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Early View

Review

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Drug-induced interstitial lung disease

Paolo Spagnolo[1*], Philippe Bonniaud[2,3], Giulio Rossi[4], Nicola Sverzellati[5], Vincent Cottin[6,7]

[1]Respiratory Disease Unit, Department of Cardiac, Thoracic, Vascular Sciences and Public Health, University of Padova, member of ERN Lung, Padova (Italy); [2]Constitutive Reference Center for Rare Pulmonary Diseases, Department of Pulmonary Medicine and Intensive Care Unit, University Hospital, Bourgogne-Franche-Comté, Burgundy University, Dijon, France; [3]Inserm U1231, Faculty of Medicine and Pharmacy, University of Bourgogne-Franche Comté, F-21000 Dijon, France; [4]Pathology Unit, Fondazione Poliambulanza, Brescia, Italy;; [5]Scienze Radiologiche, Dipartimento di Medicina e Chirurgia, University-Hospital of Parma, Parma, Italy; [6]Dept of Respiratory Medicine, National Coordinating Reference Center for Rare Pulmonary Diseases, Louis Pradel Hospital, Hospices Civils de Lyon, member of ERN-Lung, Lyon, France; [7]University of Lyon, INRAE, IVPC, Lyon, France.

*Correspondence to:
Paolo Spagnolo MD, PhD
via Giustiniani 2, 35128 Padova, Italy
Phone: 0039 049 8211272
Email: paolo.spagnolo@unipd.it

Abstract

Interstitial lung disease (ILD) secondary to drug-induced lung injury is an increasingly common cause of morbidity and mortality. The number of drugs associated with the development of ILD continues to raise, mainly due to the use of novel monoclonal antibodies and biologics for neoplastic and rheumatologic diseases, and includes, among others, chemotherapeutics, molecular targeting agents, immune checkpoint inhibitors, antibiotics, antiarrhythmics, and conventional or biologic disease-modifying antirheumatic drugs. Drug-induced ILD (DI-ILD) manifests with a variety of clinical patterns, ranging from mild respiratory symptoms to rapidly progressive respiratory failure and death. In most cases, there are no pathognomonic clinical, laboratory, radiological or pathological features and the diagnosis of DI-ILD is suspected in the presence of exposure to a drug known to cause lung toxicity and after exclusion of alternative causes of ILD. Early identification and permanent discontinuation of the culprit drug are the cornerstones of treatment with systemic glucocorticoids being used in patients with disabling or progressive disease. However, for certain drugs, such as checkpoint inhibitors, the frequency of lung toxicity is such that mitigation strategies are put in place to prevent this complication and occurrence of DI-ILD is not necessarily synonymous with permanent drug discontinuation, particularly in the absence of valid therapeutic alternatives.

Keywords
Amiodarone; Drug-induced lung disease; Iatrogenic; Interstitial lung disease; Lung toxicity; Medications; Pulmonary fibrosis.

Take home message: Interstitial lung disease is a potentially severe and even fatal adverse drug reaction. The number of culprit drugs continues to increase. Identification and discontinuation of the causative drug is the cornerstone of treatment.

Introduction

Drug-induced interstitial lung disease (DI-ILD) is a large and very heterogeneous group of adverse drug reactions, ranging from mild to progressive and life-threatening disease More than 400 drugs have been reported to cause ILD [1], the most common being disease-modifying antirheumatic drugs (DMARDs), antiarrhythmics, and antimicrobial and antineoplastic drugs [2], including immune checkpoint inhibitors (ICIs). The list of culprit drugs is constantly increasing, mainly due to the exponential development of antineoplastic drugs with specific mechanistic targets (including, among others, monoclonal antibodies and tyrosine kinase inhibitors), many of which are associated with lung toxicity.

Clinical, laboratory, radiological and histological features of DI-ILD are nonspecific and variable even with the same offending drug, suggesting that other factors, including genetics, may contribute to disease development. The diagnosis is one of exclusion and involves clinical suspicion, exposure to a drug known to cause lung toxicity and exclusion of other causes of ILD [3]. However, assessing causality is challenging, particularly when a potentially pneumotoxic drug (e.g., methotrexate) is used to treat a disease that can cause ILD (e.g., rheumatoid arthritis), in patients using multiple potentially pneumotoxic drugs (e.g. methotrexate and infliximab), or when drug toxicity occurs acutely in patients on chronic treatment with the culprit drug (Table 1). Special attention should be paid to excluding other causes of ILD, including infection, heart failure or lymphangitic carcinomatosis (Table 2). Naranjo and colleagues developed an adverse drug reaction probability scale that can also be applied to suspected DI-ILD. They classified the probability that the adverse event is related to a given drug as “definite” (total score ≥9), “probable” (total score 5 to 8), “possible” (total score 1 to 4), “doubtful” (total score ≤0)

Table 3) [4]. Discontinuation of the culprit drug is the mainstay of treatment whereas glucocorticoids are reserved to patients with disabling or progressive disease.

Search strategy and selection criteria

We performed a comprehensive (but non-systematic) literature search for articles related to drug-induced interstitial lung disease. References included in this narrative review were identified by searching PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) for articles published up to December 2021, using the terms “interstitial lung disease”, “pulmonary fibrosis”, “lung injury”, “lung toxicity”, OR “pneumonitis” AND “drug-induced”, “chemotherapy”, “antineoplastic agents”, “immune checkpoint inhibitors”, “mTOR inhibitors”, “antibiotics”, “nitrofurantoin”, “amiodarone”, “antiarrhythmic drugs”, “statins”, “disease-modifying antirheumatic drugs”, “methotrexate”, OR “biological agents”. Relevant references cited in these articles were also screened. We limited our search to articles published in English and reviewed them manually. Articles in other languages with abstracts in English were also reviewed if sufficient detail was present in the abstract. The final reference list was generated based on the relevance to the topic covered in this review article.

Table 1. Main culprit drugs based on clinical and imaging patterns

Pattern	Main culprit drugs
Acute or subacute ILD (including ARDS)	• >350 suspected drugs. • Amiodarone, chemotherapy (most of them), ICIs, TKIs (including crizotinib, EGFR inhibitors, erlotinib, gefitinib,) m-TOR inhibitors, rituximab, statins, methotrexate, nitrofurantoin, TNF-alpha antagonists. • Do Not Forget: BCG-therapy, tobacco smoke, e-cigarette and vaping, vitamin E acetate, heroin, radiation therapy, silicone fluid.
Pulmonary fibrosis	• >80 suspected drugs. • Chemotherapy (including alkylating agent – cyclophosphamide, carmustine (BCNU), lomustine (CCNU)-busulfan, bleomycin, gemcitabine) amiodarone, nitrofurantoin, bone marrow transplantation. • Do Not Forget: paraquat, radiation to the chest, tobacco smoke.
Eosinophilic pneumonia (including acute eosinophilic pneumonia and DRESS)	• >200 suspected drugs. • Antibiotics (minocycline, azathioprine, beta-lactam), amiodarone, anticonvulsant, antidepressants, NSAIDs, chloroquine, leukotriene receptors antagonists, mesalazine, nitrofurantoin, tryptophan. • Do Not Forget: tobacco smoke.
Organizing pneumonia	• >100 suspected drugs. • Amiodarone, antineoplastic including ICIs, statins, rituximab, sirolimus. • Do Not Forget: radiation therapy to the breast.
Noncardiogenic pulmonary oedema	• >200 suspected drugs. • All-trans retinoic acid, aspirin, beta-2-agonists (IV as tocolytic therapy), chemotherapy, hydrochlorothiazide, IV epoprostenol. • Do Not Forget: cocaine, heroin, chlorine gas, various inhaled chemicals, TRALI, vasodilators in patients with pulmonary hypertension.
Diffuse alveolar haemorrhage	• >150 suspected drugs. • Amiodarone, anticoagulants, antiplatelet agents, abciximab, ticlopidine, fibrinolytic agents, VEGF-inhibitors (bevacizumab), erlotinib, m-TOR inhibitors, propylthiouracil. • Do Not Forget: brodifacoum, superwarfarin (anticoagulant rodenticide), cocaine.
Granulomatosis, Sarcoid-like granulomatosis	• >40 suspected drugs. • TNF-alpha antagonists, ICIs, daclizumab, interferon. • Do Not Forget: BCG-therapy (bladder instillation).
Lupus-like syndrome	• >80 suspected drugs. • Hydralazine, TNF-alpha antagonists, isoniazid, minocycline, sulfasalazine, procainamide, beta-blockers, ICIs.

	• Do Not Forget: timolol ocular drops
Auto-immune conditions including ANCA +	• >20 suspected drugs. • Nitrofurantoin, TNF-alpha antagonists, propylthiouracil, minocycline, alemtuzumab. • Do Not Forget: adulterant levamisole induced vasculitis (cocaine users).
Pleuroparenchymal fibroelastosis	• ~ 10 suspected drugs • Cyclophosphamide and other alkylating agents manly • Do Not Forget bone marrow transplantation (both allogenic and autologous) and lung transplantation

The list of drugs is not exhaustive. You may refer to www.pneumotox.com for a comprehensive search.

Abbreviations: BCG: Bacillus Calmette-Guerin; DRESS: Drug Rash with Eosinophilia and Systemic Symptoms; EGFR: epidermal growth factor receptor; ICIs: immune checkpoint inhibitors; mTOR: mammalian target of rapamycin; NSAIDs: nonsteroidal anti-inflammatory drugs; TKIs: tyrosine kinase inhibitors; TNF: tumor necrosis factor; TRALI: Transfusion-related acute lung injury; VEGF: vascular endothelial growth factor.

Table 2. Diagnostic checklist in patients with suspected drug-induced interstitial lung disease

Steps	Checking list	To do	Comments
1	Consider the possibility of DI-ILD in every patient with ILD	This must be a mandatory step in the diagnostic workup of any ILD	The worst scenario would be to misdiagnose DI-ILD and continue the causative drug
2	Check https://www.pneumotox.com *	By pattern By drugs	May be completed with a PubMed search
3	History of exposure to the drug	– A meticulous inquiry is necessary – Easier when there is only one drug – Help from the pharmacist is helpful	– Patients are often exposed to more than one possible offending drug (e.g. older patients with rheumatic, cardiac or neoplastic conditions). – Patients may not report drugs they take only occasionally (i.e., nitrofurantoin) – Any route of administration may be responsible (i.e. ocular, intra-dermal, intra-vesical, intra-vaginal)
4	Timing of drug exposure	DI-ILD develops usually within a few weeks to a few months after treatment initiation Generally, the patient is still taking the culprit medication	– The diagnosis is easier in case of acute or subacute forms of ILD – Rarely DI-ILD develops only after cessation of exposure to the drug (amiodarone, late PPFE after cyclophosphamide…)
5	Clinical and imaging pattern	The DI-ILD patterns should match the literature (see https://www.pneumotox.com)	– Often nonspecific – Virtually every pattern of ILD has been described – Usually most of the complementary exams are not very helpful and nonspecific (i.e., blood test)
6	Exclusion of other causes for ILD	ESSENTIAL • Infection • Heart Failure • Lymphangitic carcinomatosis • Underlying disease – Cancer – Connective tissue diseases (i.e., RA, SSc) – IBD	Consider: – BAL – BNP – echocardiography
7	Drug discontinuation	Mandatory – May need the help of colleagues specialized in the underlying disease (drug withdrawal and replacement) – Improvement following drug discontinuation is the strongest diagnostic argument	– Depending on the severity, glucocorticoids are often initiated – Difficult in case of multiple suspected drugs: the most likely culprit drug should be withdrawn first – For some drug, dose reduction may lead to significant improvement (I.e. mTOR inhibitors)
8	Recurrence of symptoms after rechallenge with the drug	– May be dangerous or even lethal – Cannot be recommended	If the drug is essential and could not be replaced, rechallenge should always be discussed with a multidisciplinary team

*www.pneumotox.com
Abbreviations: BAL: bronchoalveolar lavage; BNP: Brain natriuretic peptide; DI-ILD: drug-induced interstitial lung disease; IBD: inflammatory bowel disease; ILD: interstitial lung disease; mTOR: mammalian target of rapamycin; PPFE: pleuroparenchymal fibroelastosis; RA: rheumatoid arthritis; SSc: systemic sclerosis

Table 3. Adverse drug reaction probability scale

To assess the adverse drug reaction, please answer the following questionnaire and give the pertinent score				
	Yes	**No**	**Do not know**	**Score**
1. Are there previous conclusive reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?	+1	0	0	
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in the blood (or other fluids) in concentration known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drug in *any* previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
	Total score			

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This article outlines the main features of DI-ILD and provides a framework for approaching patients with this often underrecognised form of ILD.

