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CHEST IMAGING

PICTORIAL ESSAY

Drug-induced lung disease: a brief update for radiologists

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ABSTRACT

Pulmonary adverse events and drug-induced lung disease (DILD) can occur when treating many conditions. The incidence of DILDs in clinical practice and the variety of radiological findings have increased, mainly due to the increased use of novel therapeutic agents. It is crucial to determine whether the newly emerging clinical and imaging findings in these patients are due to the progression of the underlying disease, infection, pulmonary edema, or drug use, as this will change the patient management. Although the diagnosis of DILD is usually obtained by excluding other possible causes, radiologists should be aware of the imaging findings of DILD. This article reviews the essential radiological results of DILD and summarizes the critical clinical and imaging findings with an emphasis on novel therapeutic agents.

KEYWORDS

Computed tomography, immunotherapy, lung, pneumonitis, pulmonary toxicity, therapy

When treating many diseases, pulmonary adverse events (AEs) and drug-induced lung disease (DILD) may occur due to medications. Although most of these AEs are clinically mild, they can be severe and even life threatening.[1,2] Patients with malignancy, systemic inflammatory diseases, and elderly patients are at high risk for DILD.[2] The increasing use of novel therapeutic agents, including immune checkpoint inhibitors (ICIs) and molecular targeting agents, have increased the frequency and spectrum of DILD.[3-5] It is also crucial to determine whether the clinical and imaging findings in these patients are due to an underlying condition, infection, pulmonary edema, hemorrhage, or medication. Computed tomography (CT) plays a crucial role in diagnosis and can reveal the pattern-based distribution and severity of pulmonary abnormalities.[6] This article reviews the essential radiological results of DILD and summarizes the critical clinical and imaging findings, emphasizing novel therapeutic agents.

Clinical features of DILD

The reported incidence of DILD varies widely, but a recent systematic analysis reported an incidence of DILD in 0.4–1.24/100,000 cases per year.[2] Moreover, approximately 3%–5% of all cases of diffuse interstitial lung disease are due to medication.[2,7,8] The temporal relationship between drug intake and the onset of pulmonary symptoms is essential for the clinical suspicion of DILD, but this timescale can vary widely.[2,4,6] Although the clinical condition of patients with DILD can range from asymptomatic to life-threatening, symptoms are usually mild and depend on the severity of the lung disease. Shortness of breath, coughing, and wheezing are the most frequently reported symptoms of DILD.[1,2,7]

A simple clinical grading system has been defined for drug-induced organ toxicity. It is used as an indicator, both in the management of DILD and for determining the patient's prognosis (Supplementary Table S1).[9]

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Radiological findings of DILD

Imaging methods, particularly chest CT, play a crucial role in diagnosing DILD in patients receiving medications that potentially cause pulmonary toxicity.[6] Although chest X-ray is usually the first-choice imaging tool and provides helpful information in evaluating patients with mild-to-moderate symptoms for DILD, it has low sensitivity and specificity in assessing the presence of pulmonary infiltration and disease extent.[10] Thin-slice chest CT is a valuable tool for a pattern-based assessment of DILD in the presence of appropriate medical history and clinical findings. Moreover, chest CT can reveal other causes of respiratory symptoms or pulmonary infiltrations, and the severity of pulmonary infiltrations in patients with DILD can be assessed visually or quantitatively using CT (Supplementary Figure S1).[11]

As recently stated in a Fleischner Society position paper, five commonly described radiological patterns and rare drug-induced lung abnormalities [such as sarcoid-like granulomatosis (SLG), radiation recall, and pneumonitis flare] may be encountered in chest CT due to novel therapeutic agents (Figure 1).[6] Pneumonitis flare, SLG, and radiation recall pneumonitis do not have typical radiological findings, and clinical history is of great importance when diagnosing these entities.[5,6,10]

Radiologic organizing pneumonia (OP) pattern

The OP pattern is a form of acute lung injury and is the most common form of DILD.[5,9,12] Histopathologically, it is characterized by intra-alveolar, intra-bronchial granulation tissue and interstitial inflammation.[3] Bilateral, multifocal, peripheral, and peribronchovascular ground-glass opacities (GGOs) and/or consolidation areas with mid-lower lung zone predominance are common imaging findings.[4-6,12] Areas of GGO with a peripheral rim of consolidation (also known as reverse-halo or atoll sign) can be found but are not specific (Figure 2 and Supplementary Figure S2). Airspace opacities can be migratory and change configuration over time.[4-6,12] Although eosinophilic pneumonia (EP) can be present in similar imaging findings with an OP pattern, EP is characterized by peripheral band-like opacities and predominance in the upper lobes (Figure 3).[5,6]

Radiologic non-specific interstitial pneumonia (NSIP) pattern

The NSIP pattern is the second most common form of DILD and is associated with a median of grade 1 toxic effects.[5,9,12] Histopathologically, it is characterized by the thickening of the pulmonary interstitium due to an inflammatory infiltrate (cellular NSIP) and/or fibrosis (fibrotic NSIP).[3,6] Bilateral, patchy, or diffuse GGOs with or

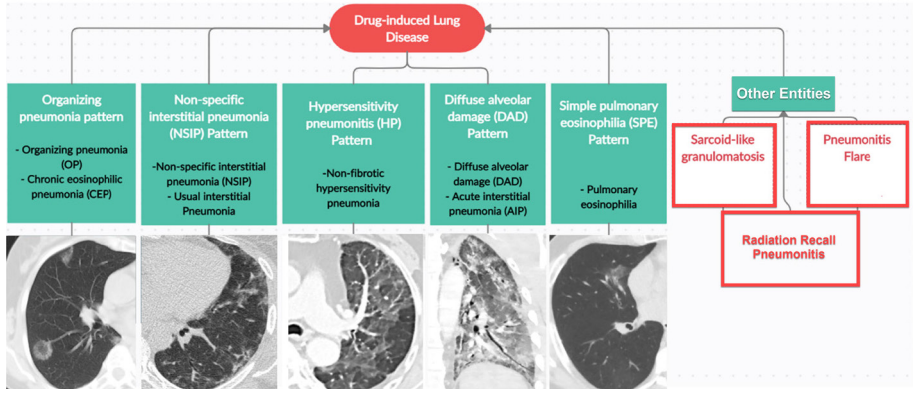

Figure 1. Radiological findings of drug-induced lung disease during chest computed tomography.

