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CLINICAL VIGNETTE

Recurrent Pneumonitis due to Osimertinib

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Introduction

Lung cancer remains the leading cause of cancer death in the USA.[1] This is thought to be due to its rapid rate of metastasis. Lung cancer is divided into two main subtypes: small cell and non-small cell lung cancer (NSCLC). Adenocarcinoma, a type of NSCLC, is the most common type of primary lung cancer. It is a glandular tumor affecting the mucin-producing cells in the lung. A gene that is commonly mutated is epidermal growth factor receptor (EGFR). In patients with localized NSCLC, a curative approach with surgical resection is preferred, with or without chemotherapy. Patients with metastatic disease, receive palliative treatment, with or without molecular targeted therapy, contingent on a targetable mutation.[2]

In patients with an EGFR mutation, Osimertinib (Tagrisso) is first line treatment with significant improvement in median survival when compared to standard EGFR-tyrosine kinase inhibitors. Osimertinib's mechanism of action is inhibition of EGFR tyrosine kinase, which blocks intracellular phosphorylation leading to tumor cell death.[3,4] Common adverse reactions of Osimertinib include dry skin, diarrhea, rash, and nail toxicity. A rare side effect in clinical trials prior to 2015 FDA approval is drug induced ILD/pneumonitis, reported in 3.3% of patients.[5]

Case Presentation

HPI: A 75-year-old male presented with worsening dyspnea for one week. Past medical history includes diabetes, hypertension, prior strokes with residual left lower sided weakness, ESRD on hemodialysis (HD), prostate cancer treated with surgery and radiation, and metastatic NSCLC on Osimertinib.

The patient reported worsening orthopnea the night prior to admission, and decreased O2 saturation to the low 80s. He also reported having cough with the sensation of phlegm stuck in his chest. He denied chest pain, palpitations, fever, chills, myalgias, diarrhea. The patient reports producing about one cup of urine daily and had not missed any HD sessions or medications. He recently returned from a Caribbean cruise 10 days prior and received his HD on the ship. There were no known sick contacts.

About 15 years prior he was diagnosed with stage 1A bronchioalveolar lung carcinoma. He underwent left lower lobectomy and followed with serial CT scans. Three years ago he was admitted to an outside hospital where CT revealed a suspicious L lower lung nodule. Biopsies were reported as inconclusive.

The patient underwent CT guided biopsy nine months ago which revealed adenocarcinoma with exon 19 deletion EGFR mutation. The patient was initiated on Osimertinib and tolerated the treatment well, reporting occasional fatigue, myalgias. PET/CT 6 months after initiation of Osimertinib showed a favorable response to treatment.

In the ED, the patient was hypoxic with increased work of breathing, which improved with high flow nasal canula oxygen. He was admitted to the MICU for his oxygen requirement and additional evaluation. Admission labs were significant for an elevated BNP of 1260, mildly elevated troponin (0.05), and mild leukocytosis (~10K). CT chest revealed extensive peribronchial consolidations and ground-glass opacities with thickening of the interlobular septa. The patient's lung adenocarcinoma appeared stable with slightly increased size of the bilateral metastatic pulmonary nodules but were obscured by the extensive bilateral peribronchial consolidations and ground-glass opacities (Figure 1).

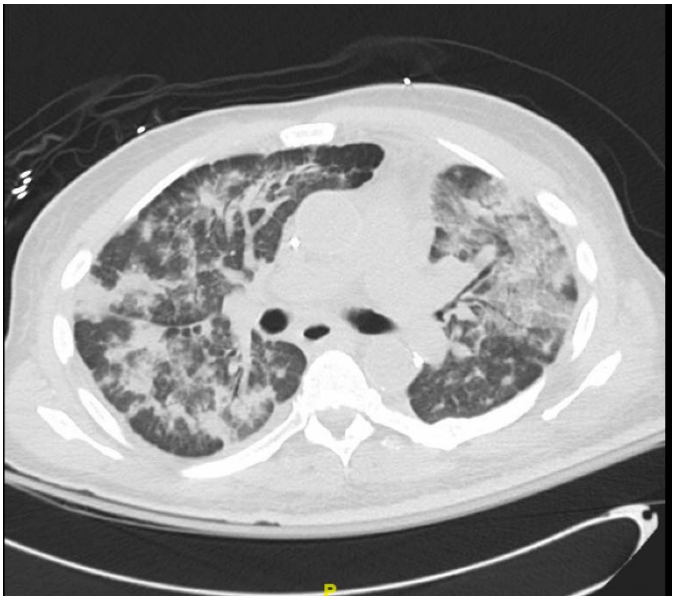

Figure 1 - presentation of acute hypoxic respiratory failure while taking Tagrisso- initial presentation.

The patient was empirically treated with IV antibiotics for pneumonia and underwent hemodialysis for volume removal. His Osimertinib was held due to concern that it may be causing his acute respiratory failure. Echocardiogram showed no acute abnormalities unchanged from prior. Ultrasound DVT evaluation was negative.

Broad infectious testing including fungal serologies and an upper respiratory viral panel were negative. However, Sputum cultures could not to be obtained even with induction by respiratory therapy.

The patient improved and was weaned to room air on the third hospital day. He euvolemic after hemodialysis and repeat chest CT showed decrease in the density and distribution of the previous parenchymal infiltrates (Figure 2). The patient was discharged with oncology and pulmonology follow up appointments. He was advised to remain off Osimertinib until his oncology appointment.

