A hypermetabolic pulmonary lesion in a patient with breast cancer

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CDK4/6 inhibitors, including ribociclib, may cause organising pneumonia that closely mimics lung cancer on CT and FDG-PET. Histological confirmation is essential in discordant cases. https://bit.ly/48nGZ3t

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A 64-year-old woman, who was an ex-smoker (smoking history of 20 pack-years) with no occupational exposures or family history of pulmonary disease, was evaluated for a newly detected pulmonary lesion. Her past medical history was notable for moderately differentiated (G2) ductal breast carcinoma of the right breast (oestrogen receptor >95%, progesterone receptor 60%, Ki67 28%, HER2 1+), treated with nipple-sparing mastectomy and sentinel lymph node biopsy with axillary dissection in October 2023 (pT2N1a), followed by reconstructive surgery. Postoperative systemic therapy included adjuvant chemotherapy with epirubicin and cyclophosphamide plus pegylated granulocyte colony-stimulating factor (December 2023, three cycles) and docetaxel (March–May 2024, 12 cycles), followed by letrozole from May 2024. Adjuvant radiotherapy was not administered. In view of the tumour biology and initial staging, ribociclib was initiated in April 2025.

In May 2025, she was referred to the Outpatient Pulmonology Unit of Fondazione Istituto di Ricovero e Cura a Carattere Scientifico San Gerardo dei Tintori in Monza for evaluation due to the onset of dry cough. No clinical signs of infection were present, and she denied dyspnoea, fever, night sweats or unintentional weight loss. There were no cutaneous or musculoskeletal features suggestive of connective tissue disease. Routine laboratory tests were within normal limits, with no leukocytosis, no elevation of inflammatory biomarkers, and no other abnormalities indicative of an underlying infectious or systemic inflammatory process. A pulmonary function test was not performed as the patient presented with an isolated cough.

A chest computed tomography (CT) performed in May 2025 revealed a 37×30 mm solid oval lesion in the apical segment of the left lower lobe, characterised by spiculated margins, pleural contact and minimal adjacent ground-glass opacities. Concomitant mild centrilobular emphysema, consistent with the patient's former smoking history, was also observed. No interstitial lung abnormalities and mediastinal or hilar lymphadenopathy were present (figure 1).

Task 1

What investigations should be ordered at this point?

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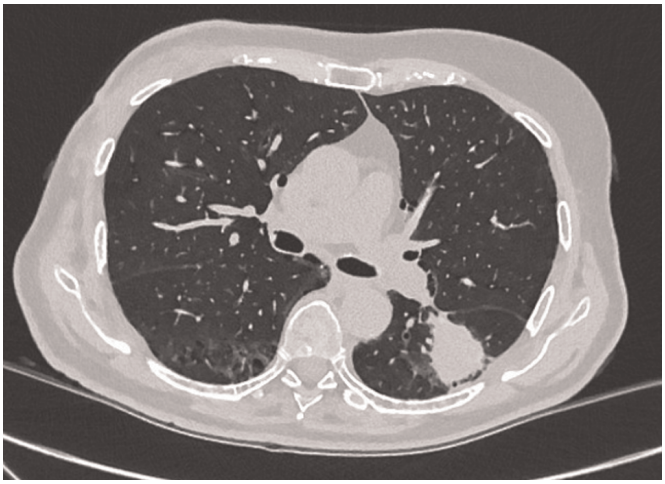

FIGURE 1 Baseline chest computed tomography showing a 37×30 mm solid, spiculated lesion in the apical segment of the left lower lobe, with pleural contact and minimal surrounding ground-glass opacities.

Given the suspicion of a primary pulmonary malignancy, an ^{18}F-fluorodeoxyglucose positron emission tomography–computed tomography (^{18}FDG-PET-CT) was performed in June 2025 and showed intense FDG uptake by the lesion (maximum standardised uptake value (SUVmax) 19.85), with mild uptake in a subpleural nodule of the left upper lobe (SUVmax 2.00) and mild uptake in hilar/mediastinal nodes (SUVmax 13.17) (figure 2a). These lymph nodes were located in the para-aortic region (station 6), which is not accessible by conventional EBUS-TBNA. Therefore, after multidisciplinary discussion, percutaneous transthoracic biopsy of the pulmonary lesion was selected as the most appropriate diagnostic approach.

Histopathological examination of the biopsy revealed intra-alveolar fibroblastic plugs (Masson bodies), myxohyaline granulation tissue and interstitial inflammatory infiltrates. Microbiological and fungal stains were not performed on the biopsy specimen (figure 2b).