Epidemiology

The incidence of DI-ILD is difficult to estimate, and varies widely depending on a number of factors, including the specific drug and dose, and the accuracy of reporting. In a retrospective cohort study of 770 consecutive Japanese patients diagnosed with advanced non-small cell lung cancer (NSCLC) between January 2004 and January 2014, 44 (6%) developed pneumonitis during systemic anti-cancer therapy with a mortality rate of pneumonitis of 36% [5]. More recently, Jo and colleagues conducted a nested case-control study to identify associations between drugs with potential risk of ILD and the occurrence of DI-ILD in hospitalized patients requiring glucocorticoid therapy, using a national inpatient database (cases, n=1,541, controls, n=5,677) [6]. Of the 42 categories of drugs

investigated, epidermal growth factor receptor inhibitors (OR: 16.84) and class III antiarrhythmic drugs (OR: 7.01) were those associated with the highest disease risk.
In cohorts of patients with ILD, between 3% and 5% of prevalent cases are drug-induced [7-9], corresponding to an incidence of DI-ILD ranging between 4.1 and 12.4 cases/million/year [10], but this is likely to be an underestimate given the significant expansion of novel oncology drugs with a high rate of DI-ILD.

Clinical features

Disease onset varies from days to even years and is unpredictable. Acute pneumonitis manifests within hours or days with shortness of breath, fever, and often peripheral eosinophilia, whereas symptoms and sign of pulmonary hemorrhage range from dyspnea, cough and fever to acute respiratory failure, hemoptysis and acute anemia depending on disease severity [11]. In DI-ILD patients with subacute or chronic onset, or with subacute worsening of an underlying chronic respiratory disease, the main symptoms are worsening dyspnea and reduced exercise capacity. Lung auscultation may reveal fine or “velcro-like” crackles, whereas digital clubbing is uncommon. In advanced disease pulmonary hypertension and right ventricular dysfunction may occur [12]. Lung function tests may vary from an obstructive to a restrictive ventilatory defect with impairment of gas exchange depending on the underlying histopathological disease pattern.

Complementary diagnostic tests

Laboratory findings are nonspecific and may help excluding alternative causes of ILD. However, white blood count may reveal increased eosinophils in DI-ILD manifesting as eosinophilic pneumonia and rarely hypersensitivity pneumonitis (HP) [2, 11]. Mild peripheral eosinophilia (0.5 to 1.5 g/L) may also accompany DI-ILD not presenting as eosinophilic pneumonia (i.e., amiodarone-induced pulmonary disease), thus raising the

suspicion of DI-ILD. Bronchoscopy plays an important role in the diagnostic work-up of patients with suspected DI-ILD, mainly by ruling out alternative diagnoses especially opportunistic infection and malignancy. The most prominent BAL feature of DI-ILD is a lymphocytic alveolitis with a preponderance of CD8+ cells, but a preferential increase of CD4+ cells may be seen with the use of methotrexate, nitrofurantoin and sirolimus [13, 14]. BAL may also help defining the underlying histopathological features of DI-ILD such as eosinophilic pneumonia (in the presence of BAL eosinophilia >25%), or alveolar hemorrhage.

Imaging

Thin-section computed tomography (CT) has a central role in the diagnosis of DI-ILD by defining the extent and distribution of the disease. In addition, HRCT may identify findings suggestive of alternative diagnoses. However, CT features are not specific for DI-ILD, and the same drug can be associated with multiple disease patterns, which can coexist in the same patient. A recent position paper from the Fleischner Society has proposed three key diagnostic criteria for DI-ILD: 1) new-onset lung parenchymal opacities at thin-section CT, commonly in a bilateral nonsegmental distribution; 2) temporal association of presentation with the administration of a systemic therapeutic agent; 3) exclusion of other causes of ILD [15]. This latter criterion may be particularly challenging, although common differential diagnoses of ILDs such as congestive heart failure, radiation pneumonitis, or lymphangitic carcinomatosis are generally differentiated from DI-ILD based on CT features.
Overall, radiologic patterns reflect the generally inflammatory/immunologic nature of DI-ILD. Accordingly, the most common disease patterns include nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP), diffuse alveolar damage (DAD), HP and simple pulmonary eosinophilia [15]. Usual interstitial pattern (UIP), which is characterized on HRCT by reticular changes and honeycombing with or without traction bronchiectasis

with a subpleural basal predominance, is a rare pattern of DI-ILD and its presence should raise the suspicion of alternative diagnoses, or pre-existing pulmonary fibrosis.

DAD, a common manifestation of DI-ILD, is characterized on HRCT by bilateral consolidation, ground glass opacity (GGO) and crazy paving with posterior and basal predominance in the exudative phase [16]. In the organizing and fibrotic phase of DAD, reticulation, traction bronchiectasis, and architectural distortion may develop. Drug-induced HP manifests as diffuse GGO and ill-defined centrilobular nodules, and may be difficult to distinguish from HP induced by inhalation of organic dusts [17]. Areas of decreased attenuation on expiratory CT scans indicate air trapping, which is caused by bronchiolar obstruction [18]. HRCT abnormalities of drug-induced NSIP are also indistinguishable from those of idiopathic NSIP, and include GGO with varying degrees of reticular changes, consolidation and traction bronchiectasis, with subpleural sparing of the dorsal regions of the lung and with a lower lobe predominance [19]. Diffuse alveolar hemorrhage (DAH) may also manifest as extensive bilateral GGO. OP is another common radiological pattern of DI-ILD, which manifest mainly as multifocal areas of airspace consolidation that are peribronchovascular or peripheral in distribution and have a predilection for the lung bases [20].

There are no CT features that are specific for a drug etiology or can differentiate DI-ILD from infection, including COVID-19 pneumonia, or other non-DI-ILD. Moreover, radiographic abnormalities poorly correlate with the underlying histopathological pattern [17, 21]. Cleverley and colleagues compared HRCT appearances, such as disease pattern and distribution, with histopathological features in 20 patients with biopsy-proven DI-ILD to determine the prognostic value of HRCT [22]. The most common CT abnormalities were GGO (n=17), interlobular septal thickening (n=15), consolidation (n=14), and centrilobular nodules (n=8). The HRCT and histological patterns were concordant in only nine of 20 cases (45%). In addition, the HRCT pattern was of limited prognostic value. In many

cases, the HRCT pattern is indeterminate, and it is likely that pathology - if available - would demonstrate cellular and possibly fibrosing ILD often remaining difficult to classify. Radiological-histological correlation may be better in ILD induced by chemotherapy, particularly in bleomycin-induced lung injury, which on HRCT may manifest as NSIP, DAD, OP, or fibrotic changes such as reticulation, traction bronchiectasis and honeycombing [21].

Histopathology

Drugs can produce a variety of histopathological patterns of interstitial pneumonia - ranging from acute/subacute to established fibrosis - and any histological pattern may be caused by a number of different drugs (Table 4). Apart from a minority of drugs that may cause specific changes of lung morphology (e.g., direct cytotoxic damage with drug accumulation leading to foamy changes of intraalveolar histiocytes and type II pneumocytes), the majority of DI-ILDs is generally reported by pathologists in descriptive terms that do not fit a unique histologic pattern. The most common morphologic patterns of DI-ILD include acute lung injury (DAD and OP), cellular and/or fibrotic NSIP, HP, granulomatous pneumonitis, eosinophilic pneumonia, pulmonary hemorrhage or edema, constrictive (obliterative) bronchiolitis and vascular modifications (e.g., veno-occlusive disease) [2]. Desquamative interstitial pneumonia (DIP), vasculitis and alveolar proteinosis are less common findings [23-25], the latter being observed mainly following tyrosine kinase inhibitor, sirolimus and everolimus treatment [26-28]

DAD is characterized by an initial exudative phase with edema hyaline membranes and acute interstitial inflammation, followed by an organizing phase with alveolar septal fibrosis and type II pneumocytes proliferation (Figure 1A). Hyaline membranes consist of cellular debris, fibrin exudate and surfactant. DAD can be associated with OP, progress to fibrosis, or resolve with restoration of normal lung structure; therefore, different histologic patterns

might be appreciated depending on the timing of sampling (i.e., DAD in the early phase and OP or NSIP in the late phases of DAD). OP is characterized histologically by excessive proliferation of granulation tissue, which consists of fibroblasts and myofibroblasts embedded in a myxoid-to-fibrotic stroma (so-called Masson bodies), involving alveolar ducts and alveoli (Figure 1B). Cicatricial OP with/without ossification is a newly described entity distinguished from conventional OP by the presence of dense fibrous bands (Figure 1C) [29]. Acute fibrinous and organizing pneumonia (AFOP) and granulomatous and organizing pneumonia (AGOP) are two additional variants of OP that

Table 4. Histologic patterns observed in drug-induced interstitial lung disease

Cellular and/or fibrotic nonspecific interstitial pneumonia (NSIP)
Diffuse alveolar damage (DAD)
Acute fibrinous organizing pneumonia (AFOP)
Organizing pneumonia (OP) or Bronchiolitis obliterans organizing pneumonia (BOOP) (conventional and cicatricial)
Usual interstitial pneumonia (UIP)
Hypersensitivity pneumonitis (HP)
Desquamative interstitial pneumonia
Pleuroparenchymal fibroelastosis
Granulomatous organizing pneumonia (GOP)
Constrictive bronchiolitis with airflow obstruction
Eosinophilic pneumonia
Pulmonary edema and hemorrhage
Pulmonary veno-occlusive disease (PVOD) with hypertension
Granulomatous inflammation
Histiocytic nodules with/without necrosis
Unclassifiable cellular/fibrotic interstitial lung disease

may be observed in drug-induced lung disease. Constrictive bronchiolitis with distortion of the bronchiolar lumen secondary to submucosal scarring and smooth-muscle hypertrophy may also be observed. NSIP, one of the most common histological patterns of DI-ILD, is characterized by relatively uniform chronic interstitial inflammation and type II pneumocyte hyperplasia in area of inflammation with or without interstitial fibrosis (Figure 1D). Eosinophilic pneumonia is characterized by alveolar and interstitial eosinophilic infiltration and foci of OP, but hyaline membranes and interstitial widening (i.e., DAD) can also be seen (Figure 2A and 2B) [30]. Granulomatous pneumonitis may resemble other forms of granulomatous lung diseases such as HP, sarcoidosis, tuberculosis and nontuberculous mycobacterial disease (Figure 3) [31-38]. Finally, a DIP-like pattern has been reported mainly following sirolimus and nitrofurantoin therapy [39-43].

The diagnosis of DI-ILD rarely requires a histological confirmation. In addition, morphologic abnormalities of lung tissue (obtained generally by transbronchial biopsy) are not specific of drug-induced lung damage.