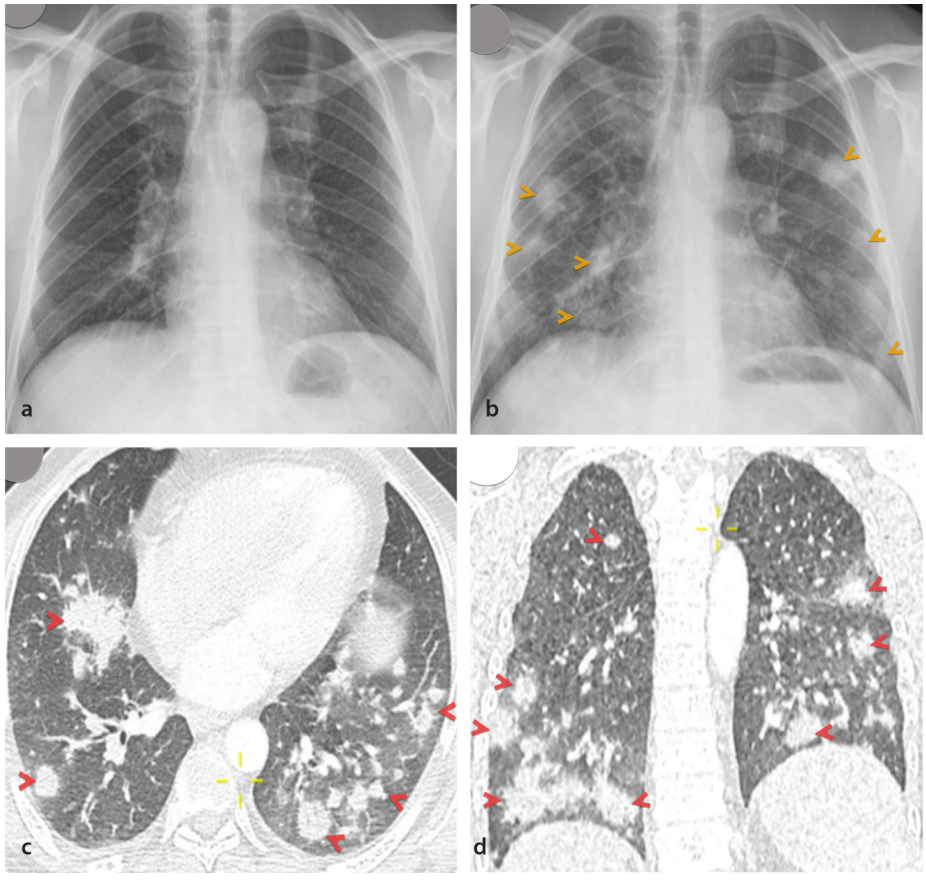

Figure 2. Nivolumab-related organizing pneumonia (OP) pattern in a 49-year-old male with metastatic malignant melanoma. **(a)** Baseline chest X-ray and **(b)** 3 weeks after the initiation of pembrolizumab therapy shows newly onset nodular lung opacities (arrowheads). **(c)** Axial and **(d)** coronal chest computed tomography images show peripheral and peribronchovascular nodular opacities consistent with the OP pattern. A chest X-ray obtained 8 weeks later, after withholding nivolumab therapy and administering 1 mg/kg/day of prednisolone therapy, demonstrates the complete regression of lung opacities (not shown).

Main points

- Pulmonary adverse events and drug-induced lung disease (DILD) can occur in treating many conditions.
- Although DILD is difficult to distinguish clinically from other causes of diffuse pulmonary opacities, radiological findings play a key role.
- Radiologists should be familiar with DILD because the proper management of DILD is vital.

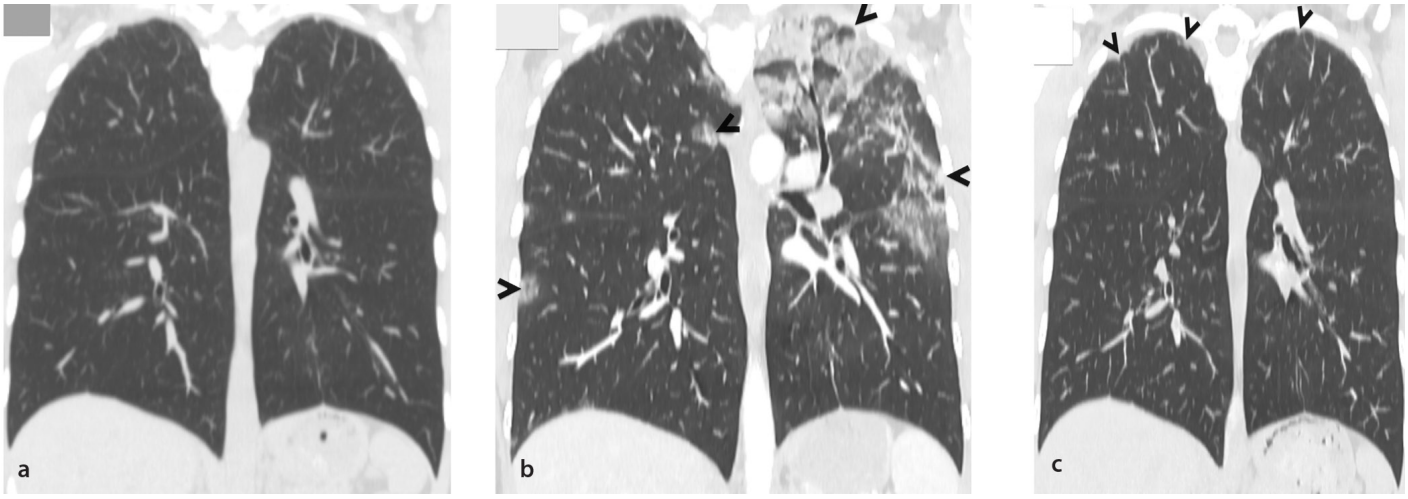

Figure 3. Pembrolizumab-related eosinophilic pneumonia in a 43-year-old female with metastatic malignant melanoma. **(a)** Baseline coronal chest computed tomography (CT) image shows the lungs before therapy and **(b)** three months after the initiation of pembrolizumab therapy, which demonstrates bilateral, peripheral ground-glass opacities with an upper lobe predominance (arrowheads). The patient had no respiratory symptoms, but laboratory analysis showed an elevated peripheral eosinophil count (857/mcL, normal range: <200/mcL) and bronchoalveolar lavage fluid (BALF) obtained from the left upper lobe bronchus revealed a high cell count (1.9×10^5/mL) with significantly elevated eosinophils (59.3%). The bacterial/fungal culture was negative for BALF. Pembrolizumab was discontinued, and no treatment was introduced for her eosinophilic pneumonia. **(c)** The chest CT obtained two months later shows the complete regression of lung opacities with millimetric subpleural atelectasis.

without reticular opacities with peripheral and basilar predominance are the common imaging manifestations of NSIP. Immediate subpleural sparing can also be seen in NSIP cases, and consolidative opacities are unusual. Lung fibrosis shows temporal and spatial homogeneity, and lung abnormalities are usually bilateral and symmetrical (Figures 4, 5).[5,9,12]

Radiologic hypersensitivity pneumonitis (HP) pattern

The HP pattern is a rare form of DILD associated with a median of grade 1 toxic effects and mild clinical symptoms.[9,12] Histopathologically, the HP pattern is characterized by cellular bronchiolitis, granulomas, multinucleated giant cells, and interstitial inflammation.[3] Areas of GGO with or without air trapping and centrilobular nodules, which may be diffuse or predominantly distributed in the upper lobes, are common CT findings (Figure 6).[5,6,12] Parenchymal abnormalities, such as traction bronchiectasis, a honeycomb appearance, and upper lobe fibrosis consistent with fibrotic HP, are unusual in DILD.[5,6]

Radiologic diffuse alveolar damage (DAD) pattern

The DAD pattern, or acute interstitial pneumonia (AIP), is a rare pattern of DILD often associated with acute clinical symptoms and diffuse pulmonary infiltrations on imaging.[6,9,12] Histopathologically, it is characterized by necrosis of type 2 pneumocytes, alveolar edema, and alveolar endothelial cell

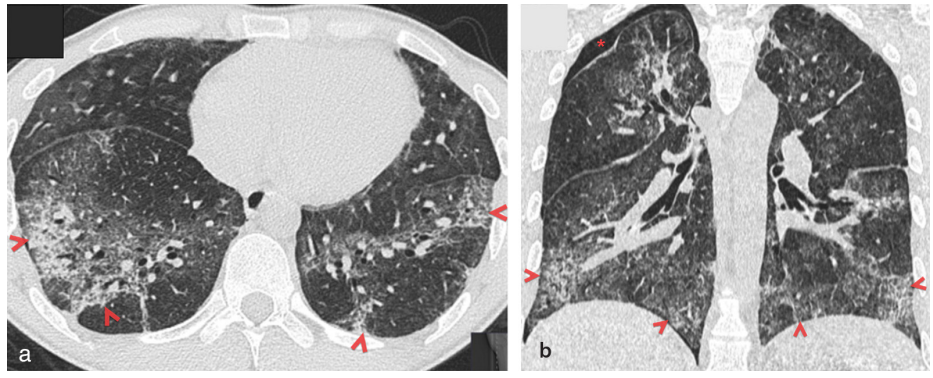

Figure 4. Bleomycin-related non-specific interstitial pneumonia pattern in a 29-year-old male with a testicular germ-cell tumor. Baseline chest computed tomography (CT) was unremarkable (not shown). **(a)** Axial and **(b)** coronal chest CT images, which were obtained three months after the initiation of chemotherapy, show bilateral, patchy ground-glass opacity areas with a peripheral and basilar predominance (arrowheads). Note the immediate subpleural sparing and right pneumothorax (*). The bleomycin was discontinued, and the patient was followed up with hospitalization. A control chest CT obtained one year later demonstrates the complete regression of lung opacities (not shown).

