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# Osimertinib in Pulmonary Manifestations: Two Case Reports and Review of the Literature

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**Abstract.** *Osimertinib is an oral, irreversible epidermal growth factor receptor inhibitor that is associated with various pulmonary manifestations including transient asymptomatic pulmonary opacities (TAPOs) and pneumonitis. We present a case of a 61-year-old female with Stage IV lung adenocarcinoma, who developed bilateral ground glass opacities on her chest-computed tomography (CT) three months after initiating osimertinib. Her imaging findings were thought to represent lymphangitic carcinomatosis responding to chemotherapy rather than drug induced toxicity, and she was continued on osimertinib. Conversely, we present a second case of a 57-year-old female with Stage IV lung adenocarcinoma who developed osimertinib-induced pneumonitis and was successfully rechallenged with osimertinib and glucocorticoids. These cases, described herein, illustrate examples of the range of pulmonary manifestations of osimertinib, as well as the safety of rechallenging patients with osimertinib and glucocorticoids following the development of pneumonitis.*

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) are the standard of care for patients with advanced non-small cell lung cancer (NSCLC) with mutant EGFR. Of the patients who progress on first-line EGFR-TKIs, many have a T790M mutation in *EGFR*. Osimertinib is an irreversible, oral, third-generation EGFR-TKI that has activity against both EGFR activating mutations (such as the exon 21 L858R point mutation, and exon 19 deletions) and the T790M point mutation that results in resistance to the first generation EGFR TKIs. Based on the results of the multicenter, double-blind randomized control trial, FLAURA NCT02296125, the FDA has recently approved osimertinib for first-line treatment of patients with metastatic NSCLC with the most common EGFR mutations (exon 19 deletion and exon 21 L858R mutation). Pneumonitis is a serious and potentially fatal adverse consequence of treatment with osimertinib (1). We present two cases of patients with advanced NSCLC harboring the T790M *EGFR* mutation on osimertinib therapy. The first case represents a patient who continues osimertinib therapy despite the development of asymptomatic pulmonary opacities on imaging. The second case is a patient who was successfully rechallenged with osimertinib after developing osimertinib-induced pneumonitis.



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## Case 1: Ground Glass Pulmonary Opacities Representing Osimertinib Induced Disease Response

A 61-year-old nonsmoking female presented in February 2017 with Stage IV lung adenocarcinoma with both L858R and T790M mutations in *EGFR* at diagnosis. She had been initiated on gefitinib at an outside institution but was found to have clear disease progression with miliary pattern pulmonary metastases within a few months of treatment (Figure 1A, B). In September 2017, she was switched to osimertinib with significant improvement in her dyspnea. Three months later, her chest CT revealed bilateral ground glass opacifications despite the fact that her miliary pattern metastases had improved significantly (Figure 1C, D). There was concern that the ground glass opacities were related to drug-induced pneumonitis, but she continued to achieve clinical improvement in her dyspnea during this period. Despite the radiographic suggestion of pneumonitis, it was thought that her opacities represented lymphangitic carcinomatosis responding to chemotherapy rather than drug-induced toxicity. Given her clinical stability, she continued to receive 80mg

Table I. *Literature review of osimertinib rechallenges.*

| Case | Age/Gender | Time to presentation | Osimertinib initial | Osimertinib rechallenge | Corticosteroid | Recurrence | Reference |
|---|---|---|---|---|---|---|---|
| 1 | 82/M | 8 months | 80 mg/day | 80 mg/eod | Yes | No | 7 |
| 2 | 60/F | 6 weeks | NA | NA | No | NA | 7 |
| 3 | 38/F | 31 days | 80 mg/day | 40 mg/day | Yes | No | 8 |
| 4 | 75/F | 64 days | 80 mg/day | 40 mg/day | Yes | No | 9 |
| 5 | 62/M | 82 days | 80 mg/day | 40 mg/day | Yes | No | 10 |
| 6 | 69 /F | 55 days | 80 mg/day | 40 mg/day | Yes | No | 11 |
| 7 | 57/F | 3 weeks | 80 mg/day | 80 mg/eod | Yes | No | Present |

eod: Every other day; NA: not reported.

osimertinib daily without the addition of steroids. Subsequent imaging over the next year on osimertinib continued to show an excellent tumor response and gradual improvement in the ground glass opacities (Figure 1E, F).