Pathogenesis and risk factors

The pathogenesis of DI-ILD is largely unknown for most drugs. However, the mechanisms through which drug-induced lung injury occurs are likely to involve direct damage to alveolar epithelial or capillary endothelial cells, dysregulation of the immune system, systemic cytokine release, cell-mediated lung damage and free radical production with oxidative injury (Table 5) [11].

Table 5. Potential mechanisms of drug-induced lung damage

Mechanisms	Examples
Direct cell toxicity / apoptosis	Bleomycin-induced pulmonary fibrosis Most chemotherapies Radiation
Cell toxicity through drug biotransformation and production of chemically reactive metabolites	Amiodarone
Drugs acting as antigens (or haptens) leading to immune-mediated (via either drug-specific antibodies or drug-specific T cells) lung toxicity. Previous sensitization to the drug may be required.	Methotrexate-induced hypersensitivity pneumonitis DRESS
Production of free oxygen radicals with alterations of the oxidant/antioxidant balance. Toxicity may be enhanced by concomitant therapeutic oxygen administration.	Alkylating agents Bleomycin Radiation Nitrofurantoin
Intracellular deposition of phospholipids	Amiodarone lung
Dysregulation of the immune system by direct biological effect of the drug	Checkpoint inhibitors Interferon-α (sarcoidosis) Anti-CD20, and others biologicals targeting the immune system
Dysregulation of the immune system: drugs may act as an adjuvant inducing a disorder in immunity	Drug-induced systemic lupus erythematosus DRESS
Direct effect of the drug as facilitator	Alveolar hemorrhage and anticoagulant Vascular damage and capillary leak syndrome : IL2, i.v. salbutamol

The development of DI-ILD is largely unpredictable, although cumulative dose and impaired renal function appear to confer an increased risk (Table 6) [44]. Preexisting ILD is a risk factor for the development of lung toxicity in patients with NSCLC treated with epidermal growth factor receptor tyrosine kinase inhibitors (EGFR/TKI) gefitinib, or erlotinib [45-47], and in patients with rheumatoid arthritis treated with leflunomide [48-51]. Conversely, whether preexisting lung disease increases the risk of developing amiodarone lung toxicity is uncertain [52, 53]. Japanese ethnicity, male sex, smoking habit and poor performance status are additional risk factors for TKI-induced ILD in patients with lung

cancer [26, 54, 55]. A seasonal distribution of ICI/TKI-induced pneumonitis has also been reported, suggesting that viral infection may act as a cofactor in the development of lung toxicity [56, 57].

Genetic factors have been suggested to contribute to the risk of developing DI-ILD. Udagawa and colleagues carried out whole genome sequencing (WGS) of genomic DNA from 26 Japanese cancer patients who developed DI-ILD and identified associations with two intronic polymorphisms located within chromosome 22 open reading frame 34 (C22orf34; rs35198919) and tea shirt zinc finger homeobox 2 (TSHZ2; rs12625311) [58]. Further, in a subgroup analysis of patients with EGFR/TKI-induced ILD (n=13), an association between seven single nucleotide polymorphisms and DI-ILD was observed. Human leukocyte antigen (HLA) alleles have also been associated with increased risk of DI-ILD. Carriage of *HLA-A*31:01* was significantly associated with methotrexate-induced ILD in Japanese patients with rheumatoid arthritis [59] while the combination of *HLA-B*15:01* and *DRB1*15:01* increased the risk of ILD in Japanese patients with advanced pancreatic cancer receiving gemcitabine plus erlotinib [60]. *HLA-DRB1*04:05* has also been associated with DI-ILD, especially chemotherapeutic agents, in Japanese patients [61]. Notably, the higher allele frequency of *HLA-DRB1*04:05* in the Japanese population compared to most other populations, may account for the high susceptibility of Japanese patients to DI-ILD [62].

Table 6. Main risk factors for drug-induced interstitial lung disease

Risk factors	Comments
Dose-dependent toxicity (amiodarone, bleomycin (500 units), carmustine (BCNU) (1500 mg/m²), mitomycin (50 mg/m²), chest radiation therapy)	For all drugs, toxicity have been described after administration of low doses including those with apparent dose-dependent toxicity
Underlying condition associated with ILD	RA, SSc Very difficult and challenging
Combination of pneumotoxic drug	Combination of chemotherapies, chemotherapy following radiation and/or ICIs
Genetics	familial pulmonary fibrosis, EGFR TKI in Japanese population
High FiO2	chemotherapy, radiation, amiodarone
Venous route / high speed of administration	Salbutamol-induced pulmonary oedema, amiodarone, Bleomycin
Rechallenge (accidentally or voluntary under strict medical surveillance)	Usually not recommended and, if needed, only after multidisciplinary discussion. Assess the possibility of class effect

Abbreviations: EGFR: epidermal growth factor receptor; FiO2: Fraction of inspired oxygen; ICIs: immune checkpoint inhibitors; ILD: interstitial lung disease; RA: rheumatoid arthritis, SSc: systemic sclerosis; TKI: tyrosine kinase inhibitor

Treatment – general principles

Discontinuation of (and avoidance of further exposure to) the culprit drug is the mainstay of treatment. However, patients with disabling or progressive disease despite drug withdrawal are generally treated with glucocorticoids, although there are no robust data on the efficacy of glucocorticoid treatment in DI-ILD. . Indeed, a systematic review that included 156 papers describing more than 6,000 DI-ILD cases found that the majority of the data was of low or very low quality. The authors concluded that glucocorticoids are commonly used to treat DI-ILD and might be useful in severe cases [10]. Dose and duration of glucocorticoid therapy vary widely, mainly based on the radiological pattern of disease. Treatment response is highly variable, ranging from minimal or no improvement in patients with DAD to resolution in those with OP. Recent data suggest that nintedanib (and possibly pirfenidone) is efficacious in patients with progressive fibrosing ILD despite appropriated treatment [63, 64]; however, whether these drugs are efficacious also in

patients with DI-ILD that progresses despite discontinuation of the culprit drug and glucocorticoid/immunosuppressive therapy is unknown.

In patients suspected to have idiopathic pulmonary fibrosis (IPF), a careful medication history, with emphasis on when the medication was started and stopped and its dosing, is a very important part of the diagnostic work-up. Based on how likely a given drug is to be the causative agent, its cessation may be indicated, although this does not always have an immediate effect on the patient's condition. Yet, disease progression following drug discontinuation is not expected in DI-ILD whereas IPF is by definition a progressive disease. Moreover, in cases with a high pretest probability of IPF (i.e., male patients, ex-current smokers, family history of IPF, age older than 60 years), the benefit of withdrawing a potentially pneumotoxic (but important) drug should be weighed against the risk of delaying a diagnosis of IPF. Lastly and most importantly, UIP is an uncommon pathological and radiological pattern of DI-ILD. Therefore, the diagnosis of IPF and the initiation of antifibrotic therapy should not be delayed unnecessarily. With all these caveats, in patients suspected to have IPF, the decision to discontinue a medication should be taken on a case by case basis.

Prognosis

Owing to the large number of drugs that can potentially cause lung toxicity, prognosis is highly variable. Discontinuation of the culprit drug with or without glucocorticoids may lead to full recovery, provided the diagnosis is made early. Indeed, broadly speaking, early identification (and discontinuation) of the causative drug is generally associated with a favorable prognosis, whereas delayed diagnosis may lead to rapidly progressive acute respiratory distress syndrome (ARDS), or pulmonary fibrosis with poor prognosis. However, particularly with antineoplastic agents, the decision to discontinue the drug requires careful consideration of risks and benefits as well as the availability of alternative

treatments. In selected cases of lung toxicity induced by checkpoint inhibitors, or mechanistic target of rapamycin (mTOR) inhibitors, continuation of the drug at a reduced dose may be justified in the absence of significant lung disease. Similarly, the decision on whether to rechallenge a patient with the same drug after a prior drug-induced lung toxicity must be made on a case-by-case basis with multidisciplinary discussion in a reference center and based on the severity of the reaction and the availability of alternative therapies. DI-ILD recurs in about one-third of re-challenged cases [65, 66]. However, successful rechallenge (i.e., the safe and efficacious readministration of a drug previously discontinued due to lung toxicity) after remission of severe DI-ILD has also been reported [67, 68].

Most common causative drugs

Chemotherapeutic agents

Lung toxicity has been reported to occur in 10 to 20% of all patients treated with antineoplastic drugs [2, 12, 69, 70]. Disease pathogenesis is poorly understood, but several mechanisms, either alone or in combination, are likely to be involved including direct damage to pneumocytes or alveolar endothelial cells, cell-mediated lung injury, oxidative stress, systemic cytokine release and dysregulated immune system in patients treated with immune-checkpoint inhibitors [71].

Pulmonary toxicity induced by antineoplastic drugs typically occurs within weeks to a few months after treatment initiation and generally manifests as shortness of breath, cough, and low-grade fever, although weight loss may also be present [71]. Chest auscultation may reveal bibasilar crackles. The most common pulmonary function abnormality is a reduced diffusing capacity of the lung for carbon monoxide (DL_{CO}), with a restrictive ventilatory defect generally being observed in advanced or fibrotic disease [12]. Radiological abnormalities include patchy or diffuse GGO, consolidation, centrilobular

nodules, interlobular septal thickening and reticular changes (Figure 4A and 4B) [72]. Pleuroparenchymal fibroelastosis (PPFE) may be a late complication of treatment with alkylating agents (i.e., cyclophosphamide and carmustine) [73]. Bleomycin-induced lung damage may progress to end-stage disease with honeycombing [17] (Figure 5) whereas hilar lymphadenopathy may be the presenting manifestation of methotrexate-induced lung toxicity [12]. Similar to other forms of drug-induced ILD, BAL reveals a lymphocytic alveolitis, although the main role of bronchoscopy is to exclude alternative diagnoses, mainly recurrent malignancy and infection. Lung biopsy has a limited role in the diagnosis of antineoplastic drug-induced lung toxicity, as there are no specific histological features and virtually all histopathologic patterns of lung damage can be observed, including UIP, NSIP, OP, DAD, alveolar hemorrhage, eosinophilic pneumonia and DIP [2]. As with other forms of drug-induced lung toxicity, drug withdrawal is the mainstay of treatment, although continuation of the drug at a reduced dose and drug rechallenge may be considered in selected cases. The use of systemic glucocorticoids is generally reserved to patients with severe/progressive pulmonary disease, but this treatment has not been evaluated in controlled clinical trials. The prognosis of chemotherapy-induced ILD is unpredictable, with severe or rapidly fatal outcomes despite drug discontinuation and glucocorticoid therapy being reported [74, 75].

Immune checkpoint inhibitors

The development of immune checkpoint inhibitors (ICIs) has revolutionized the treatment paradigm for cancer. ICIs have a broad range of indications including, among others, lung cancer, melanoma, bladder cancer and head and neck tumours, but they are also associated with high rates of pulmonary adverse effects [76]. Immune modulation resulting from checkpoint inhibition can lead to abnormal activation of autoreactive T cells leading to inflammation in any organ system, although the precise mechanisms through which

toxicity occurs remain to be established.