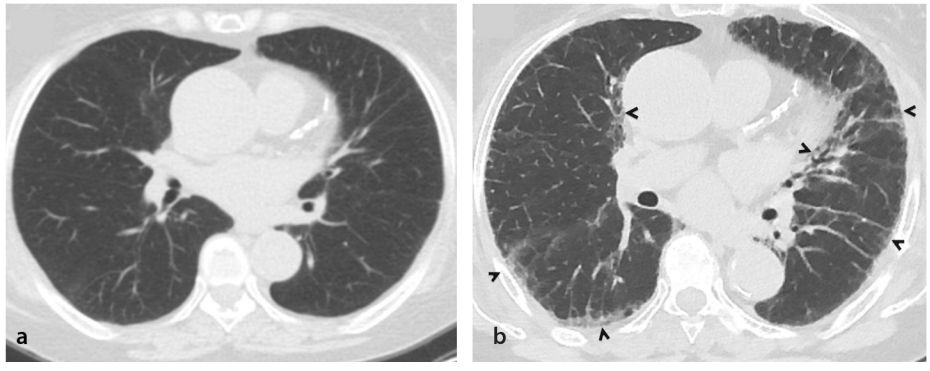

Figure 5. Combined ipilimumab and nivolumab therapy-related non-specific interstitial pneumonia (NSIP) pattern in a 65-year-old male with metastatic malignant melanoma. **(a)** Baseline chest computed tomography (CT) image shows no interstitial abnormalities. **(b)** Axial chest CT image, which was obtained six months after the initiation of therapy, shows bilateral, patchy ground-glass opacities and subpleural reticulations with peripheral predominance (arrowheads), consistent with an NSIP pattern. Nivolumab and ipilimumab were discontinued, and 0.5 mg/kg/day of prednisone was started for three months. An axial chest CT image obtained six months later demonstrates the partial regression of interstitial lung opacities (not shown).

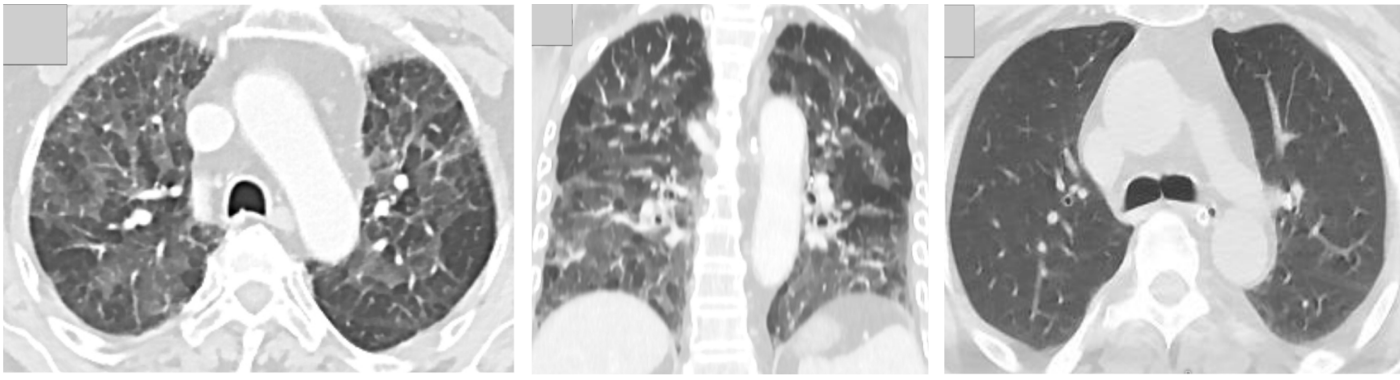

Figure 6. Nivolumab-related hypersensitivity pneumonitis pattern in a 59-year-old male with metastatic renal cell carcinoma. Baseline chest computed tomography (CT) was unremarkable (not shown). **(a)** Axial and **(b)** coronal chest CT images, which were obtained 3 months after the initiation of nivolumab, show patchy ground-glass opacity areas with air trapping, resulting in mosaic attenuation consistent with non-fibrotic hypersensitivity pneumonitis. Nivolumab was discontinued, and additional treatment was not given, because the patient's symptoms were mild. **(c)** Axial chest CT image obtained 3 months later demonstrates the regression of lung opacities.

necrosis.[3,6] The DAD pattern is characterized by GGOs or dependent consolidation areas on imaging that usually affect the majority of, and sometimes, the entirety of the lung area (Figure 7). The "crazy paving" pattern characterized by interlobular septal thickening and intralobular lines can often be seen in the DAD pattern. In addition, other patterns, such as OP, can progress to DAD if not treated early (Figures 8, 9, and Supplementary Figure S3).[5,6,12,13]

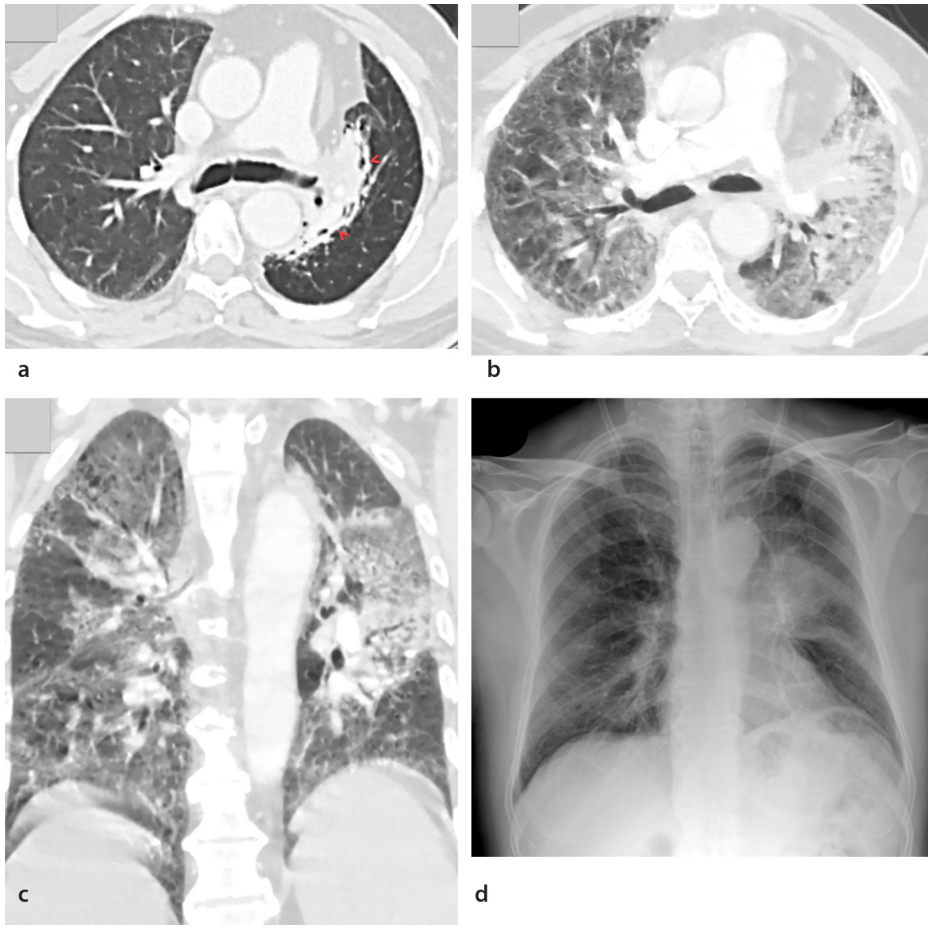

Figure 7. Pembrolizumab-related diffuse alveolar damage (DAD) pattern in a 52-year-old male with metastatic non-small cell lung carcinoma. **(a)** Baseline axial chest computed tomography (CT) image shows a left hilar mass with perilesional fibrosis due to radiotherapy (arrowheads). **(b)** Axial and **(c)** coronal chest CT images, which were obtained two weeks after the initiation of pembrolizumab, show diffuse ground-glass opacity areas that affect most lung areas consistent with a DAD pattern. The pembrolizumab was discontinued, the patient was hospitalized, and 1 mg/kg/day of prednisone therapy was started. **(d)** Two months later, a chest X-ray shows the regression of lung opacities.