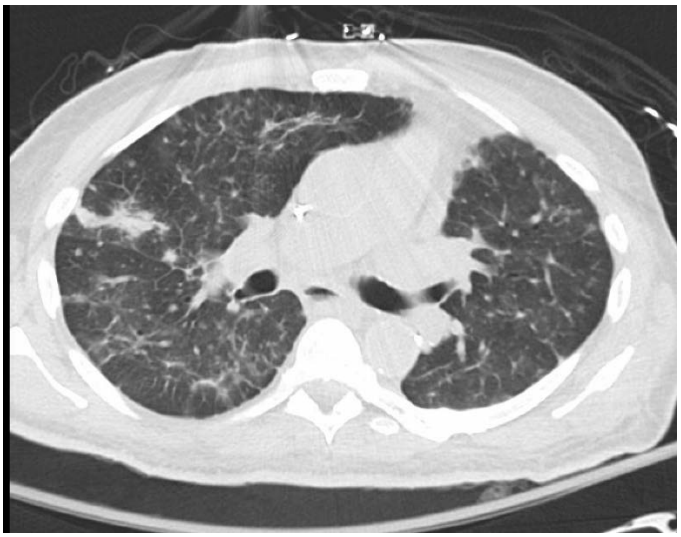

Figure 2 – Four days after discontinuation of Tagrisso and after repeat HD.

Two weeks post-discharge, the patient remained stable once he resumed Osimertinib. Over the next month, he reported ongoing dyspnea on exertion and fatigue. His dyspnea progressively worsened and his SpO2 fell to 80s on room air and required the initiation of home supplemental oxygen. He was admitted to an outside hospital a month later for acute hypoxic respiratory failure. He was treated with volume removal with hemodialysis and his Osimertinib was once again held. His discharge CT chest showed mild improvement of multifocal peribronchovascular consolidative opacities (Figure 3). His Osimertinib continues to be held with significant improvement of his fatigue and dyspnea.

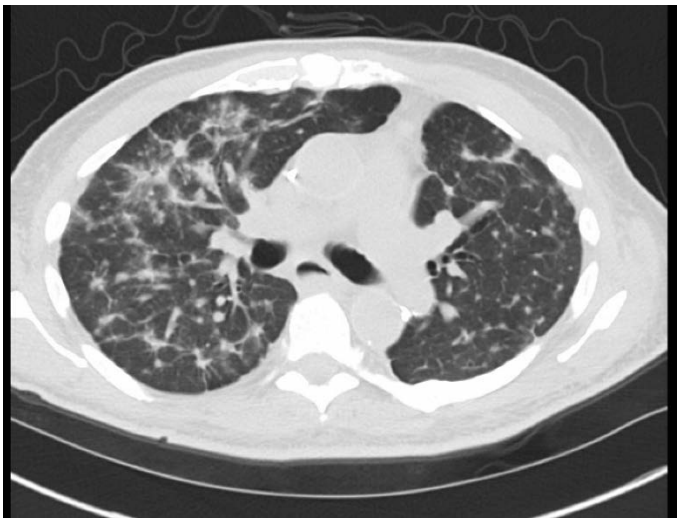

Figure 3 - months later days after a repeat episode of AHRF.

Discussion

Pulmonary toxicity is a common adverse reaction of antineoplastic agents. In the setting of NSCLC, pulmonary toxicity has a poor prognosis, with a mortality rate of 36% and a median survival of 3.5 months after diagnosis of pneumonitis.[6]

Although the pathology is not fully understood, it is suspected that the lungs are vulnerable to direct cytotoxicity. Direct cytotoxicity is related to the lungs receiving the entire blood supply and the thin alveolar blood-gas barrier alveolar surface area estimated at $75m^2$.[7] Another potential cytotoxicity method is EGFR inhibition. This impairs alveolar repair mechanisms in type 2 pneumocytes where EGFR expression is concentrated.[8]

The manifestations of pulmonary toxicity are variable. They include nonspecific dyspnea, hypoxemia, and/or cough. Evaluation typically includes chest imaging and ruling out cardiac and infectious etiologies.

Imaging, much like the symptoms can also be variable. A recent retrospective cohort study that evaluated 452 patients found 18% of patients treated with Osimertinib had drug related pneumonitis, but nearly half of these patients were asymptomatic. The imaging patterns are variable - ranging from organizing pneumonia, nonspecific interstitial pneumonia, and diffuse alveolar hemorrhage.[9,10] If needed bronchoscopy and biopsies can rule out other causes of pneumonitis.

Treatment typically consists of discontinuation of the offending drug. This patient's symptoms improved with the discontinuation of Osimertinib. In severe cases of pneumonitis, glucocorticoids are often used, but their utility in chemotherapy-induced pneumonitis has not been evaluated in controlled trials. Case reports of re-trialing Osimertinib without reoccurrence of pneumonitis, and a small cohort study reported reoccurrence of pneumonitis after retreatment of Osimertinib of 15%.[11,12] Other report cases of premedicating with steroid therapy, without a repeat episode of pneumonitis.[13,14] More investigation is needed

in re-trialing Osimertinib with and without steroids to help guide clinical decisions.

Conclusion

Osimertinib-induced pneumonitis is a challenging diagnosis as it is a rare cause of pneumonitis, with many other diseases that can mimic the condition's symptoms. There are many implications with the decision to continue or discontinue chemotherapy. As in the case presented, it is important to fully discuss the risks/benefits of any palliative chemotherapy. Shared decision making is needed when considering restarting an agent such as Osimertinib when there is concern it may be worsening the patient's symptoms and/or quality of life.

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