Annals of Clinical Radiology

Case Report
Published: 10 Feb, 2024

Osimertinib-Related Pulmonary Fibrosis, A Case Report and Review of Literature

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Abstract

Lung cancers are the leading cause of mortality worldwide. Pulmonary malignancies are grossly divided into small-cell lung carcinoma and non-small-cell lung carcinoma. Non-small cell lung carcinoma contributes to the majority of tumor burden. The treatment regimen and subsequent prognosis for lung cancer depend on the type of cancer, the grade, and the stage. With the advancement in modern immunology and genetics, targeted treatment therapies targeted against specific genetic mutations and immune markers resulted in improved survival. Though these treatment modalities are considered to have minimal to no effect on co-existing normal tissues, there have been reports of side effects among patients on these advanced treatments. Here we present a case of 72 years old female with advanced metastatic non-small cell lung carcinoma who presented with significant deterioration of respiratory status. Initially, due to elevated inflammatory markers and fever, was treated with antibiotics. However, with worsening respiratory status despite being on appropriate antibiotics, she was started on steroids for the imaging findings suggestive of pulmonary fibrosis. Initiation of steroids resulted in rapid recovery, with the improvement of imaging findings and oxygen requirements. The patient was eventually discharged home without oxygen to follow up with hematology regarding further treatment. Osimertinib has been shown to improve progression-free survival compared to the earlier generations of EGFR TKIs, however, there are adverse effects to Osimertinib, with the most common being rash, diarrhea, and dry skin. More severe and potentially fatal, side effects like QT interval prolongation, interstitial lung disease, and drug-related pneumonitis are documented potential adverse effects as well. In all the reported cases, the removal of medication results in the improvement of pulmonary fibrosis. However, a few cases have reported successful reintroduction of Osimertinib once the fibrosis improves with no recurrence. There is a need to run blinded trials to find the association of Osimertinib with co-existent factors that can contribute to pulmonary fibrosis.

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Received Date: *17 Jan 2024*
Accepted Date: *05 Feb 2024*
Published Date: *10 Feb 2024*

Citation:
Ul Rasool MH. Osimertinib-Related Pulmonary Fibrosis, A Case Report and Review of Literature. Ann Clin Radiol. 2024; 6(1): 1022.

Introduction

Lung Cancer is the leading cause of cancer death in the US and worldwide leading to approximately 127,070 deaths annually [1]. It is the second most commonly diagnosed cancer following prostate cancer in men and breast cancer in women [1]. Primary lung malignancies can be divided into two broad categories: Non-Small Cell Lung Cancer (NSCLC), and Small Cell Lung Carcinoma (SCLC). NSCLC accounts for 85%, and Small Cell Lung Cancer (SCLC) accounts for 15% of the total lung malignancy burden. NSCLC is further divided into 3 subtypes; Adenocarcinoma, Squamous Cell Carcinoma, and Large Cell Carcinoma. Lung adenocarcinoma is not only the most common type of NSCLC, but it is also the most common type of lung cancer among nonsmokers and is more prevalent among women. All other types of lung cancer are strongly associated with smoking tobacco and are more prevalent among men. Adenocarcinoma is a cancer of mucus-producing glands and it is generally located in the periphery of the lungs. Squamous Cell Carcinoma of the lungs is the second most common type of NSCLC. SCC is most prevalent amongst smokers as smoking tobacco is the main risk factor. SCC is generally located centrally within the lungs. The third subtype of NSCLC is Large Cell Carcinoma. This type of cancer is mostly found in the lung periphery and is rarely found in non-smokers [2-5].

The treatment regimen and subsequent prognosis for lung cancer depend on the type of cancer, the grade, and the stage. Before modern chemotherapeutic agents and targeted therapy, the gross survival rate after diagnosis of lung malignancies varied from 2 to 4 months [6]. Modern chemotherapeutics used to treat various lung cancers include cytotoxic drugs, targeted therapeutics, and immunomodulators. Common side effects associated with cancer therapy vary depending on the type of treatment: Cardiotoxicity, radiation pneumonitis, and pulmonary fibrosis associated with

thoracic radiation therapy, neutropenia and subsequent increased risk for infections; reversible alopecia; nausea and vomiting; anemia and fatigue associated with chemotherapy, hypertension, problems with clotting factors, skin rashes are associated with targeted therapy [7-10]. Cytotoxic drugs are the oldest class of chemotherapeutics and as of 2020, there were around 80 cytotoxic medications approved for use in lung cancer and more continue to be developed. They are further classified based on their mechanism of action or their chemical family. Their mechanisms of action vary and include inhibition of DNA/RNA synthesis, inhibition of DNA replication *via* disruption of several key enzymatic functions or by binding to DNA molecules directly, mitosis disruption, and inhibition of nucleic acid metabolism [11].