DAD–AIP findings can also be seen in extra-pulmonary causes, such as acute respiratory distress syndrome, sepsis, and transfusion-related acute lung injury (Supplementary Figure S4).[5,14] Furthermore, diffuse alveolar opacities can be observed on CT in patients with acute promyelocytic leukemia due to differentiation syndrome, which is a rare condition that occurs during all-trans retinoic acid therapy (Supplementary Figure S5).[5]

Radiologic simple pulmonary eosinophilia (SPEo) pattern

Although SPEo is generally reported in therapies with ICIs (especially with osimertinib), its etiopathogenesis is not fully understood.[6] Patients with an SPEo pattern are usually clinically asymptomatic and indicate a median of grade 1 toxic effects.[6] SPEo is radiologically characterized by unilateral or bilateral non-segmental, patchy GGOs or areas of consolidation. These lung abnormalities are typically transient and spontaneously resolve within a few weeks (Figure 10).[6,13]

Sarcoid-like granulomatosis

Sarcoid-like granulomatosis is an atypical presentation of DILD and is usually associated with ICI therapy. It has been reported in 5%–7% of patients with malignant melanoma treated with ipilimumab.[12] The condition is characterized by histopathological and imaging features identical to sarcoidosis and includes enlarged hilar, mediastinal, and

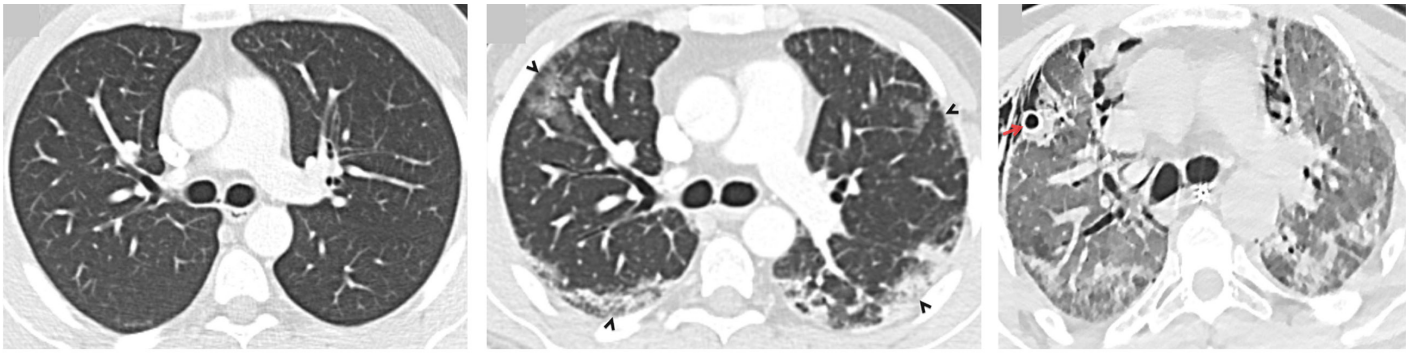

Figure 8. Erlotinib-related diffuse alveolar damage (DAD) pattern in a 42-year-old male with metastatic non-small cell lung cancer. **(a)** Baseline axial chest computed tomography (CT) image at the left main pulmonary artery level shows no parenchymal abnormality. **(b)** Axial chest CT image, which was obtained three weeks after the initiation of erlotinib therapy, shows bilateral, patchy consolidation and ground-glass opacity areas with peripheral predominance (arrowheads) consistent with an organizing pneumonia pattern. Bronchoalveolar lavage fluid (BALF) was obtained, but the BALF results were unremarkable, and the bacterial/fungal culture was negative. Erlotinib was discontinued, but the patient's general condition worsened, and he was intubated five days after CT. During the second day of intubation, pneumothorax and pneumomediastinum were detected, and chest tube replacement was performed. **(c)** Axial chest CT image obtained three days after intubation demonstrates diffuse ground-glass opacity areas that affect the entirety of the lung areas, consistent with a DAD pattern. Note the chest tube on the right side (arrow). The patient died on the eighth day of intubation.

abdominal lymph nodes and perilymphatic (along with interlobular septae and bronchovascular bundles) lung nodules (Figure 11).[4-6,10,12] In positron emission tomography CT, lymph nodes and lung nodules can mimic metastatic disease by showing intense ^{18}F-fluoro-2-deoxy-d-glucose uptake in patients with SLG. Therefore, it is important to be aware of this rare but important drug-induced disorder and consider this diagnosis appropriately to avoid false-positive interpretations of metastatic disease.[12]

Pneumonitis flare

A pneumonitis flare is a rare entity and is defined in patients on ICI therapy. Pneumonitis flares were reported in only 1 case out of 20 patients with ICI-related pneumonitis.[10] The flaring of ICI pneumonitis is characterized as a flare-up (exacerbation) of pneumonitis when tapering, or during, the cessation of corticosteroid intake without the re-treatment of ICIs (Figure 12).[6,10,12]

Radiation recall

Radiation recall is an acute inflammatory condition that occurs in a previously irradiated field after exposure to a provocative agent and is observed in many organs or systems, including the lungs.[5,12] In the past, reports of radiation recall pneumonitis were common in treatments with taxane-based chemotherapy agents and gemcitabine, although radiation recall pneumonitis due to ICI therapy has been reported recently with increasing frequency. Shibaki et al.[15] recently reported that the average time between radiotherapy and radiation recall pneumonitis

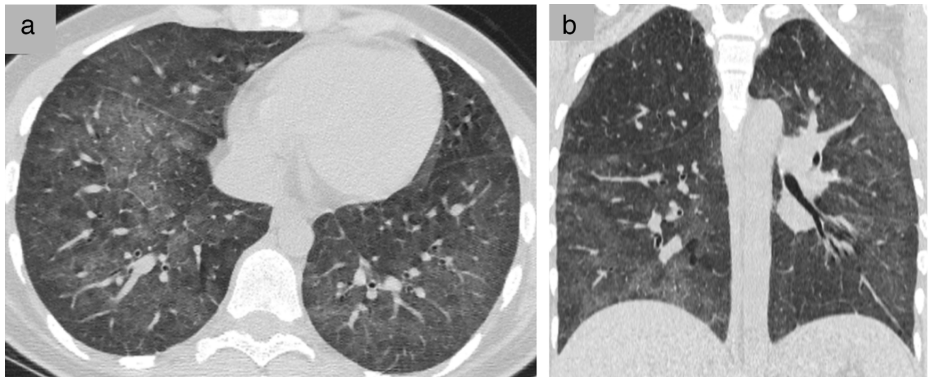

Figure 9. Bleomycin-related diffuse alveolar damage pattern in a 20-year-old female patient with Hodgkin's lymphoma. The baseline chest computed tomography (CT) was unremarkable (not shown). **(a)** Axial and **(b)** coronal chest CT scans obtained 3.5 months after the initiation of bleomycin therapy show bilateral, diffuse ground-glass opacities and centrilobular ground-glass nodules. The patient had no clinical or laboratory findings consistent with infectious pneumonia. The viral panel was negative, including for *Cytomegalovirus*, and a bronchoalveolar lavage fluid culture was negative for *Pneumocystis jirovecii*. Bleomycin was discontinued, 0.5 mg/kg/day of prednisone was started, and the patient's clinical and imaging findings were resolved.