Interstitial pneumonias are described with every class of ICIs, with an incidence varying from 3% to 6%, including 1% to 2% of grade 3-4 adverse events [77-80]. The incidence of drug-induced ILD appears higher with programmed death-ligand 1 (PDL1) vs. CTLA4 inhibitors and increases in case of combined anti-PD1/PDL1 and anti-CTLA4 treatment (10% - all grades combined) [81]. Additional risk factors include a history of smoking, pre-existing ILD, chest radiation, poor performance status and treatment indication for lung cancer vs. melanoma [81]. Interestingly, however, nivolumab may potentially be beneficial in patients with advanced NSCLC and pre-existing ILD, as recently reported in a real-world setting in France [82]. The onset of the iatrogenic lung toxicity is variable, from a few days to more than a year, with a median of 3 months [79, 83]. Clinical manifestations include cough, onset or progression of dyspnoea and chest pain, although ICI-induced lung toxicity may also be asymptomatic. Several patterns of radiological presentation have been reported, including OP, the most frequent, NSIP, HP, DAD, alveolar haemorrhage and sarcoid-like reactions [84]. Importantly, tumour hyperprogression or pseudoprogression should be included in the differential diagnosis of ICI-associated ILD. The management depends on the severity of lung disease [85]:

- Grade 1 (mild - asymptomatic, radiographic abnormalities only): ICI withdrawal should be discussed, although the benefit/risk balance of maintaining immunotherapy will generally encourage continuing ICI;
- Grade 2 (moderate - symptoms without limitation of daily activities): it requires ICI discontinuation; glucocorticoid treatment may be considered;
- Grade 3 (severe - symptoms with limitation of daily activities, or requirement of oxygen therapy): it requires definitive drug discontinuation and glucocorticoid treatment;
- Grade 4 (life-threatening or disabling): it requires definitive drug discontinuation and intravenous glucocorticoids. Immunosuppressant may be needed;

- Grade 5 (fatal).

Rechallenge with the causative agent is possible in case of grades 1 and 2 toxicities, but not recommended for grades 3 and 4.

Adverse events of immunotherapy may also manifest as sarcoid-like pulmonary and cutaneous reaction and reactive hilar and mediastinal lymphadenopathy, which is often misdiagnosed as concomitant or progressive lung cancer [86, 87]. Biopsy of these lesions is generally indicated, and reveals typical nonnecrotizing sarcoid-like granulomas. ICI-induced sarcoid-like reactions do not mandate treatment, especially if the condition is asymptomatic [88]. In cases requiring treatment, glucocorticoids with or without ICI discontinuation appear to be effective [78-80, 88-90].

The management of patients with ILD and lung cancer should always be discussed in a multidisciplinary setting, weighing carefully the expected benefits and risks for each patient, particularly when ICIs are considered. However, we believe ICIs should be avoided in ILD patients with extensive disease and/or moderate/severe lung function impairment, particularly those with idiopathic pulmonary fibrosis, because of both the risk of acute exacerbations, and the lack of safety and efficacy data on co-administration of ICIs and antifibrotics (i.e., nintedanib and pirfenidone).

mTOR inhibitors

Mammalian target of rapamycin (mTOR) inhibitors exert immunosuppressive properties by reducing T and B cell proliferation [91], and are widely prescribed to prevent solid organ transplant rejection and for treatment of cancers and lymphangioleiomyomatosis. mTOR inhibitors are significant inducers of lung toxicity, which manifests mainly as lymphocytic interstitial pneumonia, OP or alveolar haemorrhage [92]. BAL is typically lymphocytic, sometimes with increased eosinophil count, or haemorrhagic. Outcome is usually rapidly favourable following drug withdrawal or dosage reduction. Glucocorticoids may be

necessary. Notably, sirolimus-induced pneumonitis may improve after switching to another mTOR inhibitors, everolimus [93].

Antibiotics

Nitrofurantoin - a 5-nitrofuran derivative - is commonly used for the treatment and prophylaxis of urinary tract infections (UTIs). The acute form of pulmonary toxicity accounts for approximately 80% of cases and develops following a short course of therapy, although the disease may also develop insidiously following months or even years of treatment [94]. Nitrofurantoin-induced pulmonary toxicity occurs almost exclusively in women (more commonly middle-aged or elderly) because of their increased susceptibility to recurrent UTIs and more frequent use of the drug. The acute form of pulmonary toxicity results from a hypersensitivity reaction (type I or III) whereas a cell-mediated or toxic response have been proposed as the main pathogenetic mechanisms in chronic disease. Histopathological findings are also different; indeed, acute disease is characterized by mild (and often eosinophilic) interstitial inflammation whereas diffuse interstitial pneumonia with an NSIP pattern is commonly observed in chronic reactions [94-96].

Acute pneumonitis generally develops within one to two weeks of nitrofurantoin use (or earlier in case of previous exposures) and presents with fever, dyspnea and cough; peripheral eosinophilia is also common [94, 97]. In subacute and chronic disease, the most common presenting symptoms are dyspnea and cough, which develop after at last one month of treatment [96]. Radiologically, acute pulmonary toxicity manifests as diffuse GGO, whereas GGO and consolidation with or without reticular changes and traction bronchiectasis is the most common pattern in patients with chronic disease [98]. Pleural effusion may be seen in acute disease but is an uncommon finding in chronic reactions. Autoimmunity can be present in the form of antinuclear (ANA) or antineutrophil cytoplasmic (ANCA) antibodies.

Prompt discontinuation of nitrofurantoin is the cornerstone of therapy for both acute and chronic lung disease [99], but while in acute pneumonitis symptoms and radiographic abnormalities improve rapidly, over days to weeks [94, 97, 100], chronic toxicity may require weeks to months to resolve. The use of glucocorticoids is generally limited to patients with severe and progressive disease, although resolution of severe pulmonary toxicity may occur without treatment [101, 102]. Overall, the prognosis is favorable but fatal ILD has also been reported [94, 97, 103]. Drug rechallenge should be discouraged, as it invariably causes disease relapse.

Drug Rash with Eosinophilia and Systemic Symptoms

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome is a severe idiosyncratic drug reaction characterized by extensive skin rash with frequent facial edema, polyadenopathy, blood eosinophilia and a wide range of organ involvement, including hepatitis and nephritis [104]. Lung involvement (i.e., pulmonary infiltrates and pleural effusion) is present in approximately 20% of cases and is a major cause of morbidity. Fatalities caused by severe lung disease have also been reported [105]. More than 80 medications have been associated with DRESS syndrome, the most frequently incriminated being antibiotics but also anticonvulsants, allopurinol, non-steroidal anti-inflammatory drugs and antidepressants. The latency from drug initiation to symptom onset typically ranges from two to eight weeks. The pathogenesis of DRESS syndrome is poorly understood, but host factors (i.e., carriage of certain HLA alleles) and viral infection, mainly HHV-6, are believed to be involved [106].

Cardiovascular drugs

Amiodarone lung

Amiodarone is an iodine-containing compound commonly used to treat supraventricular and ventricular arrhythmias. Up to 5% of patients may develop pulmonary toxicity [12, 107-

109], which may manifest as interstitial pneumonia, OP, ARDS, eosinophilic pneumonia and, rarely, diffuse alveolar hemorrhage, lung nodules and masses [110].

Interstitial pneumonia

Interstitial pneumonia, the most common manifestation of amiodarone-induced lung toxicity, generally develop within 6 to 12 months of treatment, although cases of lung disease occurring within few weeks or after several years of treatment have also been reported [12, 111, 112]. Risk factors for pulmonary toxicity include a daily dose higher than 400 mg, long-term treatment and age of 60 years and over [113]; conversely, whether preexisting lung disease increases the risk of developing lung toxicity remains controversial. Disease pathogenesis is incompletely understood, although both a direct cytotoxic effect and an indirect immunologic reaction are believed to be involved [114, 115]. An additional pathogenetic hypothesis postulates that the drug induces alveolar cell apoptosis by acting as a non-selective thyroid-hormone receptor antagonist thus disrupting TH-signaling pathway. In addition, amiodarone accumulates in adipose tissue, thus exhibiting an increased half-time life [108, 116]. The mode of presentation is insidious in about 55% of cases (over a period of one to three months) and rapidly progressive in 40% of cases (acute amiodarone pneumonitis); the disease may be asymptomatic in 5% of cases. Dyspnea and nonproductive cough are the most common presenting symptoms [12, 114, 115]. Fever is present in up to 50% of cases, whereas weight loss, malaise and pleuritic chest pain are less common manifestations [114, 115]. Inspiratory crackles may be heard on chest auscultation. Laboratory abnormalities are nonspecific and blood levels of amiodarone are generally normal [114, 115].

HRCT reveals areas of increased attenuation in the lungs - wherein infiltrates may be diffuse, unilateral or predominant on one side - but also in the liver and spleen, owing to the tendency of amiodarone to accumulate in tissue macrophages (Figure 6A) [117].

Additional HRCT features include diffuse GGO and thickened interlobular septa; traction bronchiectasis and honeycombing can also be observed (Figure 6B) [118, 119]. A restrictive ventilatory defect with reduced DL_{CO} is the most common functional abnormality. Bronchoscopy with BAL is more helpful in ruling out alternative diagnoses, such as infection, or malignancy, than confirming the diagnosis of amiodarone lung toxicity, as the BAL cellular pattern is nonspecific. The presence of “foamy” macrophages, which is due to the accumulation of phospholipids in alveolar macrophages, although typical, is not pathognomonic of pulmonary toxicity, as these cells can be found in up to one-half of patients receiving amiodarone [114, 115]. On the other hand, in the absence of foamy macrophages the diagnosis of amiodarone lung is unlikely [114, 115].

A clinical diagnosis of amiodarone-induced lung toxicity is supported by the following features: insidious onset of dyspnea and/or cough; new GGO or reticular abnormalities on chest X-ray/HRCT; presence of foamy macrophages in the BAL; exclusion of other causes of lung disease; clinical and radiological improvement following amiodarone discontinuation (with or without glucocorticoids). Treatment consists primarily of amiodarone discontinuation and, in symptomatic patients, systemic glucocorticoids. However, because of the long half-life of amiodarone and its accumulation in fatty tissues, pulmonary disease may progress despite drug withdrawal. Overall, improvement is slow and disease recurrence is possible even weeks or even months after the drug has been discontinued [120], therefore, low dose glucocorticoids are often maintained for a few months even after improvement or recovery has been obtained. In patients who have experienced amiodarone lung toxicity, the drug should not be reintroduced because of the high risk of disease recurrence potentially more severe than the first episode.

Eosinophilic pneumonia

Amiodarone lung toxicity may manifest as acute (more commonly) or chronic eosinophilic pneumonia. Acute eosinophilic pneumonia (AEP) manifests acutely with fever, dyspnea, and dry cough, whereas in chronic eosinophilic pneumonia (CEP) respiratory symptoms may be accompanied by weight loss and night sweats [121]. Peripheral blood eosinophilia may be observed in both AEP and CEP. On chest HRCT, diffuse GGO and consolidation, which, in CEP, tend to distribute peripherally (“photographic negative" of pulmonary edema), are the most common radiological abnormalities [122]. The diagnosis is supported by the presence in the BAL of foamy macrophages with eosinophilia >25%, and requires the exclusion of other causes of eosinophilic pneumonia (e.g., parasitic and fungal infection, and vasculitis. Treatment consists of drug discontinuation, with systemic glucocorticoids being reserved to patients with symptomatic or progressive disease.

Organizing pneumonia

OP occurs in about one-quarter of cases of amiodarone lung toxicity and manifests as dyspnea, dry cough and fever; pleuritic chest pain may also be present. Chest radiograph typically reveals patchy consolidation, often with an air bronchogram, which mimics bacterial pneumonia, whereas HRCT shows also GGO and septal thickening [123]. Opacities tend to migrate. A histological confirmation of the diagnosis may be needed to when OP manifests as chronic consolidation or mass. Histologically, OP is characterized by excessive proliferation of granulation tissue - loose collagen-embedded fibroblasts and myofibroblasts - involving alveoli and alveolar ducts. Treatment consists of drug discontinuation generally associated with systemic glucocorticoids.

