resistant tumor clones that eventually emerge, leading to disease progression. The poor response of the pleural nodules further suggests that metastatic niches may reside within a more profoundly immunosuppressive ecological milieu. After developing resistance to targeted therapy, the patient received four cycles of pemetrexed-carboplatin-bevacizumab, which resulted in shrinkage of the pleural nodules but no significant reduction of the primary lesion. However, due to severe gastrointestinal adverse effects attributed to pemetrexed intolerance, the regimen was adjusted. We transitioned to a sintilimab-based quadruple regimen, replacing pemetrexed with nab-paclitaxel. This decision was based on several considerations: the family's strong preference to continue therapy, evidence supporting the efficacy and safety of nab-paclitaxel/carboplatin/bevacizumab,[8,9] and findings from trials such as IMpower130[10] and ORIENT-31,[11] Crucially, nab-paclitaxel is a more rational partner for immunotherapy. Unlike pemetrexed or solvent-based paclitaxel, it does not require routine steroid premedication, thereby avoiding potential immunosuppression. Moreover, nab-paclitaxel has demonstrated superior immunomodulatory effects and, due to its unique formulation, achieves higher intratumoral drug concentrations.[12,13]

The remarkable success of this subsequent combination regimen hinges on its synergistic remodeling of the previously immunosuppressive TIME, as outlined in a prior review:[7] 1. The "Priming" Effect of Chemotherapy: Platinum-based agents and nab-paclitaxel induce immunogenic cell death, releasing tumor antigens and damage-associated molecular patterns (DAMPs). This process effectively "sounds the alarm" for the immune system. Concurrently, chemotherapy selectively depletes immunosuppressive Tregs, thereby "creating space" for effector T cells to function optimally. 2.The "Pathway" Effect of Anti-angiogenesis: Bevacizumab, by inhibiting VEGF, promotes the "normalization" of disordered tumor vasculature. This enhances intratumoral blood perfusion, alleviates hypoxia, reduces immunosuppression, and facilitates the infiltration and activation of cytotoxic T cells within the tumor core.3. The "Releasing" Effect of Immune Checkpoint Inhibitors: Building upon the successful "preparation of the battlefield" and "opening of pathways" achieved in prior steps, sintilimab (a PD-1 inhibitor) releases the "brakes" (PD-1/PD-L1 signaling) on infiltrating T cells. This reinvigoration restores their potent tumor-killing function, ultimately leading to a pathologically confirmed complete response.

This remarkable outcome is supported by several factors:1. Synergy of Anti-angiogenesis and Immunotherapy: Bevacizumab simultaneously inhibits angiogenesis and enhances the durability of the immune response,[14] promoting sustained effector T-cell activity. This mitigates immune evasion and extends therapeutic efficacy. The Phase III ATTLAS trial, where the same ABCP regimen significantly improved progression-free survival (PFS) in EGFR/ALK-positive NSCLC with a profound benefit in high PD-L1 expressors (HR 0.24),[15] underscores this potential. 2.Favorable Biomarker Profile: The patient's high PD-L1 expression (TPS >50%) is a recognized predictor of immune checkpoint inhibitor (ICI) efficacy, as demonstrated in the CheckMate 77T trial where perioperative nivolumab significantly improved event-free survival (EFS) in PD-L1-positive patients (HR 0.52).[16] 3.Aggressive Surgical Intervention and pCR: Postoperative pathology confirmed pCR, which is associated with excellent long-term outcomes. In the CheckMate 816 trial, pCR was linked to improved EFS.[1] No adjuvant therapy was administered post-surgery, and the patient has remained recurrence-free throughout an extended follow-up period of 25 months.

In conclusion, for patients with stage IV lung adenocarcinoma harboring EGFR mutations and high PD-L1 expression accompanied by pleural metastases, a multimodal approach that incorporates sequential targeted therapy, immune checkpoint inhibition in conjunction with chemotherapy, and anti-angiogenic treatment can result in a pCR. Subsequent surgical intervention may facilitate long-term disease-free survival, providing a successful and instructive model for patients with similar profiles. This treatment trajectory, which deviates from the current therapeutic paradigm, warrants in-depth consideration and further investigation.

Ethical Approval

The ethics Statement was not applicable for case reports according to the No.2 People's Hospital of Fuyang City; however, informed consent was obtained from the patient. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Disclosure

The authors report no conflicts of interest in this work.

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