Drug-Induced Interstitial Lung Disease in a patient treated with a combination of palbociclib and fulvestrant

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Abstract

A 59-year-old patient without a history of pulmonary disease presented with episodes of hemoptysis and acute respiratory failure after receiving fulvestrant and palbociclib for metastatic breast cancer. The High-Resolution chest CT demonstrated diffuse ground glass opacities, as well as diffuse smooth thickening of the interlobular septa and peribronchovascular interstitium, which are consistent with Drug-Induced Interstitial Lung Disease (DIILD). A few days of high-dose steroid therapy improved the patient's gas exchange from PaO_2/FiO_2 of 75 to 200. After hospital discharge, the oncologist resumed fulvestrant therapy, with no additional adverse events occurring during the subsequent follow-up.

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Introduction

Due to drug toxicity, Drug-Induced Interstitial Lung Disease (DIILD) is characterized by variable degrees of inflammation and/or fibrosis in the lungs. Currently, over 1300 pharmaceuticals have been reported in the scientific literature as being causal agents. The clinical phenotype, imaging, and histopathology patterns of drugs and patients exposed to the same drug may vary significantly.[1,2] DIILD diagnostic criteria include a plausible temporal relationship between symptom onset and drug exposure, the absence of an alternative, more probable cause of ILD, and improvement upon withdrawal of the suspected causative agent with or without corticosteroid therapy. As a diagnosis of exclusion, DIILD presents the physician with unique challenges.

We report a case of DIILD caused by the chemotherapy medications palbociclid and fulvestrant, which are used to treat metastatic breast cancer.

Case Report

A 59-year-old woman with no history of respiratory disease was referred to our clinic for deteriorating dyspnea, which began a few days after the first administration of palbociclid and fulvestrant for her metastatic breast cancer. Additionally, the patient reported at least three instances of hemoptoe. She was subjected to standard laboratory tests, serological and microbiological tests for pneumotropic viruses and bacteria, and a chest Computed Tomography (CT) scan.

Despite oxygen therapy with a non-rebreathing respirator, vital parameters measured a peripheral oxygenation of 86% upon admission to the hospital. Blood pressure in the arteries, heart rate, and body temperature were all normal. With the initiation of high-flow oxygen therapy at 60 liters per minute and FiO_2 of 90%, oxygenation was improved. Laboratory investigations revealed mild leukocytosis (white blood cell count of 11.45x109) and elevated markers of inflammation (C reactive protein concentration of 127 mg/L). Microbiological assays were performed, including *Mycoplasma pneumoniae* serology. Negative results were obtained for *Chlamydia pneumoniae, Legionella, Streptococcus pneumoniae*, influenza and parainfluenza viruses, adenovirus, respiratory syncytial virus, quantiferon, and sputum culture. The chest CT demonstrated diffuse ground glass opacities, diffuse smooth thickening of the interlobular septa and peri-bronchovascular interstitium, bilateral pleural effusion, and confirmed the presence of consolidation in the middle and lower right lobe (consistent with lung metastasis).

After two days of clinical observation, the patient's respiratory conditions worsened, as evidenced by a PaO_2/FiO_2 of 72 in the arterial blood gas analysis. Under the suspicion of a DIILD, chemotherapy was halted, and a rescue therapy consisting of high-

dose intravenous pulse steroids was initiated at 1 g per day for three days, followed by a decline. After ten days of steroid treatment, the patient's blood gas analysis revealed a PaO_2/FiO_2 of 287. The patient's clinical conditions improved gradually. A chest CT scan performed as a follow-up revealed a decrease in ground glass opacities and the disappearance of pleural effusion (Figure 1).

After sixteen days of hospitalization, the patient was released. Laboratory examinations revealed the absence of inflammation markers and a healthy white blood cell count. The doctor instructed the patient to continue oxygen therapy at home using a Venturi mask with a FiO_2 of 28% at repose and 31% during sleep and physical activity.

The steroid treatment was continued at home, with the dosage gradually tapered down to 5 mg per day, which was maintained for approximately six months. The attending oncologist resumed fulvestrant therapy 15 days after the patient's discharge, and no adverse reactions were observed following the drug's reintroduction. The patient began chemotherapy with capecitabine and vinorelbine two months after hospitalization, upon the advice of a second oncologist due to the ineffectiveness of fulvestrant in treating breast cancer.

Three months after hospitalization, a follow-up chest CT scan revealed a significant reduction in the multiple bilateral ground glass areas, most pronounced in the lower lobes, along with extensive thickening of the bronchial walls and inter and intra lobular septa. At a 6-month follow-up visit, despite a further improvement in gas exchange at rest, it was recommended to continue long-term oxygen therapy with a Venturi Mask containing 24% FiO_2 during physical activity and sleep, despite a further improvement in gas exchange at rest.