## Case 2: Successful Osimertinib Rechallenge in Osimertinib Induced Pneumonitis

A 57-year-old female with a twelve pack-year smoking history was diagnosed with Stage IV adenocarcinoma with an exon 19 deletion in *EGFR* in September 2013 when she presented with a malignant pleural effusion. She was initiated on erlotinib in October 2013 and maintained an excellent response for 4 years. In November 2017, a positron emission tomography (PET) scan showed disease progression with new hepatic and osseous metastases. Given erlotinib treatment failure, she underwent mutation analysis and was found to be harboring the T790M point mutation. She was initiated on osimertinib in December 2017 (Figure 2A). Within three weeks of osimertinib therapy, she developed severe dyspnea with acute hypoxic respiratory failure (peripheral capillary oxygen saturation, 93% on high flow nasal cannula) requiring intensive unit level care. Chest CT showed new, extensive bilateral ground glass opacities (Figure 2B). An extensive infectious work-up was unrevealing. Drug-induced pneumonitis was suspected and she was immediately taken off osimertinib. She was treated with 60 mg methylprednisolone every six hours for five days followed by a two-month prednisone taper. Within two days on corticosteroids, she had significant improvement in her shortness of breath and hypoxia. Within one month, she was no longer requiring supplemental oxygen. She initiated chemotherapy with carboplatin and pemetrexed. She completed four cycles of carboplatin and pemetrexed followed by maintenance pemetrexed, but was found to have disease progression in her liver after three months. Despite understanding the risk of pneumonitis redevelopment, the patient opted for re-challenge with osimertinib. She was started initially on osimertinib 80 mg every other day along with 0.5 mg/kg daily prednisone in May 2018. Over the next three months, prednisone was tapered down to 5 mg every other day, and she remained on daily 80 mg osimertinib with evidence of significant tumor response and without clinical or radiographical signs of pneumonitis. She remained on osimertinib until April 2019 when she developed progressive disease with leptomeningeal carcinomatosis (Figure 2C). At that time, a chest CT showed right-sided nodular infiltrates that were felt to more likely to represent progressive disease.

## Discussion

Osimertinib use has been associated with the development of several pulmonary manifestations, ranging from asymptomatic findings on imaging to life threatening pneumonitis. The first case in this report demonstrates that continuing treatment with osimertinib despite new onset ground glass pulmonary lesions may be reasonable if the patient remains asymptomatic.

Given the range of pulmonary manifestations in NSCLC patients on osimertinib, benign features may be mistaken for pneumonitis. The most common imaging findings of anti-neoplastic agent-induced pneumonitis are multifocal ground-glass opacities with intralobular interstitial thickening (4). However, there are multiple diagnoses that overlap with this radiographic pattern such as pulmonary adenocarcinoma in-situ, lymphangitic carcinomatosis, infection, pulmonary hemorrhage or pulmonary edema (5). In addition to the identifiable causes above, transient asymptomatic pulmonary opacities (TAPOs) have been described in 20-35% of patients while on osimertinib therapy (1)). These TAPOs are clinically benign areas of ground glass opacities that resolve despite continued dosing with osimertinib. Much like the patients in these reports, our patient was entirely asymptomatic when the new ground glass opacities developed. However, unlike the TAPOs cases described, despite monitoring for several months, our patient had persistent imaging findings that corresponded to clinical