Acute respiratory distress syndrome

ARDS is a rare but severe form of amiodarone lung toxicity that has been reported in patients undergoing surgery or pulmonary angiography [124-127]. ARDS is defined by the acute onset (≤1 week) of respiratory failure, bilateral infiltrates on chest radiograph, hypoxemia as defined by a PaO2/FiO2 ratio ≤200 mmHg and no evidence of cardiogenic edema or fluid overload. More common causes of ARDS, such as sepsis, aspiration, transfusion, and drug toxicity need to be excluded. In patients with ARDS, the main role of BAL is to rule out infection, hemorrhage and malignancy. The histological pattern of ARDS is DAD. Disease management includes drug discontinuation, supportive measures and mechanical ventilation. Most patients are also treated with systemic glucocorticoids. ARDS secondary to amiodarone toxicity has a mortality rate of approximately 50 percent [128].

Diffuse alveolar hemorrhage

Amiodarone lung toxicity may rarely manifest as diffuse alveolar hemorrhage (DAH), which tends to occur after few days or months of treatment, generally in patients with pre-existing pulmonary, cardiac or renal disease [129-131]. DAH presents acutely with cough, dyspnea, and fever; hemoptysis may also be present. Chest radiograph reveals diffuse and bilateral GGO and consolidation, whereas BAL is characterized by progressively more hemorrhagic returns [132]. Increased levels of hemosiderin-laden macrophages in BAL is an additional typical finding. The diagnosis of amiodarone-induced DAH requires the exclusion of other causes of alveolar bleeding, such as vasculitis, systemic lupus erythematosus (SLE), drugs other than amiodarone, or inhaled toxins. Similar to other forms of amiodarone lung toxicity, treatment consists of drug withdrawal and systemic glucocorticoids are the mainstay of treatment. Additional drugs that can induce DAH include, among others, anticoagulants, antiplatelet agents, new direct oral anticoagulants, thrombolytic agents.

Statins

Statins are lipid-lowering medications that are widely used for the prevention and treatment of cardiovascular disease. While generally safe and well tolerated, they can cause muscle aches or cramps in approximately 5% of patients. Whether statin use increases the risk of developing ILD remains controversial. Indeed, while a systematic review of the literature and the US Food and of the Drug Administration adverse event reporting database suggested that the use of statins may be associated with an increased risk of ILD [133], a large cohort study that included users of respiratory medications (over 1.4 million patients, of which 6,665 possible or probable cases of ILD) did not find an association between statin use and incidence of ILD [134].

Disease-modifying antirheumatic drugs

Disease modifying antirheumatic drugs (DMARDs) are medications with immunosuppressive and immunomodulatory properties that are used for the treatment of a number of conditions including rheumatoid arthritis (RA), psoriatic arthritis, ankylosing spondylitis and SLE. DMARDs are commonly classified as conventional or biologic. The conventional DMARDs most commonly used are methotrexate, hydroxychloroquine, leflunomide and sulfasalazine whereas biologic DMARDs include, among others, infliximab, adalimumab, etanercept, rituximab, abatacept, tocilizumab and tofacitinib. Pulmonary toxicity has been reported with virtually all of the DMARDs, but the frequency and pattern of lung disease vary widely based on the drug involved [1].

Methotrexate (MTX) is the DMARD most commonly used in RA, but it is also used for the treatment of other rheumatologic diseases, psoriasis, and some malignancies. Lung toxicity tends to occur after weeks to months of low-dose therapy, but has also been reported after short treatment with higher doses [135, 136]. The frequency with which MTX-induced lung disease occurs is difficult to estimate due to its nonspecific clinical,

radiological and histological features, the concomitant use in the same patient of multiple potentially pneumotoxic drugs, and the possible presence of coexisting or preexisting lung involvement from the disease for which MTX is used. However, in a systematic review of the long-term safety of MTX monotherapy in 3,463 RA patients receiving the drug up to 36.5 months, only 15 cases (0.43%) of MTX-induced pneumonitis occurred [137]. On the other hand, in patients with RA-ILD, MTX does not seem to exert deleterious effects, and possibly is beneficial [138]. In a retrospective, case-control study of RA patients with (n=410) or without (n=673) ILD, MTX use was associated with a decreased risk of ILD [139], although, due to the retrospective design of the study, it cannot be excluded that some confounding factors might have affected this finding. Moreover, in a previous study of RA-ILD patients, MTX treatment was strongly associated with longer survival after adjusting for confounding variables [140], suggesting that the increased risk of ILD in RA patients treated with MTX reported in older studies might be accounted for, at least in part, by cases of pre-existing RA-ILD misdiagnosed as MTX-induced lung fibrosis [141]. Overall, there is no high-quality data suggesting that MTX is associated with chronic pulmonary fibrosis. HP is the most common form of MTX-induced lung toxicity and is characterized by lymphocytic (and, less commonly, eosinophilic) interstitial infiltration and poorly formed granulomas [142]. However, OP, acute interstitial pneumonia and pleural effusion have also been described following MTX use [66]. As with most drugs, the mechanisms through which MTX-induced lung injury occurs are largely unknown, although a direct toxic effect of the drug or a hypersensitivity reaction may be involved [143]. Factors that increase the risk of MTX-induced lung toxicity include older age (e.g., higher than 60 years), preexisting lung disease, previous use of DMARDs and diabetes [144]. MTX-induced lung toxicity may present in an acute, subacute (the most common), or chronic form. Acute pneumonitis manifests with rapidly progressive (over several days) dry cough, dyspnea, fever, malaise, and chest pain, whereas subacute pneumonitis is

characterized by a more insidious onset. Mild peripheral eosinophilia is present in up to 50% of patients.

Chest radiograph shows diffuse (nodular or ill-defined) parenchymal infiltrates and, in severe cases, bilateral consolidation with air bronchogram, while HRCT displays patchy, widespread or diffuse GGO with or without consolidation or septal lines, and poorly-defined centrilobular nodules [145, 146]. Hilar or mediastinal lymphadenopathy and pleural effusion are less common findings. PFTs typically show a restrictive ventilatory defect with impaired gas exchange. As with other drug-induced lung diseases, bronchoscopy with BAL is more helpful in excluding alternative diagnoses, such as infection, than in diagnosing MTX-induced pulmonary toxicity. However, BAL shows increased cellularity and is typically lymphocytic with an increased CD4/CD8 ratio [147, 148]. Cellular interstitial infiltration (with or without granulomas) and acute and organizing DAD are the main histological abnormalities, but lung biopsy is rarely required to confirm the diagnosis [66].

The diagnosis of MTX-induced pulmonary toxicity is based on a combination of clinical, radiological, BAL and histological (when available) features, exclusion of alternative causes of lung disease and clinical response to drug discontinuation.

Cessation of MTX may be sufficient for clinical improvement and even disease reversal to occur, whereas patients with severe or progressive disease despite drug withdrawal generally require glucocorticoid treatment. Overall, the prognosis of MTX pneumonitis is favorable; however, persistent radiological and functional abnormalities and even fatalities have been reported [66, 149, 150].

Table 7. Main respiratory side effects induced by biotherapies and other promising inhibitors indicated for the treatment of autoimmune diseases

	Frequency	Exposure delay	ILD severity	ARDS	Exacerbation of pre-existing ILD	Systemic reactions	Sarcoid-like	Nodules	Other respiratory side effects	Infectious risk
TNF-alpha inhibitors – **etanercept** – **adalimumab** – **infliximab** – **certolizumab** – **golimumab**	5	ILD: >3 months Granulomatosis: 1 month to several years	++ moderate to severe + Fibrosis	++	++	++ Lupus ++ autoimmune abnormalities Vasculitis	+ + (mainly with etanercept)	+	Pleural effusion AH asthma	+++
Anti CD20 - **rituximab**	4	Acute: <24h from the first administration ILD: >4 administration OP, nodules: late	+ moderate to severe Fibrosis	+	--	+ autoimmune abnormalities + + hypersensitivity ++ anaphylaxis	+	+	 AH Pulmonary oedema OP	+++
anti CTLA4-Ig - **abatacept**	2	Acute	severe	+	+	ANA +	--	--	EP	--
Anti-IL6 - **tocilizumab** (Sarilumab)	1	Months (?)	+	--	+	ANA +	+	--	OP	+
anti-BLyS - **belimumab**	1	Acute	--	--	--	anaphylaxis	--	--	--	- ?
Anti-IL1R - **Anakinra**	1	--	--	--	+ ?	anaphylaxis	+ (cutaneous)	-	--	+
Anti-IL1 - **canakinumab**	1	--	--	--	--	--	--	--	--	+
Anti IL12/IL23 **- ustekinumab**	1	?	+ subclinical/ moderate (?)	--	--	--	+	--	EP HP	++
Anti IL23 **- guselkumab**	--	--	--	--	--	--	--	--	--	? upper airways
Anti IL17 **--secukinumab** **- ixekizumab**	--	--	?	--	--	--	--	--	--	+ upper airways
Anti-JAK - **tofacitinib/Anti JAK 1/3** - **baricitinib/Anti JAK 2** - **upadacitinib/Anti JAK 1** - **filgotinib/Anti JAK 1**	2	Weeks (?)	--	--	--	--	--	--	PAH (Tofacitinib) ?	++
Phosphodiesterase inhibitors **- apremilast**	--	--	--	--	--	--	--	--	--	?

This table cannot be considered exhaustive; it may evolve and must therefore be regularly updated.
The reported frequency of drug-related side effects (column 2) corresponds to that found on the pneumotox website (www.pneumotox.com, i.e., --: unknown; 1: <10 cases; 2: 10-50 cases; 3: 50-100 cases; 4: 100-200 cases; 5: >200 cases), and is related to the number of cases declared and/or published. This frequency is not limited to the risk of DI-ILD but may include other respiratory iatrogenic effects.
Legend: + (the risk is described); +++ (well-known and frequent risk); ? Isolated published cases with uncertainties; --: insufficient data.
Abbreviations: AH: alveolar haemorrhage; ANA: antinuclear antibodies; ARDS: acute respiratory distress syndrome; EP: eosinophilic pneumonia; HP: hypersensitivity pneumonitis; ILD: interstitial lung disease; OP: organizing pneumonia; PAH: pulmonary arterial hypertension.

Biological agents

Biological agents are an increasingly recognized cause of DI-ILD, and tumor necrosis factor (TNF) inhibitors - apart from the increased incidence of pneumonia including tuberculosis reactivation - represents the most common causative drugs (Table 7). ILD induced by biological therapies is relative rare, although the exact prevalence of the disease is unknown [151]. Similar to other forms of DI-ILD, the most common presenting manifestations are nonproductive cough, dyspnea and pulmonary infiltrates on chest radiograph. Perez-Alvarez and colleagues reported on 122 cases of new-onset or exacerbation of ILD following biological therapies [152]. The drugs associated with ILD were almost exclusively anti-TNF agents (e.g., etanercept in 58 cases and infliximab in 56 cases) and were used for treatment of RA in most cases (108/122, 89%) [152]. DI-ILD was confirmed histologically in 26 cases: UIP (seven cases), NSIP (six cases) and OP (five cases) were the most common pathological patterns. Notably, drug discontinuation (with or without glucocorticoids) led to ILD resolution or improvement in only two-thirds of patients, with mortality being particularly high among patients with preexisting ILD [152]. Older age (e.g., >65 years) and concomitant immunosuppressive drugs were additional factors associated with increased mortality. Therefore, when considering a biological treatment, the benefit of the drug should always be weighed against the potential risk of pulmonary toxicity, particularly in elderly patients with RA and with a UIP pattern of disease. Sarcoid-like granulomatosis, pulmonary hemorrhage and OP have also been described with TNF inhibitors. Sarcoid-like granulomatosis affects more frequently the lung (followed by the skin), and etanercept is the drug most often incriminated [153]. Following drug discontinuation, symptoms (cough, fatigue and dyspnea) and radiographic abnormalities (especially mediastinal lymphadenopathy) tend to improve spontaneous over 2 to 6 months. TNF inhibitors can also induce antinuclear antibodies (ANA) [154]. The majority of patients with positive ANA are asymptomatic but vasculitis and lupus-like syndromes have

also been described [155]. Pleuro-pulmonary involvement may occur but less frequently than in other forms of drug-induced lupus.