Discussion

Both the United States and Europe have approved the Cyclin-Dependent Kinase (CDK) 4/6 inhibitors (palbociclib, abemaciclib, and ribociclib) for women with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer.[5] All CDK 4/6 inhibitors exert their antitumor effect by inhibiting the cyclin D-CDK 4/6 complex, which in turn inhibits the activation of the RB-E2F pathway. However, a number of adverse effects have been observed in the pivotal clinical trials of currently approved CDK 4/6 inhibitors.[6] It has been hypothesized that palbociclib and the class of CDK 4/6 inhibitors may cause pneumo-

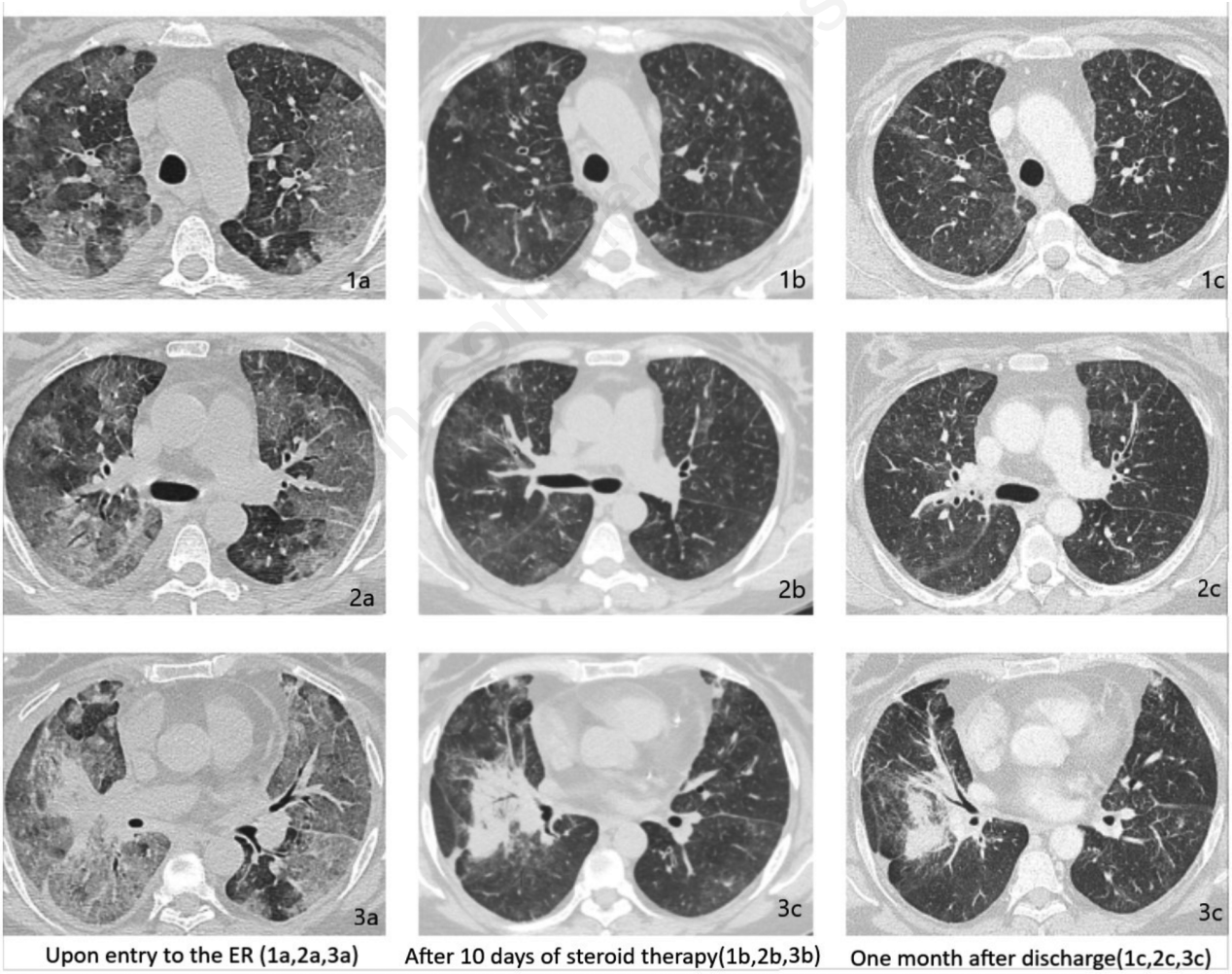

Figure 1. Scans of the patient **a**) upon entry to the Emergency Room, **b**) after 10 days of steroid therapy and **c**) one month after discharge.

nia/ILD.[4,5] It has been described that early treatment of ILD induced by CDK 4/6 inhibitors with steroid therapy favors regression of lung injury.[6] On the other hand, a patient treated with palbociclib and letrozole developed a fatal case of ARDS. Three weeks later, despite treatment with antibiotics and corticosteroids, the patient passed away.[3]

In this case report, the patient developed DIILD after receiving palbociclib and fulvestrant concurrently. Since fulvestrant was reintroduced without additional adverse effects, it appears that palbociclib may be to blame for the pulmonary injury.

Conclusions

For an accurate differential diagnosis in patients undergoing oncological therapies, an accurate pharmacological history is essential. In addition to infectious disease, drug toxicity must be considered as a possible cause of interstitial pneumonia in these fragile patients, particularly given the generally positive response to steroid treatment.

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