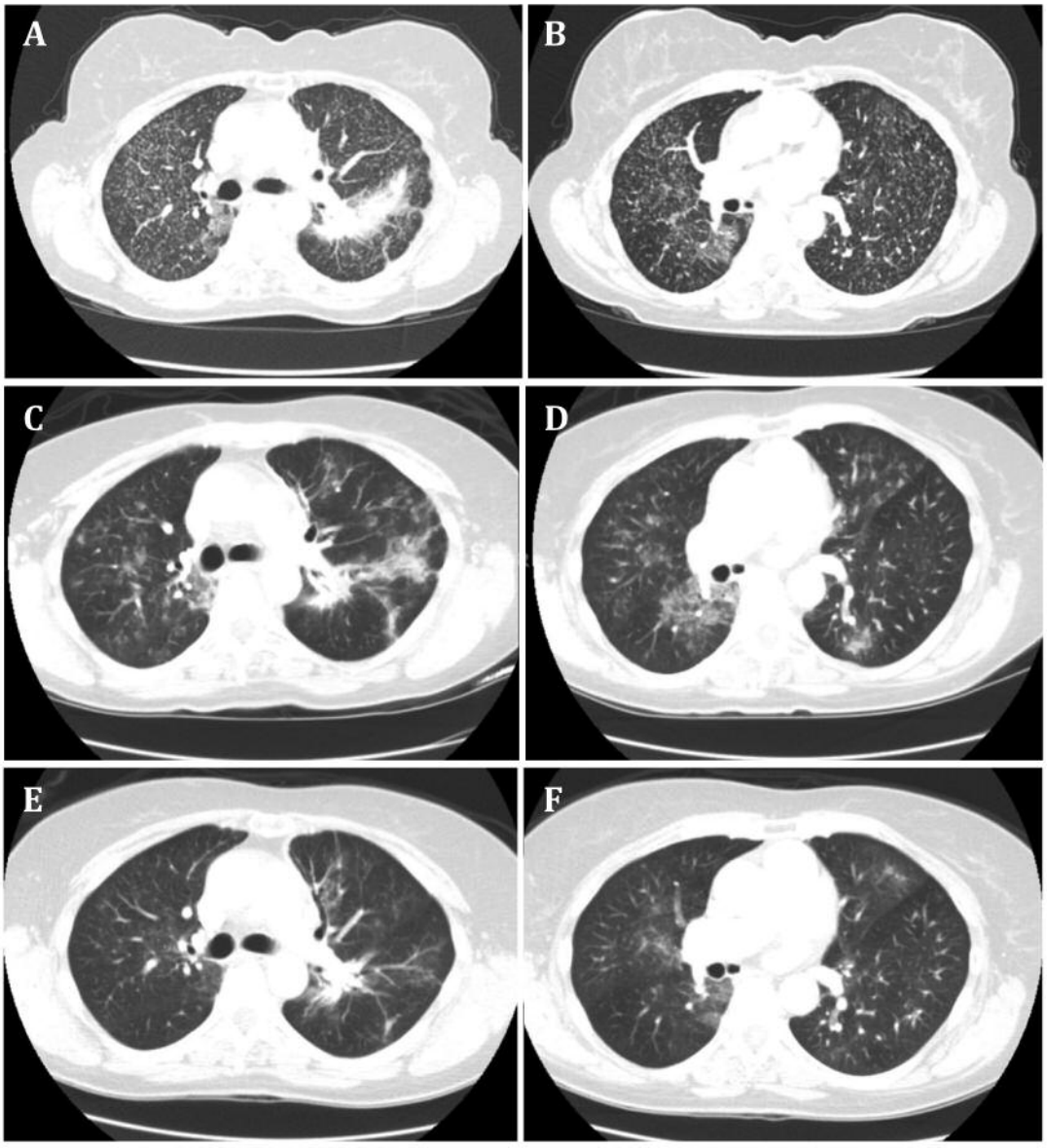


Figure 1. *Chest CT of ground glass opacities. A chest CT performed prior to initiation of osimertinib with miliary type pattern metastases (A, B). A chest CT performed 3 months after initiation of osimertinib shows that the extensive miliary type pattern has largely resolved but now with patchy areas of ground glass infiltrate and intralobular septal thickening (C, D). Stable patchy ground glass infiltrates bilaterally on a chest CT 20 months after continued osimertinib use (E, F).*

improvement, and therefore more likely represented disease response. It is critical to distinguish between the various pulmonary manifestations to make a decision about continuation or discontinuation of osimertinib, as there are limited further treatment options.

The second case illustrated that rechallenging with osimertinib and a glucocorticoid was an effective option for a metastatic lung cancer patient who had previously developed osimertinib-induced pneumonitis. Our patient was monitored after her osimertinib rechallenge for 11 months, which to our knowledge, is the longest described period.

Serious complications such as pneumonitis and interstitial lung disease (ILD) have been reported after osimertinib use. In the FLAURA trial, 4% of patients in the osimertinib group developed ILD or pneumonitis (3). In comparison, only 2% of patients in the standard EGFR-TKI group (gefitinib or erlotinib) developed ILD. In this study, treatment discontinuation was mandated because of ILD/pneumonitis,

and there were no fatalities due to ILD/pneumonitis. As osimertinib continues to reach a greater population, osimertinib-induced pneumonitis will also affect more patients. While permanent discontinuation of the drug continues to be the standard of care following this adverse event, a few case reports have described success with osimertinib rechallenge along with steroid therapy (Table I) (8-12).