The anti-CD20 rituximab is widely used for treatment of malignant lymphoma and various autoimmune disorders including RA. Acute lung injury with bilateral infiltrates has been described within the first 24 hours after the first injection - mostly in patients with neoplastic/hematological disorders - and may be fatal [156]. The mechanism of lung damage is unknown but could be linked to a massive release of cytokines from lysed neoplastic cells. Most cases of rituximab-induced ILD occur on average three months after the first rituximab infusion and two weeks after the last rituximab infusion at the time glucocorticoids are withdrawal [156, 157]. Bilateral alveolar infiltrates and OP may be observed on chest imaging. Withdrawal of rituximab along with glucocorticoids is usually very effective. Glucocorticoids given prophylactically to prevent the production of anti-rituximab antibodies may also reduce the rate and severity of drug-induced adverse events, including acute infusion reactions, cytokine release syndrome and lung toxicity [158]. Rechallenge should be avoided.

Conclusion

DI-ILD is a wide and highly heterogeneous group of conditions, and the list of culprit drugs is constantly increasing. The clinical, radiological and histopathological features of DI-ILD, though suggestive, are not specific; therefore, the diagnosis requires a high index of suspicion and the exclusion of alternative causes of ILD. Knowledge of the most common causative drugs and a diagnostic framework are also crucial. However, the diagnosis can be particularly challenging when multiple potentially pneumotoxic drugs are used for the treatment of diseases that frequent cause pulmonary complications, such as connective tissue diseases. Identification and discontinuation of the culprit drug (with or without glucocorticoids) is the cornerstone of treatment (Figure 7), although for some agents, such

as checkpoint inhibitors, the potential benefit of the drug and the frequency of lung toxicity are such that the occurrence of DI-ILD is not necessarily synonymous with drug discontinuation, particularly in the absence of valid therapeutic alternatives.

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Captions to figures

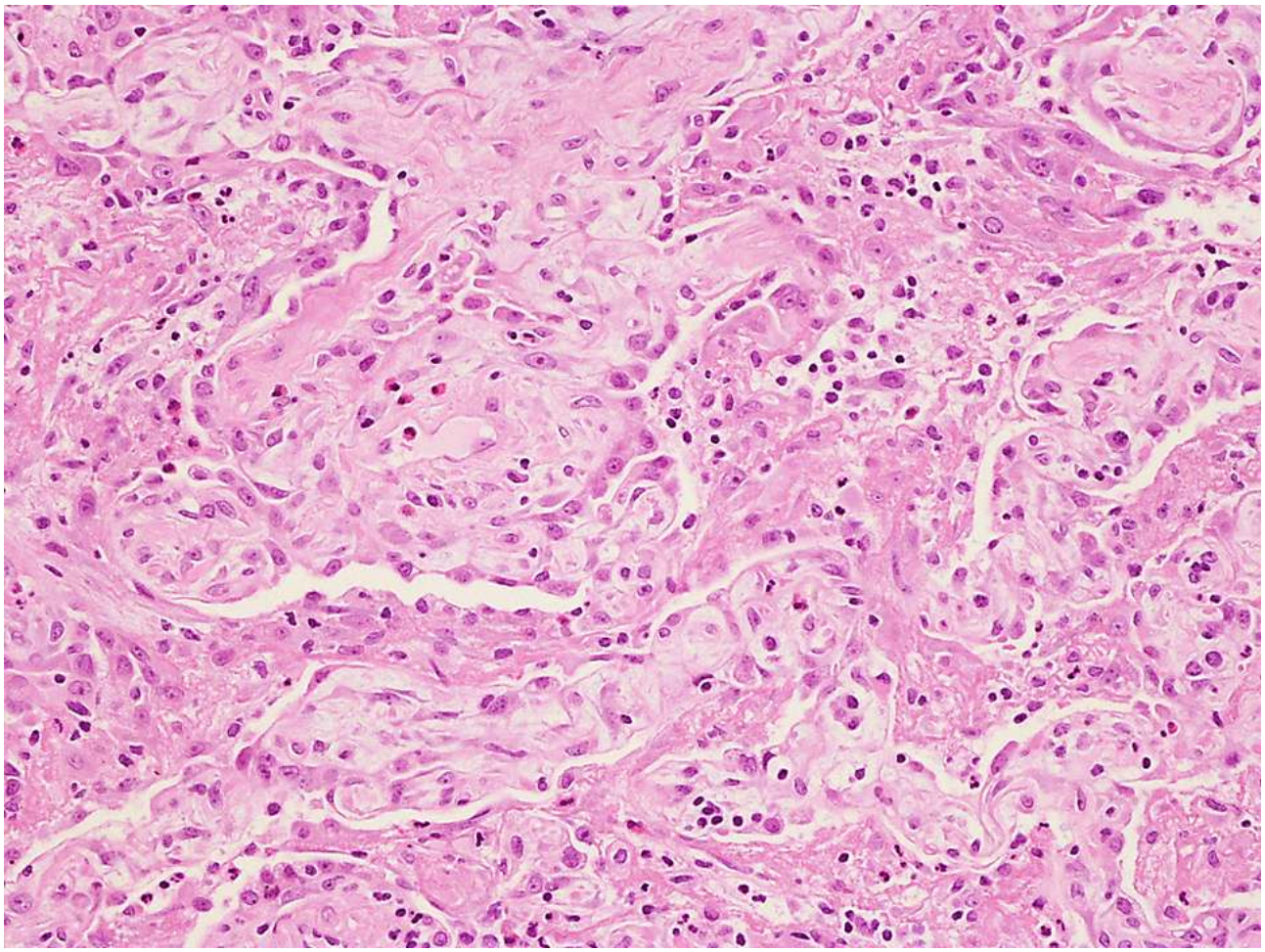


Figure 1A. Diffuse alveolar damage. Thickened and oedematous interstitial space, hyperplastic pneumocytes and intraalveolar fibrin deposition with scattered inflammatory cells in a patient with non-small cell lung cancer treated with pembrolizumab.

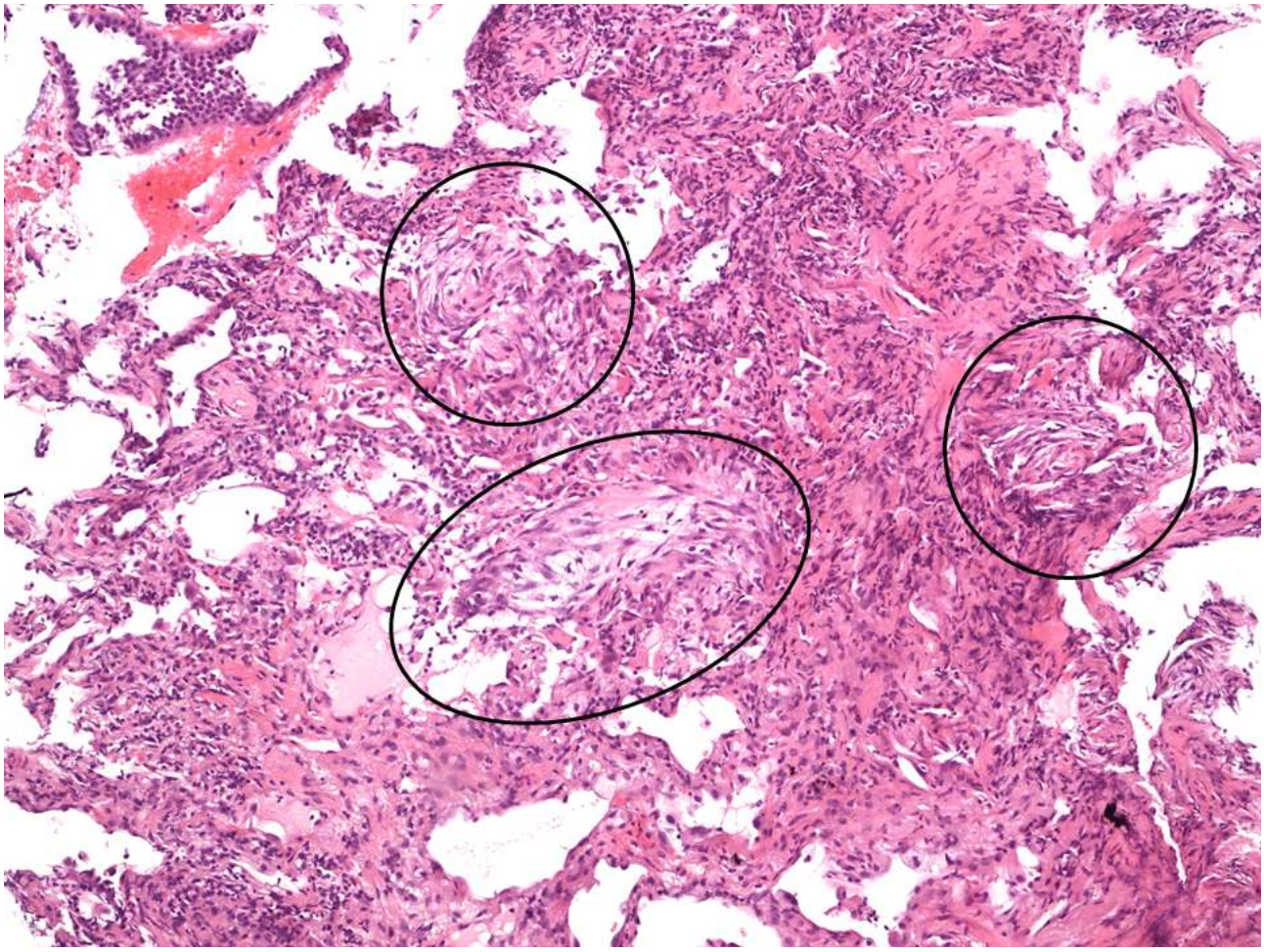


Figure 1B. Transbronchial lung biopsy showing organizing pneumonia with intraalveolar plugs consisting of active fibrosis (black circles) on a background of nonspecific interstitial pneumonia in a patient with rheumatoid arthritis treated with tocilizumab.