Targeted therapy targets upregulated pathways responsible for the malignant phenotypes, and is indicated for advanced or metastatic NSCLC with a known oncogenic gene mutation. With the development of advanced technologies in medical diagnostics, especially within genetics such as next-generation sequencing, it has been made possible to study and cater the treatment targeted against specific gene mutations. There are now several viable classes of molecular targeted therapies available to treat patients, and they can be individually tailored based on the genomic aberrations found in their particular type of cancer. Examples of such genetic aberrations include EGFR activating mutations, ALK translocations, ROS1 rearrangements, overexpression of HER2, and RET gene mutations amongst several others. Each class of targeted therapy is defined by which pathway is being inhibited [12]. As EGFR TKIs are a relatively new first-line chemotherapeutic agent used in the treatment of lung cancer, evidence of their side effect profile and management of adverse events has been studied and documented in recent years. Treatment-related adverse events are reported in 70% of cases ranging from skin disorders, diarrhea, fatigue, and elevated liver enzymes [13-15]. However, much less prevalent but more severe and potentially fatal adverse events such as Interstitial Lung Disease (ILD) have been observed. In a total of 21 clinical trials with 1,468 patients between 2006 and 2014, the incidence of ILD of grade three or higher reached approximately 2% [16].

Another treatment option is immunotherapy, which is based on altering T-cell function to improve cell-mediated immunity response towards the cancer cells. While both SCLC and NSCLC have been traditionally viewed as non-immunogenic tumors, advancements in immunology and success with immunotherapies have brought this class of medication to the forefront of research and treatment [14]. Functional studies of tumor-infiltrating lymphocytes within NSCLC tumor samples specifically, and their activity against cancer cell lines have led to the increased use of this class of medications and it is now indicated for locally advanced or metastatic NSCLC [17]. These drugs help to increase immune system activity against tumor cells, especially CD8+ cytotoxic T-cells which is accomplished by inhibiting immune checkpoints such as CTLA-4, PD-1, and PD-L1 which ultimately increase antitumor activity [17]. Surgical resection is the primary treatment for NSCLC stage I and stage II and it can be an option for early-stage SCLC [18,19]. Radiation therapy, a form of therapy that causes damage to cells through ionizing radiation, is commonly used in conjunction with chemotherapy.

Case Presentation

A 72-year-old African-American female with a past medical history of bronchial asthma, hypertension, anemia, systemic lupus erythematosus, osteoporosis, and hyperparathyroidism, stage IV Lung adenocarcinoma, with metastasis to bone and brain and on treatment with Osimertinib Mesylate (Tagrisso) presented to the Emergency Department with shortness of breath that began a few hours before presentation. The shortness of breath was associated with a runny nose, fatigue, and a worsening productive cough for 4 days. Of note, before the onset of this episode at baseline, she did not require home oxygen therapy and was able to ambulate independently. There was no recent travel history. The patient's current outpatient medications included albuterol sulfate, amlodipine, budesonide-formoterol, famotidine, metoprolol tartrate, morphine, ramipril, and cholecalciferol. The patient has received 6 cycles of combined carboplatin, paclitaxel, and Bevacizumab with the last dose given 21 months before the current illness. 12 months before admission, the patient finished 12 cycles of Pemetrexed combined with Pegfilgrastim (Alimta with Onpro), and 3 cycles of Gemcitabine were completed 7 months prior. The patient underwent stereotactic radiosurgery for lesions to the left side of her head and calvarium 3 weeks before admission. Due to poor response to prior interventions, and the discovery of an exon 19 EGFR mutation on ctDNA analysis, she was started on a trial of Tagrisso, a tyrosine kinase inhibitor, 4 weeks before admission.