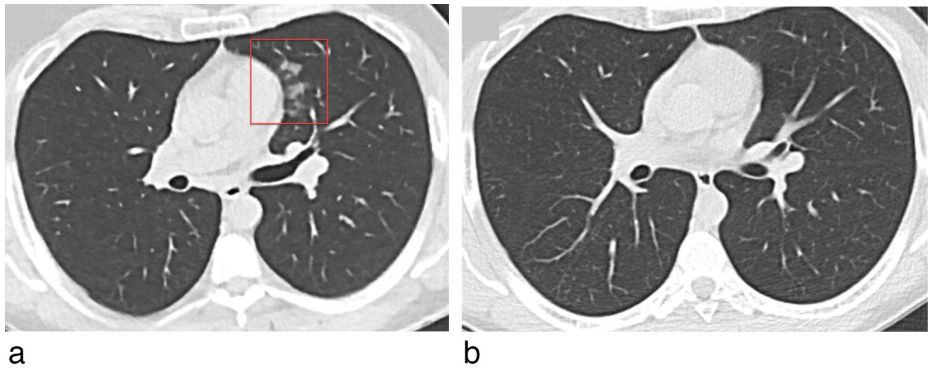

Figure 10. Osimertinib-related simple pulmonary eosinophilia pattern in a 40-year-old male with lung adenocarcinoma. **(a)** Axial chest computed tomography (CT) image at the level of the proximal left upper lobe bronchi shows multifocal ground-glass nodules (red rectangle) during osimertinib therapy. The patient was completely asymptomatic, and laboratory findings were within normal limits. Osimertinib therapy was continued. **(b)** Axial chest CT image, which was obtained 10 weeks later, shows that pulmonary opacities had disappeared entirely without any additional therapy.

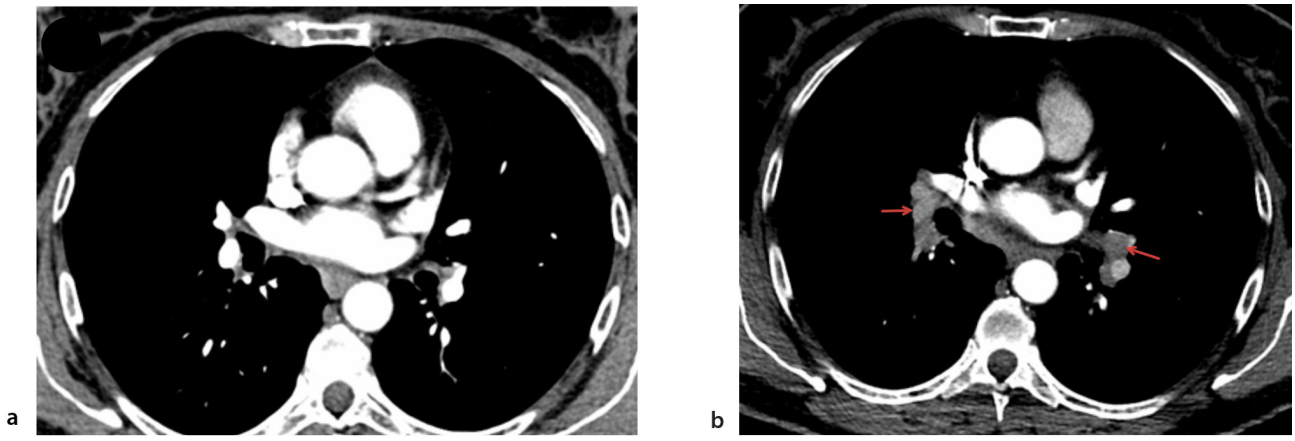

Figure 11. Ipilimumab-related sarcoid-like granulomatosis in an asymptomatic 41-year-old female patient with metastatic malignant melanoma. **(a)** The baseline contrast-enhanced axial chest computed tomography (CT) image at the left atrium levels shows no lymphadenopathies. **(b)** Contrast-enhanced axial chest CT scan obtained six months after the initiation of ipilimumab therapy shows new bilateral symmetric hilar (arrows) lymphadenopathies resembling sarcoidosis. A lymph node biopsy was performed for suspicion of metastasis, and a non-caseating granulomatous reaction was found histopathologically.

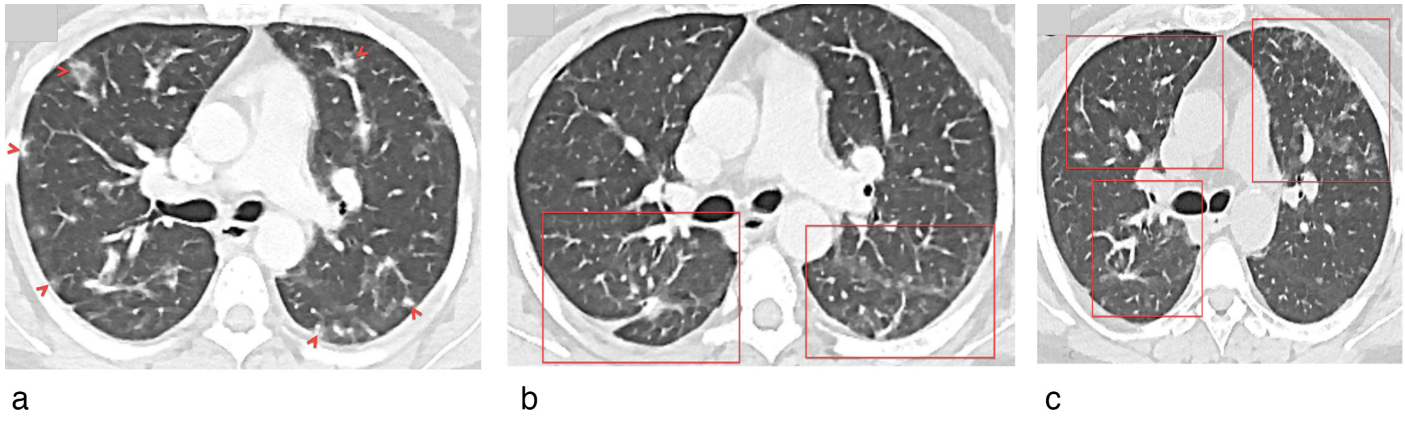

Figure 12. Nivolumab-related pneumonitis flare in a 44-year-old symptomatic female patient with metastatic urothelial carcinoma. Baseline chest computed tomography (CT) was unremarkable (not shown). **(a)** Axial chest CT scan obtained 2 months after the initiation of nivolumab therapy shows the bilateral, multifocal, peripheral, and peribronchovascular distribution of ground-glass opacity nodules compatible with an organizing pneumonia pattern (arrowheads). The patient had no clinical or laboratory findings consistent with infection. Nivolumab was discontinued, 1 mg/kg/day of oral prednisone was started, and the patient's clinical findings were resolved. **(b)** Axial chest CT scan obtained 3 months later shows mild residual ground-glass opacity areas (red rectangles) and pulmonary opacities that had regressed almost completely. Corticosteroid treatment was discontinued. **(c)** Chest CT obtained 1 month after the discontinuation of corticosteroid therapy shows newly emerged patchy ground-glass opacities and nodules in both lungs (red rectangles). The patient was treated with anti-TNF-α (infliximab) and 1 mg/kg/day of oral prednisone, and the patient's clinical and imaging findings were resolved.