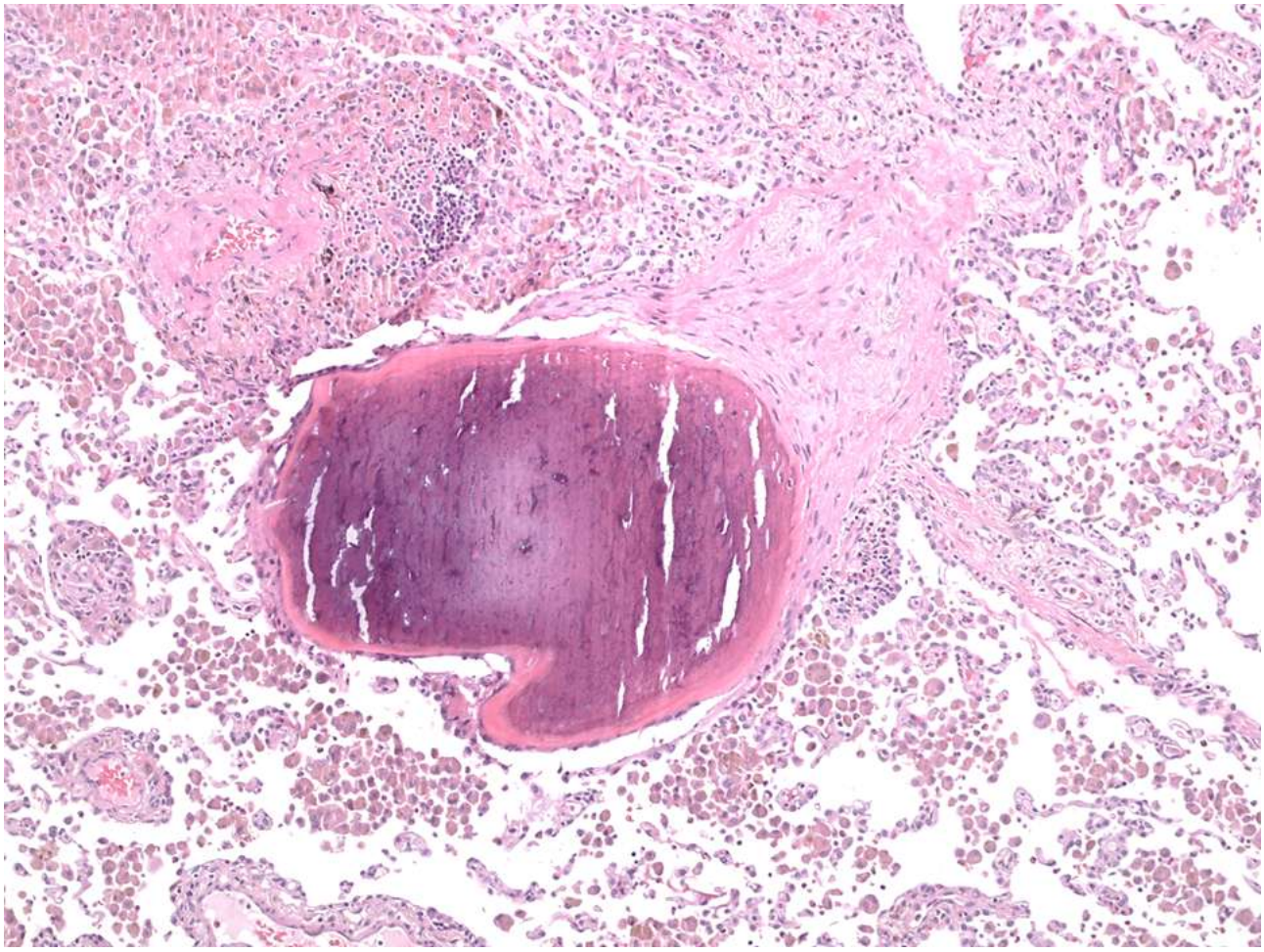


Figure 1C. Cicatricial organizing pneumonia characterized by polypoid lesions of dense collagenous fibrosis within the alveolar spaces with preserved lung architecture in a patient on chemotherapy (FOLFOX [folinic acid, fluorouracil, oxaliplatin] regimen) for colorectal cancer (left panel). Over time, interalveolar fibrosis with metaplastic ossification developed (right panel).

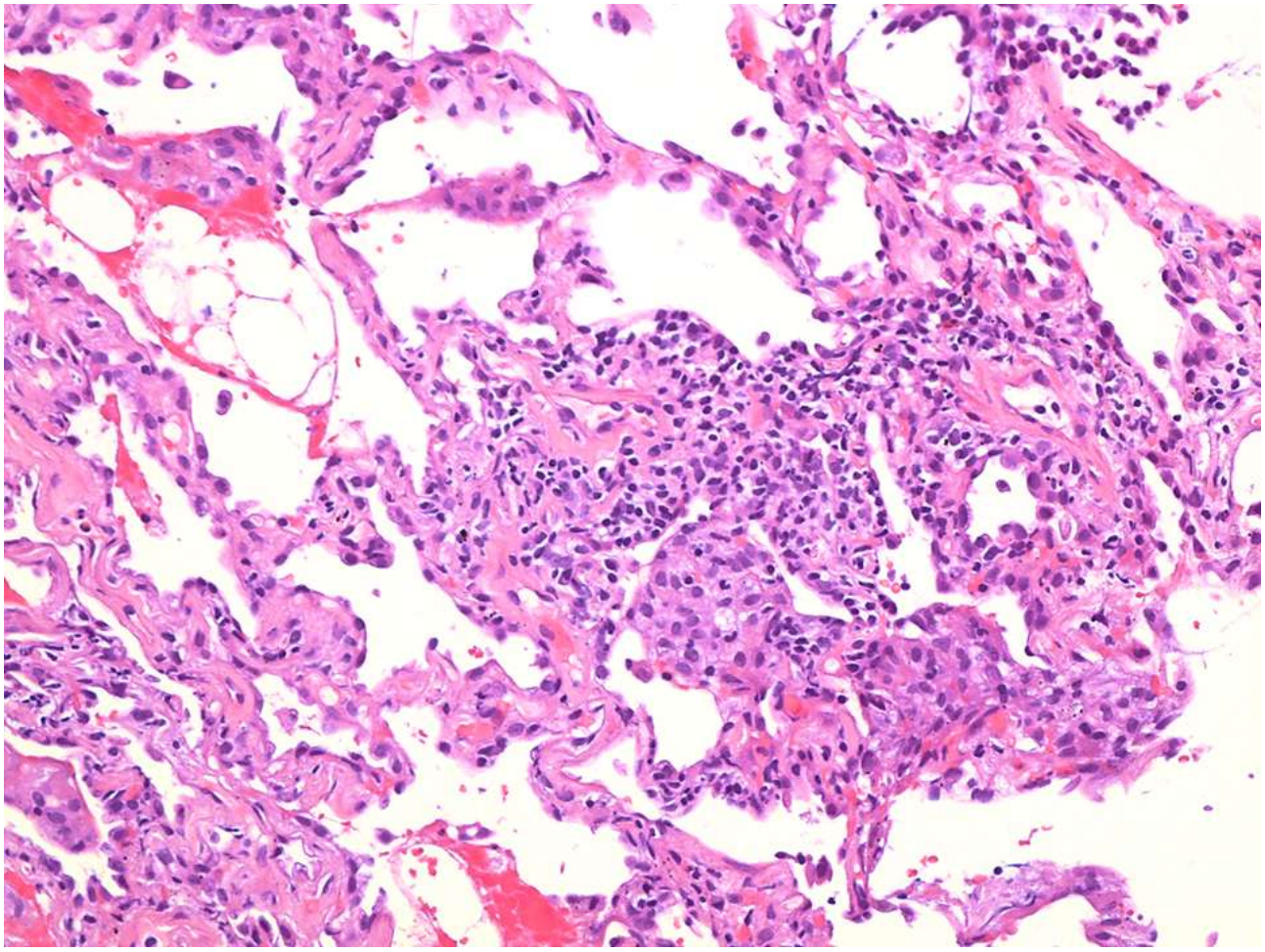


Figure 1D. Mixed fibrotic and cellular nonspecific interstitial pneumonia pattern with homogeneous interstitial fibrosis and lymphocytic infiltrate in a patient with advanced lung adenocarcinoma treated with nivolumab (transbronchial lung biopsy).

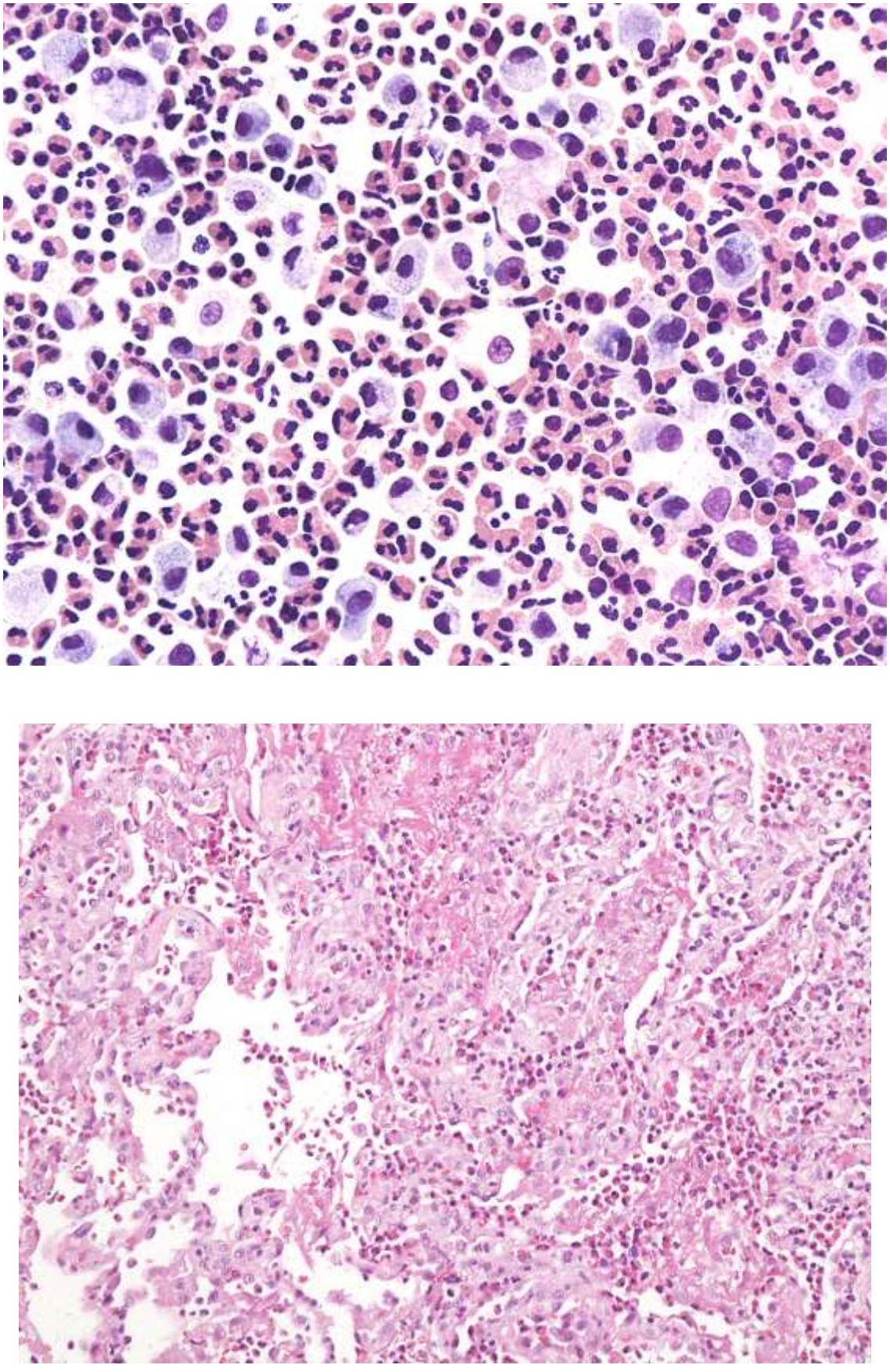


Figure 2 A and B. Eosinophilic pneumonia: marked eosinophilic infiltrate among macrophages (A, bronchoalveolar lavage), and alveolar fibrin exudate with organizing pneumonia (B, transbronchial biopsy) in a patient treated with daptomycin.