Task 2

What is the most likely diagnosis?

a) Primary lung adenocarcinoma
b) Pulmonary metastasis from breast carcinoma
c) Invasive pulmonary aspergillosis
d) Organising pneumonia
e) Sarcoidosis

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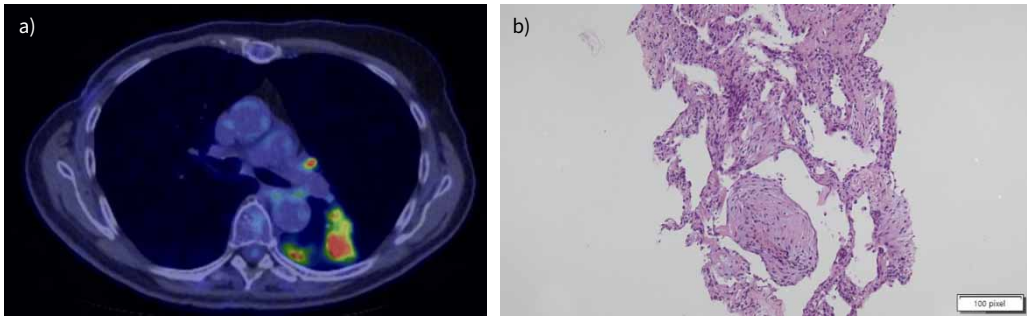

FIGURE 2 a) ^{18}F-FDG PET/CT demonstrating intense hypermetabolic activity of the lesion (maximum standardised uptake value 19.85), raising initial suspicion for primary lung malignancy. b) Histopathological examination of the percutaneous transthoracic biopsy revealing intra-alveolar fibroblastic plugs (Masson bodies), myxohyaline granulation tissue and interstitial inflammatory infiltrates (haematoxylin and eosin stain).

The combination of compatible clinical features, histopathological findings and the temporal relationship with treatment initiation strongly supported the diagnosis of ribociclib-induced organising pneumonia.

Task 3

What is the most appropriate management?

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Consequently, ribociclib was discontinued, and corticosteroid treatment with prednisone at a dose of 0.5 $mg \cdot kg^{-1} \cdot day^{-1}$ (25 mg daily) was initiated.

1 month after the initiation of corticosteroid therapy, the patient's clinical condition markedly improved with complete resolution of cough. Follow-up chest CT demonstrated significant radiological improvement, with near-complete resolution of the parenchymal lesion and only minimal residual fibro-atelectatic changes (figure 3).

At the subsequent pulmonology visit a gradual tapering of corticosteroid therapy was initiated. Following oncological consultation, a cautious reintroduction of ribociclib was undertaken under ongoing corticosteroid tapering. This decision was made after multidisciplinary discussion, considering the mild clinical presentation of lung toxicity, the rapid improvement observed after treatment interruption and corticosteroid therapy, and the significant oncological benefit in improving progression-free survival and overall survival in patients with hormone receptor-positive breast cancer [1, 2]. Follow-up imaging and clinical assessment were scheduled to monitor for recurrence of pulmonary toxicity. A chest CT performed 2 months after ribociclib was reintroduced, showed no radiological evidence of pulmonary consolidations. At the time of this follow-up imaging, the patient was still receiving prednisone 12.5 $mg \cdot day^{-1}$ as part of a gradual tapering regimen.

Discussion

Drug-induced interstitial lung diseases (ILDs) represent a heterogeneous group involving a wide spectrum of pulmonary toxicities triggered by various drugs, including chemotherapeutic agents, targeted therapies and immune-modulating agents [3, 4]. Among novel targeted therapies, cyclin-dependent kinase 4/6 (CDK4/6) inhibitors have been recognised as a cornerstone in the management of hormone receptor-positive, HER2-negative metastatic breast cancer [1, 2, 5–7].

Although generally well tolerated, CDK4/6 inhibitors have been associated with ILD. In a pharmacovigilance analysis using data from the US Food and Drug Administration Adverse Event Reporting System, ILD accounted for 2.1% of all adverse event reports for abemaciclib and 0.3% for palbociclib and ribociclib, highlighting that this uncommon toxicity is nevertheless observed across the class [8].

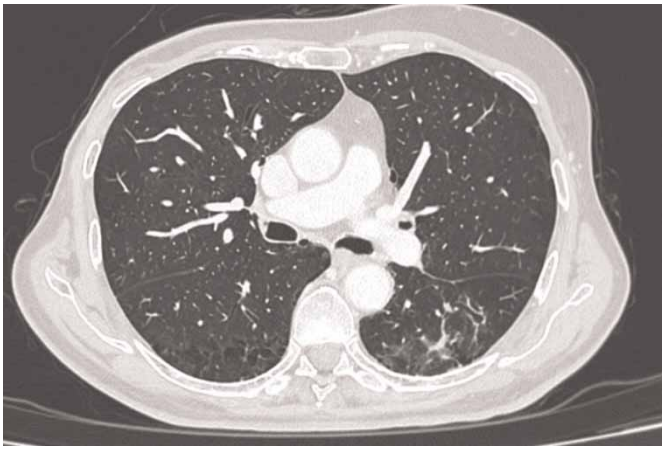

FIGURE 3 Follow-up chest computed tomography obtained after corticosteroid therapy and ribociclib discontinuation, showing near-complete resolution of the previously described lesion with minimal residual fibro-atelectatic changes.