diagnosis due to ICI therapy was approximately two years. The frequency of radiation recall pneumonitis was reported as 4.4% in patients who had previously received radiotherapy and were treated with tyrosine kinase inhibitors.[16] Although its etiopathogenesis is unclear, an awareness of this condition is essential to avoid the misdiagnosis of underlying disease progression.[12]

Diagnosis and management of DILD

Early diagnosis and prompt clinical management are essential for DILD. Although DILD is difficult to distinguish clinically from other causes of diffuse pulmonary opacities, radiological findings play a key role (Table 1).[5,6] Additionally, laboratory findings, along with clinical and medication history, are complementary in the diagnosis of DILD. Bronchoscopy and biopsy may rarely be preferred for diagnosis depending on the clinical situation and benefit–risk analysis. Recently, the Fleischner Society recommended the following diagnostic criteria for DILD: (a) newly identified pulmonary opacities, (b) temporal relationship of presentation with the initiation of medication, and (c) exclusion of other possible causes.[6]

Multidisciplinary discussion is recommended when determining the diagnosis and management of patients with suspected DILD.[5,6,17] The clinical grading and management of drug-induced organ toxicity are shown in Supplementary Table S1, and the drugs that are most likely to cause pulmonary toxicity are shown in Supplementary Table S2.

Conclusion

Radiologists should be familiar with DILD, as the condition requires a prompt diagnosis to initiate the appropriate treatment and prevent further morbidity and mortality.

Table 1. Drug-induced pneumonitis patterns and differential diagnoses

Radiological findings	Imaging features	Differential diagnosis	Median grade of toxicity[9]
Organizing pneumonia (OP)	Peripheral or peribronchovascular, multifocal GGO or consolidation areas. Mid-lower lung predominance. Air bronchogram and reverse-halo sign (atoll sign). Opacities can be migratory and change configuration over time.	**Progression of malignancy** (concurrent worsening of disease in other body areas). **Infectious pneumonia, especially COVID-19 pneumonia** (clinical and laboratory findings compatible with infection). **Chronic eosinophilic pneumonia** (eosinophilia, peripheral, band-like opacities, upper lobe predominance). **E-cigarette or Vaping Product Use-Associated Lung Injury (EVALI)** (history of e-cigarette or vaping product use). **OP unrelated to medication** (no temporal relationship with drug, long-term process).	Grade 2
Non-specific interstitial pneumonia (NSIP)	Bilateral, symmetric, patchy, or diffuse GGO areas, with or without reticular opacities. Peripheral and basilar predominancy. Immediate subpleural sparing can be seen. Lung fibrosis is temporarily homogeneous.	**Infectious pneumonia** (clinical and laboratory findings compatible with infection, response to appropriate treatment). **Usual interstitial pneumonia** (subpleural sparing is not seen, lung fibrosis is temporarily heterogeneous). **NSIP associated with connective tissue disease** (appropriate medical history and disease-specific laboratory markers, no temporal relationship with drug).	Grade 1
Hypersensitivity pneumonitis (HP)	Diffuse or upper lobe predominant GGO areas with or without centrilobular lung nodules. Air trapping.	**Atypical infection** (clinical and laboratory findings compatible with infection, response to appropriate treatment). **Respiratory bronchiolitis** (history of smoking, presence of emphysema, and bronchial wall thickening on CT). **Follicular bronchiolitis** (history of underlying connective tissue disease or acquired immunodeficiency syndrome, lung cysts with a peribronchial distribution on CT). **EVALI** (history of e-cigarette or vaping product use). **Exposure-related HP** (appropriate exposure and occupational history, no temporal relationship with drug).	Grade 1
Diffuse alveolar damage (DAD)	GGO or consolidation areas that affect the majority, and sometimes, the entirety of the lung. Predominantly affect dependent lung areas. "Crazy paving" pattern.	**Infectious pneumonia** (clinical and laboratory findings compatible with infection, response to appropriate treatment). **Pulmonary edema** (cardiomegaly, pleural effusion, pulmonary vascular redistribution, peribronchial cuffing, Kerley lines). **Alveolar hemorrhage** (underlying coagulopathy or capillaritis, hemoptysis, anemia).	Grade 3
Simple pulmonary eosinophilia	Unilateral or bilateral, non-segmental, patchy GGO or consolidation areas. Opacities are migratory and spontaneously resolved within a few weeks.	**Infectious pneumonia** (clinical and laboratory findings compatible with infection, response to appropriate treatment). **Alveolar hemorrhage** (underlying coagulopathy or capillaritis, hemoptysis, anemia).	Grade 1
Sarcoid-like granulomatosis	Enlarged hilar and mediastinal lymph nodes. Perilymphatic lung nodules.	**Progression of malignancy** (concurrent worsening of disease in other body areas). **Infection** (clinical and laboratory findings compatible with infection, response to appropriate treatment). **Sarcoidosis** (no temporal relationship with drug, long-term process).	N/A
Pneumonitis flare	Flare-up of pneumonitis.	**Infectious pneumonia** (clinical and laboratory findings compatible with infection, response to appropriate treatment). **OP unrelated to medication** (no temporal relationship with drug, long-term process).	N/A
Radiation recall	GGO or consolidation in a previously irradiated field.	**Infection** (clinical and laboratory findings compatible with infection, response to appropriate treatment). **Progression of malignancy** (concurrent worsening of disease in other body areas).	N/A

GGO, ground-glass opacity; CT, computed tomography; HP, Hypersensitivity pneumonitis; COVID-19, coronavirus disease-2019

Conflict of interest disclosure

The authors declared no conflicts of interest.

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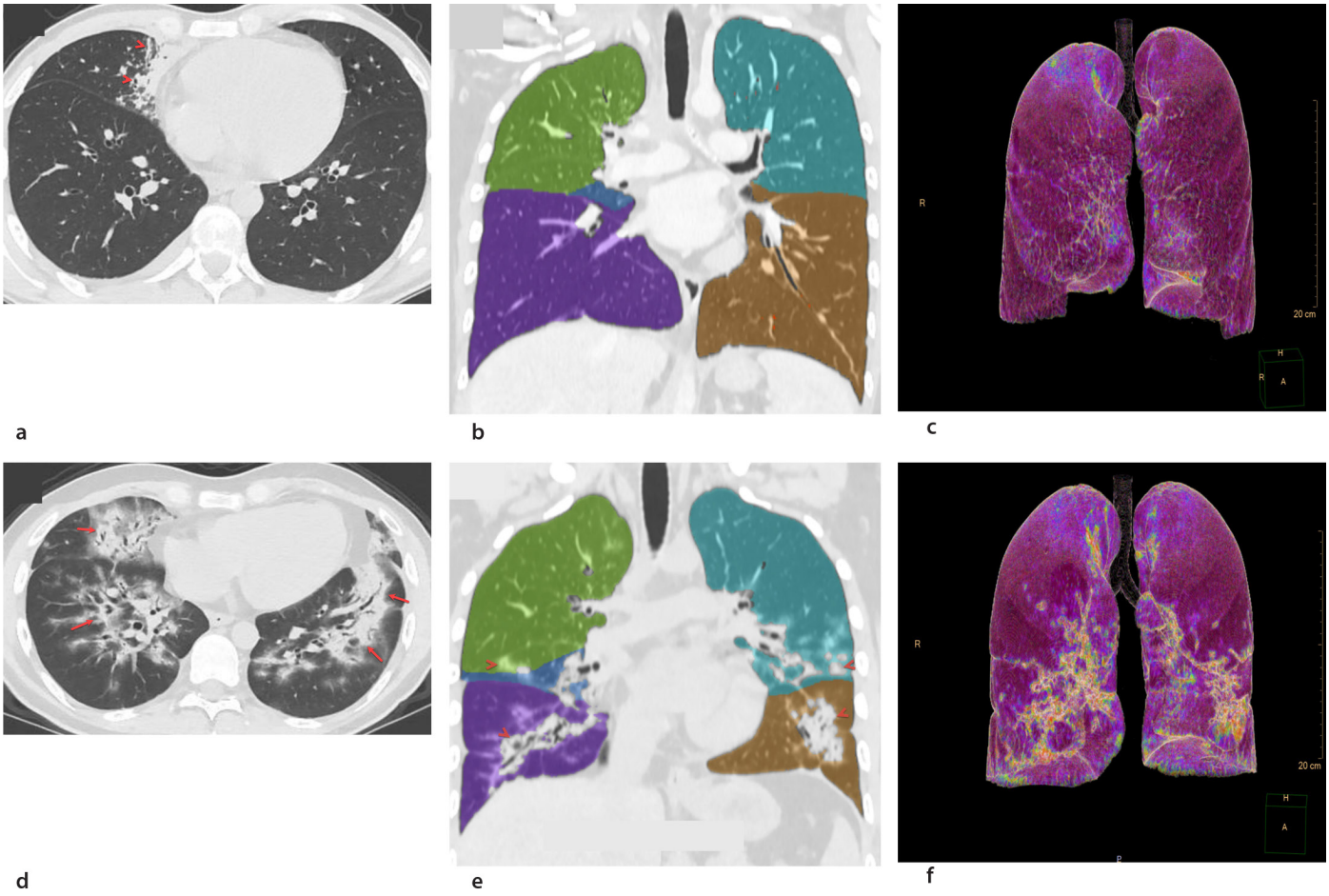
Supplementary Table S1. Clinical grading system of drug-induced lung disease[9]