The mechanism for osimertinib induced pneumonitis is unknown and more than one mechanism may be responsible for the drug induced lung injury. One suggested mechanism of lung injury involves immune mediated facilitation of inflammatory signals. Based on this hypothesis, we rechallenged our patient with corticosteroids to blunt any excessive immune system response. Another mechanism involves cytotoxic lung injury by impairing anti-apoptotic mechanisms. The EGFR-TKI, gefitinib, has been suggested to augment underlying pulmonary fibrosis through inhibiting EGFR phosphorylation and reducing regenerative epithelial proliferation (13, 14).

It is also unclear whether osimertinib induces direct or dose-dependent toxicity. Without clinical trials to guide the dose with which to rechallenge patients after osimertinib-induced pneumonitis, we initially decreased the frequency of dosing to every other day and gradually increased the dosing to daily. Other case reports have also described success with initiating with a reduced daily dose (Table I). As the use of osimertinib increases, oncologists should be familiar with potential strategies for re-challenge with osimertinib after the development of pneumonitis.

## Conclusion

Osimertinib has been associated with pneumonitis and other radiographic abnormalities. The cases presented here highlight radiographic changes that mimic pneumonitis but may not require discontinuation of osimertinib as well as the safety of carefully rechallenging patients with osimertinib and corticosteroids after the development of drug-induced pneumonitis. While re-exposing patients who have developed drug induced pneumonitis to osimertinib carries potential risk for the patient, clinicians should be aware that the benefits may be worthwhile in patients with limited alternative treatment options.

## Conflicts of Interest

The Authors certify that they have no conflicts of interest regarding the subject matter or materials discussed in this manuscript.

## Authors' Contributions

All Authors have participated in the drafting and critical revision of the manuscript. The decision to submit the final report for publication was made by all authors. Each Author certifies that this material has not been and will not be published in any other publication.

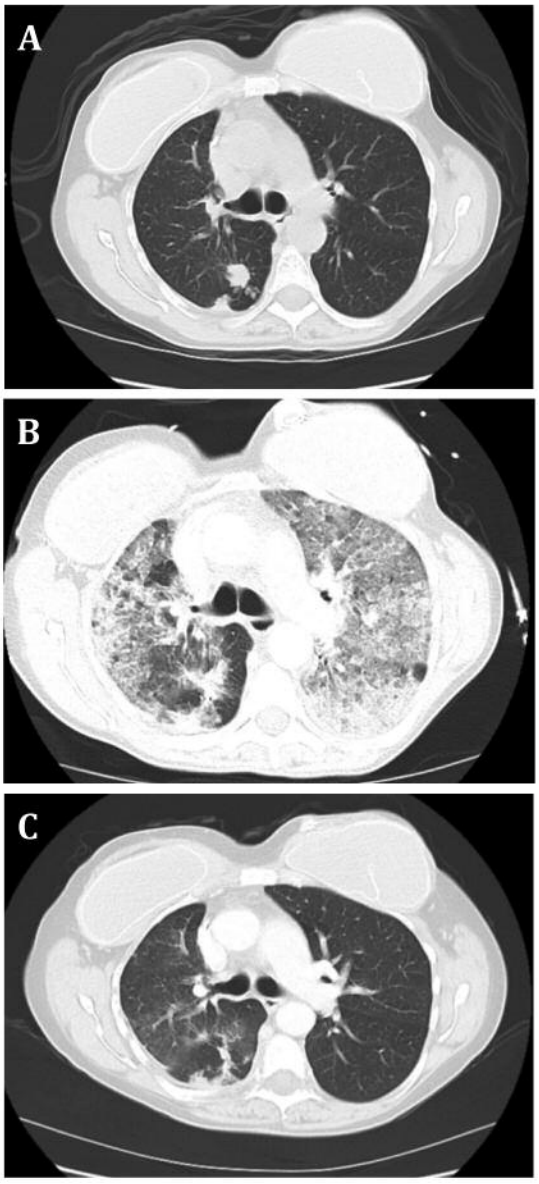


Figure 2. *Chest CT of osimertinib-induced pneumonitis. Before treatment with osimertinib, a chest CT shows a mass at the right lung base and multiple nodules in the right lower lung (A). Three weeks after osimertinib initiation, a chest CT shows new diffuse bilateral ground glass opacities (B). Four months after rechallenging with osimertinib and steroids, a chest CT shows no evidence of recurrence of pneumonitis (C).*

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