Additional insights derive from the recent retrospective multicentre study by İLHAN *et al*. [9], which evaluated 454 patients with metastatic breast cancer treated with CDK4/6 inhibitors. In this cohort, 10 patients (2.2%) developed ILD, with a median onset of 161 days from treatment initiation. Chest CT evaluation showed that the predominant radiological patterns were hypersensitivity pneumonitis (HP) in four patients (40%) and nonspecific interstitial pneumonia (NSIP) in four patients (40%), while acute interstitial pneumonia/acute respiratory distress syndrome (AIP/ARDS) was observed in two patients (20%). No significant differences were identified between patients with and without ILD in terms of menopausal status, prior thoracic radiotherapy, previous chemotherapy, line of CDK4/6 inhibitors therapy, or the presence of lung metastases. Due to ILD-related complications, CDK4/6 inhibitors treatment was permanently discontinued in nine patients (90%). Corticosteroids were administered to all patients, oxygen supplementation was required in nine cases (90%), and one patient (10%) required admission to the intensive care unit for severe respiratory distress reflecting substantial respiratory compromise [9].

A further contribution to the understanding of CDK4/6 inhibitor-related pulmonary toxicity emerges from the large Japanese real-world study by NAKAYAMA *et al*. [10] (NOSIDE study), which specifically investigated abemaciclib-associated ILD. In this nationwide retrospective analysis including 1189 patients with advanced breast cancer, the incidence of ILD was 5.0%, with a mortality rate of 0.7%. The timing of ILD onset varied but occurred most frequently within 180 days of beginning abemaciclib treatment. The most frequent CT pattern was organising pneumonia (66%), followed by AIP (22%), while NSIP and HP patterns were less common. Multivariate analysis identified poor performance status (Eastern Cooperative Oncology Group performance status $\geqslant 2$) and a prior history of interstitial pneumonia as the strongest independent risk factors [10].

Several additional case reports, summarised in table 1, have further characterised CDK4/6 inhibitor-related pulmonary toxicity [11–14]. Notably, organising pneumonia emerges as the most frequently reported pattern across published cases, and in one abemaciclib-related case the diagnosis was histologically confirmed by transbronchial cryobiopsy [14].

Organising pneumonia usually appears radiologically with bilateral patchy consolidations, ground-glass opacities, or a perilobular pattern, often with a peripheral or peribronchial distribution [15, 16]. A solitary mass-like lesion with spiculated margins, as seen in our patient, is a rare presentation and may closely resemble primary lung malignancy, especially when associated with intense FDG uptake on PET imaging.

TABLE 1 Summary of published case reports describing CDK4/6 inhibitor-associated interstitial lung disease

Drug	First author [ref.], year	Patient age, years	HRCT pattern	Histology	Treatment	Outcome
Ribociclib	ALGWAIZ [11], 2021	46	OP	Only BAL	Steroids+drug discontinuation	Improvement
Ribociclib	RAJENDRAN [12], 2021	63	OP	No	Steroids+drug discontinuation	Improvement; recurrence after rechallenge
Ribociclib	ÜNSAL [13], 2023	48	OP	No	No	Development of a new parenchymal consolidation
Ribociclib	İLHAN [9], 2025	59	HP	No	Steroids+drug discontinuation	Resolution
Ribociclib	İLHAN [9], 2025	62	HP	No	Steroids+drug discontinuation	Resolution
Ribociclib	İLHAN [9], 2025	58	HP	No	Steroids+drug discontinuation	Resolution
Palbociclib	İLHAN [9], 2025	67	HP	No	Steroids+drug discontinuation+MMF +infliximab	Death
Palbociclib	İLHAN [9], 2025	68	NSIP	No	Steroids+drug discontinuation	Resolution
Palbociclib	İLHAN [9], 2025	49	NSIP	No	Steroids+drug discontinuation	Resolution
Palbociclib	İLHAN [9], 2025	70	NSIP	No	Steroids+drug discontinuation+MMF	N/A
Palbociclib	İLHAN [9], 2025	63	NSIP	No	Steroids+drug discontinuation	Resolution
Palbociclib	İLHAN [9], 2025	81	AIP	No	Steroids+drug discontinuation	Resolution
Palbociclib	İLHAN [9], 2025	48	AIP	No	Steroids	Resolution
Abemaciclib	KABURAKI [14], 2024	82	OP	Yes (transbronchial lung cryobiopsy)	Drug discontinuation	Improvement

HRCT: high-resolution computed tomography; OP: organising pneumonia; BAL: bronchoalveolar lavage; HP: hypersensitivity pneumonitis; MMF: mycophenolate mofetil; NSIP: nonspecific interstitial pneumonia; N/A: not available; AIP: acute interstitial pneumonia.