Upon arrival at the Emergency Department (ED), the patient was alert and oriented x3, tachycardic, tachypneic, and normotensive with a temperature of 103.5°F, and an oxygen saturation of 89% on room air. Physical examination was significant for a cachectic-appearing female in acute respiratory distress with scattered rhonchi, and rales within the middle and lower lung zones bilaterally. Initial laboratory investigations in the ED included an elevated proBNP of 2,461 pg/mL, reduced eGFR of 48 mL/min/1.73m^2, elevated total bilirubin of 2.30 mg/dL with a direct bilirubin of 1.00 mg/dL, a lactate of 2.6 mmol/L, and an elevated procalcitonin level of 8.13 ng/mL. The patient's white blood cell count was within normal limits at 6.05 × 10^3/mcL without neutrophilia. Electrolyte levels, blood pH, CO_2, and troponins were all within normal limits. The viral panel for respiratory viruses was negative. The initial chest X-ray was positive for a layering moderate right pleural effusion, bilateral heterogeneous pulmonary opacities superimposed on pulmonary neoplastic processes, and bony metastatic disease. A CT angiogram of the chest was performed for concern for pulmonary embolism, which illustrated scattered patchy ground glass alveolar opacities bilaterally with superimposed micronodules but did not show any filling defects in the central pulmonary arteries to suggest a pulmonary embolism. A transthoracic echocardiogram was performed which revealed mild left ventricular hypertrophy with an adequate LV ejection fraction (75%), and an impaired relaxation pattern with normal left atrial pressure. The pulmonary artery systolic pressure was 51 mmHg and the right atrium was mildly dilated. Mild to moderate regurgitation was noted across the aortic and tricuspid valves. Sinus tachycardia was present on the ECG without acute deviations of the ST segment. Two sets of blood cultures were obtained and the patient was subsequently started on an empiric broad-spectrum antibiotic regimen consisting of vancomycin, cefepime, and azithromycin. Morphine was started for pain control. She required 3 L/min oxygen via nasal cannula to saturate at 98%. The patient was admitted to the medical inpatient floor for further management and observation under the impression of possible sepsis secondary to multi-focal pneumonia *vs.* drug-induced pneumonitis with concurrent acute hypoxic respiratory failure.

Table 1: Lab results by day of admission.

Laboratory Test	On Presentation	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Reference Range
Hemoglobin (g/dL)	8.5	7.3	7.4	6.4	8.5	8.1	8.3	8.5	8.8	9.2	**12.0-16.0**
WBC (10^3/mcL)	6.05	4.97	11.29	10.36	14.73	13.57	10.07	13.01	10.54	10.61	**4.80-10.80**
Procalcitonin (ng/mL)	8.13						2.54				**0.02-0.10**
pH venous	7.35		7.27	7.43							**7.32-7.43**
pH arterial					7.46			7.45			**7.35-7.45**
pO_2 venous (mmHg)	36		<30	87							**30-50**
pO_2 arterial (mmHg)					137			96			**83-108**
pCO_2 venous (mmHg)	40		49	37							**38-41**
pCO_2 arterial (mmHg)					42			49			**32-35**
Lactate venous (mmol/L)	2.6		3.9	2.1							**0.6-1.4**
Lactate arterial (mmol/L)					1.3			2.4			**0.4-0.8**
eGFR (ml/min/1.73m^2)	48	>60				>60				>60	**≥ 60**
proBNP (pg/mL)	2,461										**1-125**
Total Bilirubin (mg/dL)	2.3			0.9							**0.00-1.20**
Direct Bilirubin (mg/dL)	1			0.4							**0.00-0.3**

The patient`s Tagrisso regimen was continued as per the recommendation from the oncology consult as the risk of drug-induced pneumonitis was deemed low in the setting of fever, productive cough with yellow sputum, a sick contact, and an elevated procalcitonin. On day 2 of the hospital course, the patient was noted to again be in acute respiratory distress and hypoxic with an O_2 saturation in the 70s while on 3L *via* NC. At this time, a venous blood gas analysis was obtained and showed a pH of 7.27, PCO_2 of 49, a PO_2 of <30, and an increase in lactate to 3.9 mmol/L. A repeat chest X-ray showed interval worsening of diffuse alveolar opacities in the right lung and worsening alveolar opacities in the left lower lung field. New developing opacities were now present in the left upper lung field. The patient was placed on Bilevel-Positive Airway Pressure (BIPAP) and transferred to the Intensive Care Unit (ICU). The patient tolerated BIPAP well with adequate O_2 saturation in the ICU but remained tachypneic with accessory muscle use. The decision to discontinue Tagrisso was made due to worsening respiratory function while on antibiotic therapy. On day 5 of admission, accessory muscle use decreased and a trial of High-Flow Oxygen *via* Nasal Cannula (HFNC) was initiated as the patient was no longer desaturating when temporarily taken off of BIPAP. The patient tolerated HFNC well and maintained their oxygen saturation. The patient was later downgraded to 4L NC and continued to saturate adequately with less work of breathing. On day 6, a third chest X-ray illustrated improvement in aeration bilaterally in the upper and middle lung zones with residual scattered bilateral alveolar opacities and a small right pleural effusion. The procalcitonin level was also found to be reduced by day 6 ng/mL to 2.54 ng/mL. While in the ICU, vitals and electrolytes were monitored closely and repleted as necessary. The patient remained medically stable and home medications were resumed except for Tagrisso. She was downgraded back to the medical service while on 4L *via* NC on day 7 of hospitalization. The patient was weaned from oxygen and saturating well on room air. An outpatient follow-up appointment was scheduled with oncology and the patient was discharged home with a final diagnosis of drug-induced pneumonitis (Table 1).