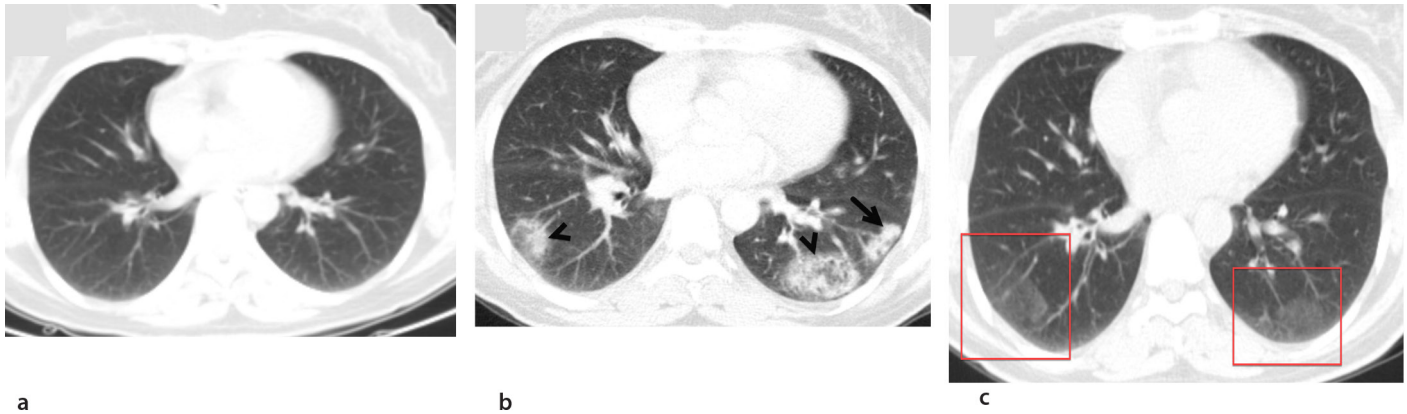
Pneumonitis grade	Clinical findings	Management
1	Asymptomatic	Clinical observations only, intervention not recommended
2	Symptomatic (limitation of instrumental daily living activities)	Medical intervention indicated
3	Severe symptoms (limitation of self-care living activities)	Oxygen indicated
4	Life-threatening respiratory compromise	Urgent medical intervention indicated (e.g., intubation, mechanical ventilation)
5	Death	-

Supplementary Table S2. Drug-related radiological findings and the drugs most likely to cause them

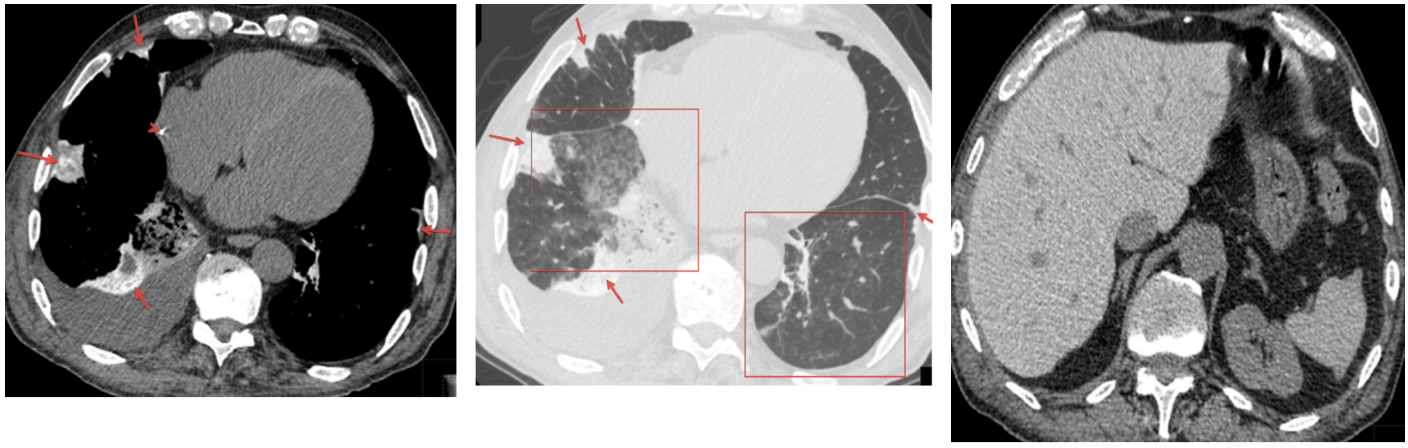
Radiological findings	Most likely causative drugs
Organizing pneumonia	Adalimumab, amiodarone, amphotericin B, azathioprine, bleomycin, busulfan, cocaine, crizotinib, cyclophosphamide, dasatinib, doxorubicin, erlotinib, etanercept, FOLFOX chemotherapy regimen, imatinib, infliximab, ipilimumab, methotrexate, nitrofurantoin, nivolumab, pembrolizumab, penicillamine, rituximab, sirolimus, sulfasalazine
Non-specific interstitial pneumonia	Adalimumab, alemtuzumab, amiodarone, azathioprine, bleomycin, busulfan, crizotinib, cyclophosphamide, docetaxel, etanercept, gemcitabine, imatinib, infliximab, methotrexate, nitrofurantoin, osimertinib, pembrolizumab, vincristine
Hypersensitivity pneumonitis	Atezolizumab, cytarabine, durvalumab, erlotinib, gefitinib, osimertinib, methotrexate, nitrofurantoin, non-steroidal anti-inflammatory drugs, penicillin, rituximab, sirolimus
Diffuse alveolar damage	Amiodarone, bleomycin, busulfan, carmustine, cyclophosphamide, cytosine arabinoside, erlotinib, fluorouracil, gefitinib, gemcitabine, methotrexate, paclitaxel, pembrolizumab, rituximab, vinblastine
Simple pulmonary eosinophilia	Adalimumab, osimertinib, nivolumab, non-steroidal anti-inflammatory drugs, pembrolizumab, sulfasalazine
Sarcoid-like granulomatosis	Adalimumab, alemtuzumab, anakinra, atezolizumab, capecitabine, etanercept, FOLFOX chemotherapy regimen, infliximab, interferon, ipilimumab, methotrexate, nivolumab, pembrolizumab, rituximab
Pneumonitis flare	Ipilimumab, nivolumab, pembrolizumab
Radiation recall	Cabazitaxel, carmustine, erlotinib, gemcitabine, nivolumab, paclitaxel, pembrolizumab



