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**Recommended Citation**


ISSN: 2769-2779

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CASE REPORT

A Case Report of CDK 4/6 Inhibitor Drug-induced Pulmonary Toxicity

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1. Introduction

The FDA issued a report in 2019 regarding the possible association of CDK4/6 inhibitors (palbociclib, ribociclib and abemaciclib) with severe lung inflammation.1 These drugs are often used as first line therapy in combination with hormonal therapy for the treatment of breast cancer.2

2. Case Presentation

An 80 year old female with a past medical history of hypertension, anxiety, depression, and metastatic breast cancer on combination CDK4/6 inhibitor and endocrine therapy, presented to the emergency department with dyspnea on exertion. The timeline of events starting from diagnosis of breast cancer to presentation with dyspnea on exertion is depicted in Fig. 1.

Recent history was significant for left lower extremity edema noted at her appointment with her oncologist. Two days later she was diagnosed with deep venous thrombosis (DVT) at an urgent care center and transferred to the emergency department where she was started on Rivaroxaban. Chest radiographs done at that time demonstrated findings suggestive of pneumonia, thus the patient was started on antibiotics as well. She was discharged five days later.

Six days following her most recent discharge, the patient developed dyspnea on exertion and again presented to the emergency department. On presentation, she was hypertensive 189/79 and hypoxic with SpO2 of 80 %, requiring 2 L of supplemental oxygen via nasal cannula. Labs revealed an alarmingly elevated D-dimer, 1668.

It was suspected that she had a pulmonary embolism (PE) due to her recent diagnosis of DVT, along with current hypoxia and elevated D-dimer. Thus CT angiogram was ordered, which was negative for PE. Rather, the CT demonstrated upper lobe predominant ground glass/alveolar opacities, interlobular septal thickening and bronchiectasis (Fig. 2). Given the pattern of airspace disease, interlobular septal thickening and bronchiectasis, suggesting chronic process, the leading differential was drug-induced pulmonary toxicity. Differential also included multifocal pneumonia, pulmonary edema, lymphangitic spread of primary tumor, and pneumocystis jirovecii pneumonia (PJP).

Patient was taking a CDK4/6 inhibitor, abemaciclib, 100 mg twice daily for 9 weeks prior to presentation for treatment of her breast cancer. Due to radiologic findings suggestive of drug-induced pulmonary toxicity due to CDK4/6 inhibitor, this therapy was stopped and steroid treatment was initiated in consideration of possible drug-induced toxicity. Steroid treatment consisted of prednisone 40 mg for 4–6 weeks. Five days after admission her oxygen requirements increased to 4 L via nasal cannula and even further up to high flow within one week of admission. However within another week of prednisone treatment the patient was improving and breathing room air.

Follow up CT performed 6 weeks after the initial scan demonstrated improvement in the previously noted bilateral upper lobe predominant airspace opacities (Fig. 3). There was some mild residual opacity noted which was most predominant in the upper lobes.
3. Discussion

Considerations of differential diagnoses in this case are important, as drug-induced pulmonary toxicity is a diagnosis of exclusion. Multifocal pneumonia commonly presents as airspace opacifications and bronchograms on CT; however, the
presence of bronchiectasis, as seen in our patient, is not a typical finding. Pulmonary edema commonly presents as ground glass opacification, interlobular septal thickening and bronchovascular bundle thickening on CT. While our patient's CT does demonstrate some of these findings, pulmonary edema is more likely to present in position-dependent positions in the lungs, and our patient has upper lobe predominant findings on CT. Lymphangitic spread of tumor classically presents as a “dot in box” appearance on CT imaging which appears as polygonal arcades with prominent intravascular bundles. PJP commonly presents on CT with a ground glass pattern predominantly involving perihilar or mid zones of the lung. Drug induced pulmonary toxicity may have many different presentations on imaging, but all of the imaging findings on our patients CT have been associated with drug-induced pulmonary toxicity. Further, given the clinical correlation in our patient with initiation of CDK4/6 inhibitor in a few months prior, drug-induced pulmonary toxicity is the leading diagnosis.

The Federal Drug Administration has previously reported an association of CDK4/6 inhibitors (palbociclib, ribociclib and abemaciclib) and severe lung inflammation in 2019. Given improvement of airspace disease with steroid treatment and cessation of CDK4/6 inhibitor therapy, there is sufficient evidence to suggest CDK4/6 inhibitor induced pulmonary toxicity in this patient.

Several previously published case reports also noted findings of ground glass opacities on imaging. However, there is limited data on the subject as these medications are newer to the market. Further, drug-induced injury is a diagnosis of exclusion, which may make diagnosis difficult. Having said that, the association of these medications with pulmonary toxicity in prior case reports gives strong evidence for this diagnosis.

Further, the timeline from initiation of therapy to presentation correlates with a timeline of drug-induced pulmonary toxicity. A systematic review on the subject from 2022 notes, “previous real-world study based on the FAERS database showed that a median latency of 63 days (range 21–136) for CDK4/6 inhibitor-associated ILD”. In our patient, time from initiation of therapy to presentation was 65 days, which is very close to the mean presented in the systematic review.

This case demonstrates the importance of considering clinical context when interpreting imaging. This patient was on therapy which has a reported possible association of severe lung inflammation. Further, this case demonstrates the reality of the consequences of many medications, specifically cancer therapy.

Conflict of interest

The authors have no conflict of interest to declare.

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