When drug-induced organising pneumonia is strongly suspected, re-exposure to the suspected agent is generally discouraged due to the potential risk of recurrence. However, in selected cases where the suspected drug provides substantial therapeutic benefit and the initial pulmonary toxicity is mild and reversible, cautious re-challenge may be considered after multidisciplinary evaluation and under close clinical and radiological surveillance. In conclusion, ribociclib-induced organising pneumonia is a rare but clinically relevant adverse event. This case report highlights the importance of integrating clinical history, temporal association with drug exposure, and characteristic radiological findings to guide suspicion for drug-related ILD. When feasible, histopathological confirmation provides decisive diagnostic support. Early recognition of this entity is crucial, as prompt discontinuation of ribociclib and institution of corticosteroid therapy typically leads to rapid clinical and radiological improvement.

Key points

- Ribociclib and other CDK4/6 inhibitors can cause organising pneumonia presenting as a mass-like, hypermetabolic pulmonary lesion, closely mimicking primary lung cancer on CT and ^{18}F-FDG-PET.
- Histopathological confirmation is crucial in atypical or discordant cases, as intense FDG uptake and spiculated morphology may also reflect drug-induced inflammatory lung disease.
- Early recognition, drug discontinuation and corticosteroid therapy usually result in rapid clinical and radiological resolution, and cautious drug rechallenge may be feasible in selected cases under close multidisciplinary monitoring.

Answer 1

Given the radiological features highly suggestive of a malignant pulmonary lesion, further diagnostic work-up is warranted. A whole-body ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) should be performed to assess metabolic activity of the lesion and to evaluate for potential mediastinal or metastatic disease. Subsequently, histological confirmation is mandatory. The choice of the biopsy technique should be guided by lesion location, size and local expertise, and may include transthoracic needle aspiration for peripheral lesions or endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) if mediastinal staging or nodal sampling is indicated. Additionally, advanced bronchoscopic techniques, such as navigational bronchoscopy or robotic-assisted bronchoscopy, may serve as valuable alternatives in experienced centres for sampling peripheral pulmonary lesions.

<< Go to Task 1

Answer 2

a) Incorrect: although the radiological appearance and intense FDG uptake initially raised suspicion for primary lung malignancy, histopathological examination showed no malignant epithelial cells. Instead, biopsy revealed intra-alveolar fibrin and granulation tissue. These findings are not typical of lung adenocarcinoma and should be interpreted within the clinical and radiological context.

b) Incorrect: pulmonary metastases from breast cancer typically present as multiple, well-circumscribed nodules and demonstrate histological features consistent with the primary tumour. In this case, the absence of malignant cells and the presence of inflammatory and organising features argue strongly against metastatic disease.

c) Incorrect: invasive aspergillosis usually occurs in severely immunocompromised patients and is characterised radiologically by nodules with halo sign or cavitation, and histologically by tissue invasion with septate hyphae. None of these features were observed in this patient.

d) Correct: the presence of intra-alveolar fibrin and myxohyaline granulation tissue with interstitial inflammatory infiltrates is characteristic of organising pneumonia. The temporal relationship with ribociclib initiation supports a diagnosis of drug-induced organising pneumonia.

e) Incorrect: sarcoidosis typically presents with bilateral hilar lymphadenopathy and perilymphatic micronodules, with histology demonstrating non-caseating granulomas, none of which were present in this case.

<< Go to Task 2

Answer 3

The most appropriate initial management consists of discontinuation of ribociclib, given the strong temporal association with symptom onset and the histological pattern consistent with drug-induced lung toxicity. Systemic corticosteroid therapy should be initiated to control the inflammatory process typical of organising pneumonia, which is expected to lead to clinical and radiological improvement. Close clinical and radiological follow-up with repeat chest CT is recommended to document lesion regression and to exclude alternative diagnoses.

<< Go to Task 3

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Availability of data and materials: Data are available from the corresponding author upon request.

Ethics statement: the study was conducted in accordance with the World Medical Association Declaration of Helsinki. The patient gave written informed consent for their personal or clinical details along with HRCT images to be published in this study.

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Conflict of interest: D.L. Cortinovis reports consulting fees from Amgen, AstraZeneca, Beone, Boehringer Ingelheim, Bristol Meyers Squibb, Daiichi Sankyo, GSK, Johnson & Johnson, Lilly, Merck KGaA, Merck Sharp & Dohme, Novartis, Pfizer and Roche. The others authors had no conflicts of interest to declare.

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