Supplementary Figure S1. Nivolumab-related organizing pneumonia (OP) pattern in a 24-year-old male with Hodgkin's lymphoma. **(a)** Baseline axial chest computed tomography (CT) image at the middle lobe level shows centrilobular nodules and consolidation area (arrowheads) in the middle lobe compatible with radiation pneumonitis. **(b)** Automatic lung segmentation map of the baseline CT image. **(c)** Three-dimensional reconstruction CT image with rainbow colors according to CT attenuation values. In the baseline CT, healthy lung volume [(HLV), attenuation values between −950 and −800 HU] were calculated as 4.384 cc, and the mean lung attenuation as −878 HU. **(d)** In the axial chest CT image obtained 1 week after the initiation of nivolumab treatment, ground-glass opacities and consolidation areas (arrows) were observed in both lungs and were consistent with an OP pattern. **(e)** The automatic lung segmentation map of the control CT image shows lung opacities (arrowheads) and interval lung volume loss compatible with OP. **(f)** Three-dimensional reconstruction CT image with rainbow colors according to CT attenuation values. In the control CT, the HLV was calculated as 3.975 cc, and the mean lung attenuation was −856 HU.

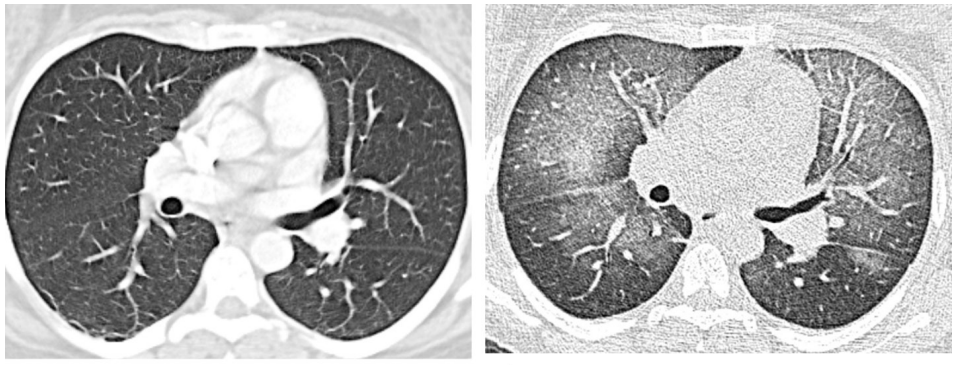


Supplementary Figure S2. Organizing pneumonia (OP) pattern in a 51-year-old female during FOLFIRINOX (5-fluorouracil/leucovorin, irinotecan, oxaliplatin) therapy for metastatic pancreas adenocarcinoma. **(a)** Baseline axial chest computed tomography (CT) image at the inferior pulmonary vein level shows the lungs before chemotherapy was initiated. **(b)** Axial chest CT image obtained three months later, after FOLFIRINOX therapy, shows peripheral consolidation (arrow) and airspace opacities with reverse halo sign (arrowheads) consistent with an OP pattern of pneumonitis. **(c)** Axial chest CT image obtained four weeks later, after withholding FOLFIRINOX therapy and administering 0.5 mg/kg/day of prednisolone therapy, demonstrates that the residual ground-glass opacities and lung opacities had significantly improved (red rectangles).



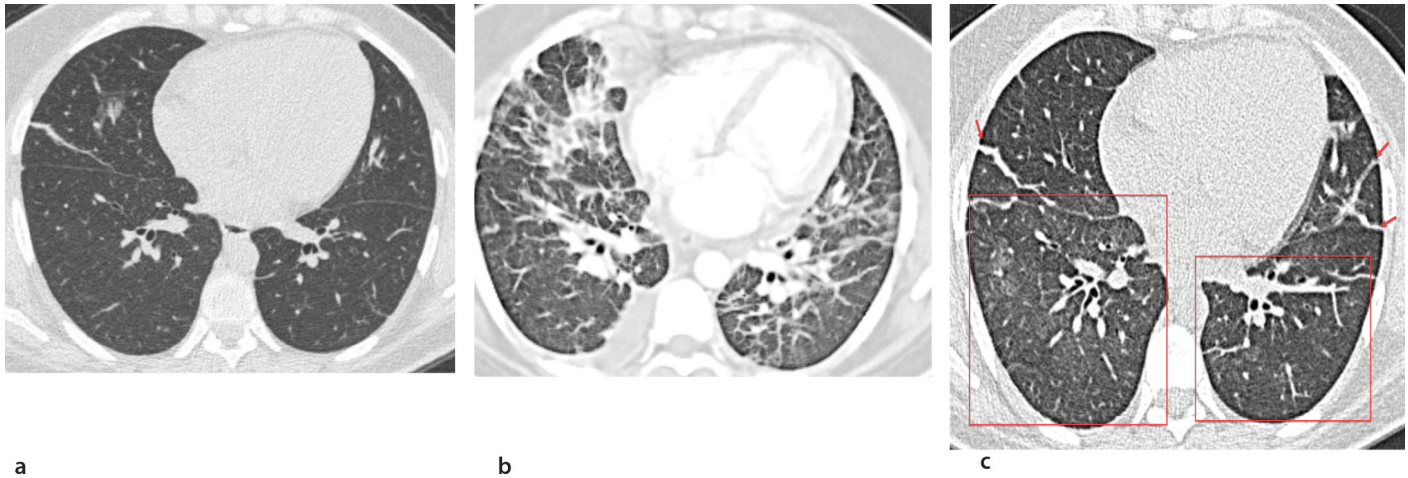
a b c

Supplementary Figure S3. Amiodarone-related alveolar pattern in a 64-year-old male patient with arrhythmia and heart failure. **(a)** Axial unenhanced chest computed tomography (CT) image shows right pleural effusion, peripheral consolidation areas with high attenuation (arrows), and a pacemaker catheter (arrowhead). **(b)** Axial CT image with lung window settings shows peripheral consolidation areas with high attenuation (arrows) and centrilobular ground-glass nodules in both lower lobes (red rectangles). **(c)** Axial unenhanced CT images at the adrenal gland levels show the increased attenuation of the liver with 108 HU. Bronchoalveolar lavage fluid was obtained, and lipid-laden macrophages were detected. Additionally, amiodarone-induced corneal toxicity was found, and amiodarone was discontinued.



a b

Supplementary Figure S4. Transfusion-related acute lung injury in a 31-year-old female with known acute myeloid leukemia who developed dyspnea shortly after transfusion. **(a)** Pretransfusion axial chest computed tomography (CT) image shows clear lungs. **(b)** Post-transfusion axial chest CT image obtained approximately six hours after transfusion shows developing alveolar opacities with perihilar predominance in the bilateral lung zones.



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Supplementary Figure S5. All-trans retinoic acid (ATRA)-related alveolar pattern in a 24-year-old male with acute promyelocytic leukemia. **(a)** Pre-treatment axial unenhanced chest computed tomography (CT) image shows clear lungs except for linear atelectasis and a small area of ground-glass opacity in the right middle lobe. **(b)** The patient developed respiratory distress 12 hours after the initiation of therapy, and an axial CT image shows bilateral patchy ground-glass opacities, interstitial thickening, and bilateral mild pleural effusion. The ATRA was discontinued, and intravenous systemic corticosteroid therapy (dexamethasone 8 mg/m^2) was initiated. The patient's clinical condition improved rapidly. **(c)** Axial chest CT image obtained one month later shows mild residual ground-glass opacities (red rectangles) and linear atelectasis (red arrows).