CDK4/6 Inhibitor–Induced Interstitial Lung Disease: A Rare but Severe Complication in Breast Cancer Treatment

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Introduction

Cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors are a class of targeted therapies that inhibit two enzymes involved in regulating the cell cycle. CDK4/6 inhibitors are widely used in patients with hormone receptor-positive (HR), human epidermal growth factor receptor-2 (HER2) negative breast cancer for early-stage and metastatic breast cancer. While these therapies have improved clinical outcomes, they carry a risk of rare but serious adverse events, including interstitial lung disease (ILD)/pneumonitis. We present a case of a patient with CDK4/6 inhibitor-induced grade 4 pneumonitis and ILD, requiring consideration for lung transplantation.

Clinical Case: Presentation and Pathology

Patient: 61-year-old female
Past Medical History: Hypothyroidism, hypertension, and hormone-receptor-positive breast cancer
Breast Cancer Diagnosis:

- Ultrasound showed a 3 cm irregular spiculated right breast mass and enlarged right axillary lymph nodes
- Core needle biopsy revealed invasive ductal carcinoma with confirmed involvement of the right axillary lymph node
- Estrogen-receptor positive (ER, 90%), progesterone-receptor positive (PR, 90%), HER-2 negative (1+), and Ki-67 20%

Breast Cancer Staging: Stage IIb (T2N1Mx)
Breast Cancer Treatment:

- Oncotype DX score: 28
- Completed 4 cycles of neoadjuvant docetaxel/cyclophosphamide followed by bilateral mastectomy with reconstruction in October 2023
- Right total mastectomy revealed pT2N2a disease with 6/10 positive lymph nodes
- Postoperative course was complicated by a tissue expander infection requiring removal in December 2023

Genetic Testing: Negative except for *ATM* variant of uncertain significance (VUS)

Clinical Case: Treatment Complications

Breast Cancer Treatment:

- Completed adjuvant radiation therapy in March 2024
- Started aromatase inhibitor, anastrozole in November 2023
- Started CDK 4/6 inhibitor, Abemaciclib in April 2024

Treatment Complications: Abemaciclib-induced Pneumonitis

- After 6 months of adjuvant treatment, she developed acute hypoxic respiratory failure, requiring hospitalization in October 2024.
- Bronchoscopy with BAL and lung biopsy indicated focal fibrosis with acute and chronic inflammation without infection, granuloma, or malignancy.
- Treated with high-flow nasal cannula oxygen, high-dose corticosteroids (methylprednisolone 1mg/kg daily), and 3 doses of infliximab for abemaciclib-induced pneumonitis.
- Abemaciclib was permanently discontinued, and she was discharged on a prednisone taper in December 2024.
- No history of smoking or prior lung injury.
- Evaluated by the pulmonology team given her severe, chronic pulmonary fibrosis and advanced interstitial lung disease with worsening hypoxia and dry cough despite prolonged high doses of prednisone.
- Mycophenolate (MMF) was initiated as a steroid-sparing agent with both anti-inflammatory and anti-fibrotic effects.
- Referred for lung transplantation evaluation in the setting of a serious, chronic, and irreversible lung disease with poor prognosis and increased risk for sudden, unpredictable, acute, and life-threatening exacerbations.

Figure 1: Imaging

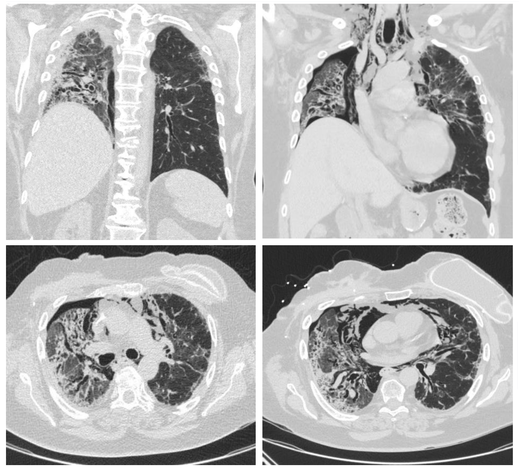


Figure 1a. CT coronal view

Figure 1b. CT axial view

Figure 1a and 1b: CT chest showing progression of bilateral (right > left) ground-glass and consolidative opacities with septal thickening and air trapping, consistent with treatment-related pneumonitis. Right pleural effusion with compressive atelectasis, persistent pneumomediastinum, subcutaneous emphysema, and right pneumothorax on a background of advanced pulmonary fibrosis.

Figure 2: Pathology

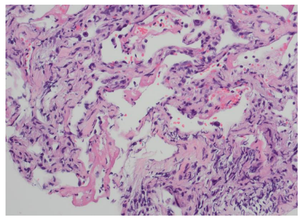


Figure 2: H&E stain 20x, right upper lobe lung biopsy with focal fibrosis in the alveolate parenchyma

Discussion

CDK4/6 inhibitors are used for HR-positive, HER2-negative breast cancer, with expanded use in high-risk early-stage disease following the NATALEE and monarchE trials. This drug class carries a rare yet life-threatening adverse event that requires early recognition and monitoring. A meta-analysis of 12 randomized trials (>16,000 patients) reported an increased incidence of ILD/pneumonitis in treated patients (1.6% vs. 0.7%; OR 2.12, 95% CI [1.57-2.86], $P < 0.00001$). The exact mechanisms underlying CDK4/6 inhibitor-induced pneumonitis and ILD remain unclear, and retrospective studies have found no significant correlation between ILD and risk factors such as smoking history, lung metastases, or prior thoracic radiotherapy. Further research is needed to clarify mechanisms, risk stratification, and standardized management protocols for CDK4/6 inhibitor-induced ILD.

Conclusions

- CDK4/6 inhibitors are standard of care for HR-positive, HER2-negative breast cancer in high-risk early-stage and metastatic settings, improving progression-free and overall survival.
- CDK4/6 inhibitors are associated with a rare, but increased risk of ILD and pneumonitis, with an overall incidence of 1.6%.
- Abemaciclib demonstrates a higher incidence of ILD (up to 2.5%) compared to palbociclib (0.5%) and ribociclib (1.1%), likely due to differences in pharmacologic properties.
- Most CDK 4/6 inhibitor-induced ILD occurs within the first 3 months of therapy, but onset can be variable.
- Early recognition and multidisciplinary management, including medical oncology, pulmonology, and infectious disease, are critical to optimize outcomes.

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