Discussion

The discovery of genetic drivers in NSCLC has led to the development of therapies against these mutations. In NSCLC, one such genetic mutation is the EGFR gene, which occurs in 10% to 30% of patients with NSCLC [20]. First and second-generation EGFR Tyrosine Kinase Inhibitors (TKIs), such as erlotinib and afatinib, are useful in targeting and inhibiting this gene and treating NSCLC. However, first and second-generation EGFR TKIs are limited by acquired resistance in the EGFR gene, with most patients developing drug resistance to first-generation EGFR TKIs within a year due to point mutations [21]. The third-generation EGFR TKI, Osimertinib, addresses these acquired mutations while also sparing the wild-type EGFR. Osimertinib has been shown to improve progression-free survival compared to the earlier generations of EGFR TKIs [22]. However, there are adverse effects to Osimertinib, with the most common being rash, diarrhea, and dry skin [22]. More severe and potentially fatal, side effects like QT interval prolongation, interstitial lung disease, and drug-related pneumonitis are documented potential adverse effects as well. In the FLAURA trial, 2% of participants had pneumonitis as a result of Osimertinib [22]. A retrospective multicenter cohort study conducted by Sato et. al. evaluated 452 patients who received Osimertinib as first-line treatment for advanced EGFR+ NSCLC and found that 18% of patients experienced DRP and 9% developed Transient Asymptomatic Pulmonary Opacities (TAPOs) [17].

Specific cases of DRP due to Osimertinib treatment, similar to our patient, have been reported with resolution of symptoms after removal of the offending agent and concomitant corticosteroid therapy. One such case was reported in May of 2020 where a 79-year-old male non-smoker with stage IV EGFR+ lung adenocarcinoma with metastasis to the bones and adrenal glands was started on a standard 80 mg dose of Osimertinib per day and subsequently developed subpleural and bilateral lung opacities. Three weeks after starting Osimertinib, the patient developed acute hypoxic respiratory failure, requiring intubation in the intensive care unit. Laboratory investigations showed an elevation in infection parameters so blood cultures, serology, and bronchoalveolar lavage were performed which did not reveal a causal pathogen. At this point, Osimertinib was discontinued and prednisolone therapy was initiated which led to improvement in respiratory function and resolution of lung opacities

[17]. There has been some success in rechallenging patients with Osimertinib after developing DRP and using steroids to treat any pneumonitis flare-ups [23]. This treatment strategy is promising and should be investigated further considering Osimertinib has a longer Progression-Free Survival (PFS) rate compared to first- and second-generation EGFR TKIs [22].

In our patient, Osimertinib therapy was also continued initially as the risk of DRP was considered low due to an elevation in infection parameters, history of sick contact, fever, and productive cough. As the patient's condition continued to worsen on antibiotic therapy and viral panels and blood cultures returned negative, drug-induced pneumonitis became the leading differential and Osimertinib was discontinued. Once the offending drug was removed the pneumonitis resolved within a few days, in both cases, pneumonia of an infectious etiology was considered to be the most likely differential diagnosis initially. Further study needs to be done to assist clinicians in differentiating between the two etiologies, as the treatment for each differs dramatically. Another important avenue of research to consider is possible risk factors for developing DRP in the setting of Osimertinib use. For example, our patient had a history of asthma, yet to date, there have not been studies looking into the association between asthma and the development of DRP.

Conclusion

Osimertinib continues to be a first-line treatment for NSCLC, however, its use is limited by severe side effects such as pneumonitis. Clinicians need to recognize the potential for lung injury in patients undergoing EGFR TKI treatment, especially with Osimertinib, and be familiar with the proper management which involves removal of the offending agent and corticosteroid therapy. Further research into the prevalence, treatment, and risk factors of drug-related pneumonitis is required to further stratify treatment options in patients with NSCLC. Future studies should also further investigate potential treatments that do not require the removal of Osimertinib.

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