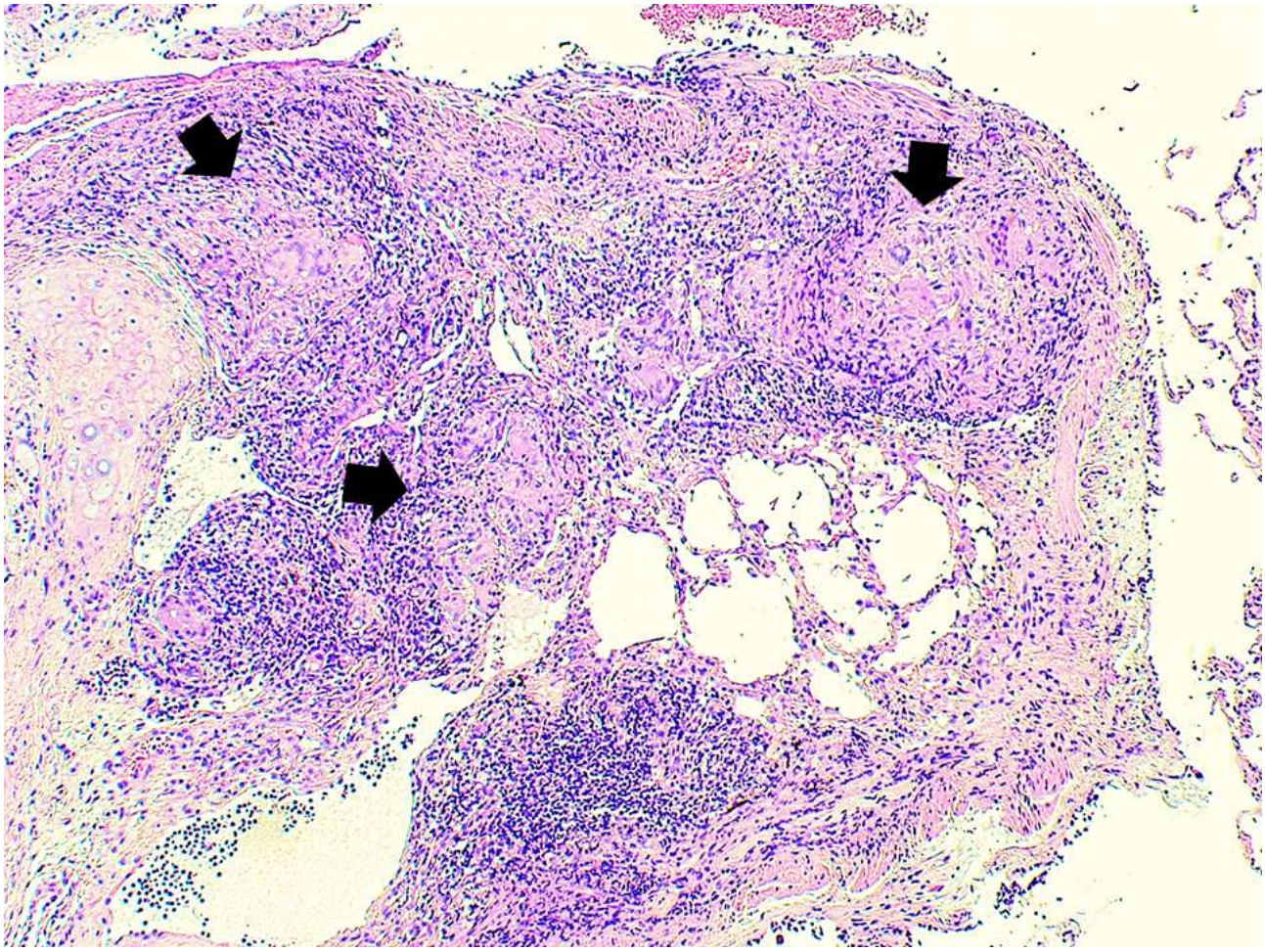


Figure 3. Transbronchial lung biopsy showing a sarcoid-like reaction with marked lymphocytic infiltration and scattered non-necrotizing granulomas (black arrows) mimicking sarcoidosis in a patient treated with ipilimumab for metastatic melanoma.

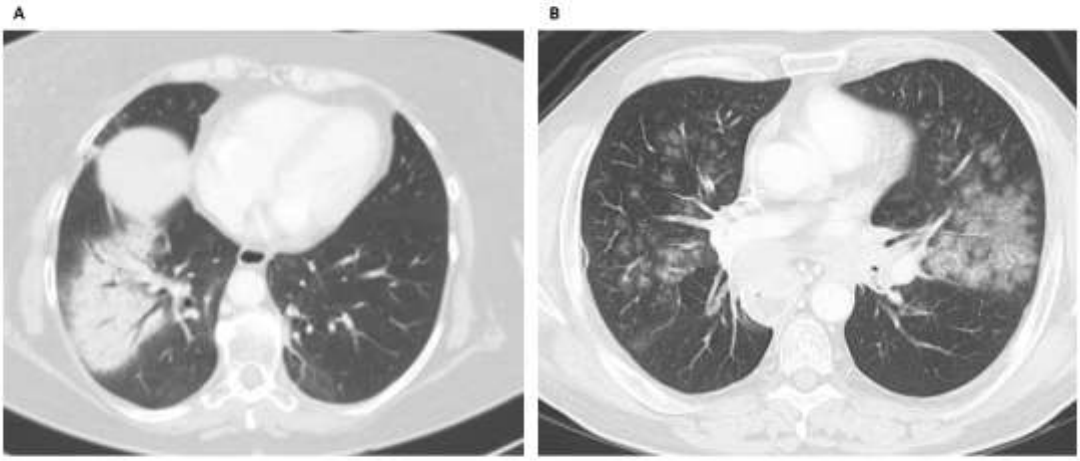


Figure 4. Trastuzumab-induced interstitial lung disease in a patient with breast cancer. CT scan shows airspace consolidation in the right lower lobe (A). FOLFIRI (folinic acid, fluorouracil, irinotecan)-induced acute alveolar haemorrhage in a 52-year-old man with oesophageal cancer. Bilateral ground-glass opacities on high-resolution CT are due to subtotal alveolar filling with blood (B). Alveolar haemorrhage resolved rapidly following glucocorticoid treatment, but the patient died due to metastatic disease.

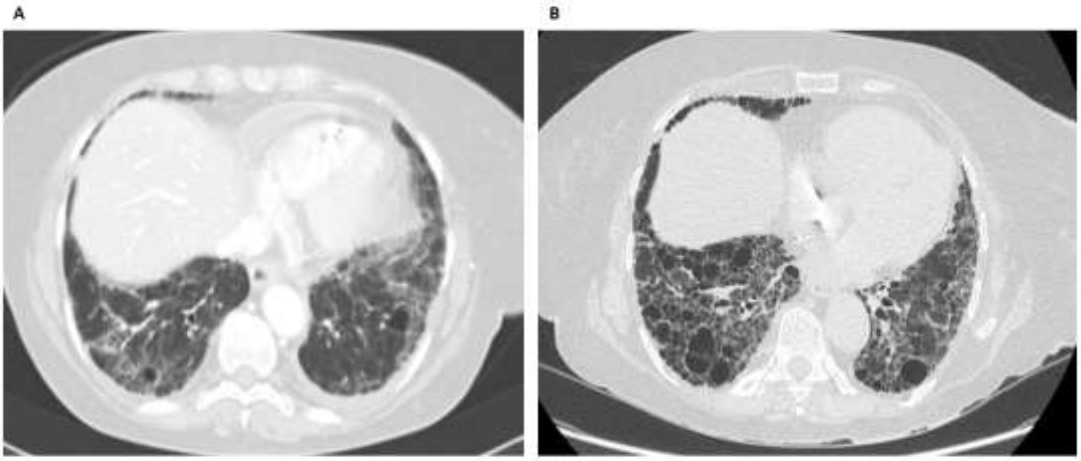


Figure 5. Bleomycin-induced interstitial lung disease. This 70-year-old woman with Hodgkin lymphoma was found to have new bilateral subpleural interstitial infiltrates following completion of a chemotherapy regimen containing bleomycin (A). Over time (8 years), interstitial infiltrates progressed to end-stage disease despite glucocorticoid therapy (B).

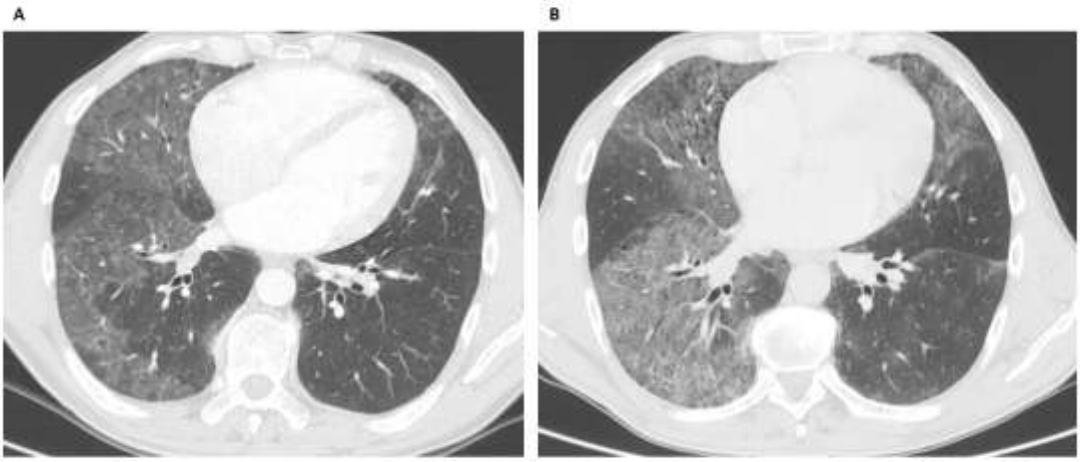


Figure 6A. Amiodarone-induced interstitial lung disease. 48-year-old man with atrial fibrillation. Lung window images from axial CT show extensive ground glass opacities identified after two years of treatment with amiodarone (A). After one year, despite drug discontinuation and initiation of glucocorticoids, ground glass opacities became more extensive (B).

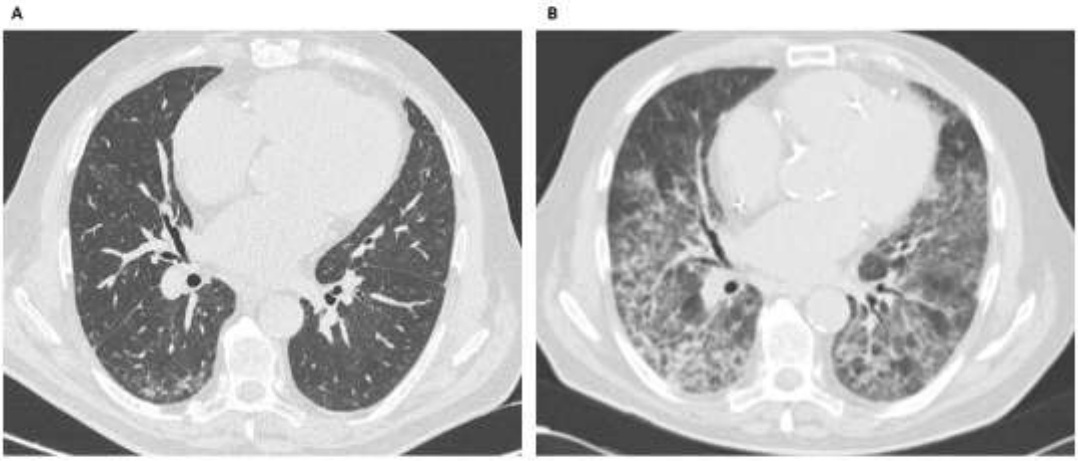
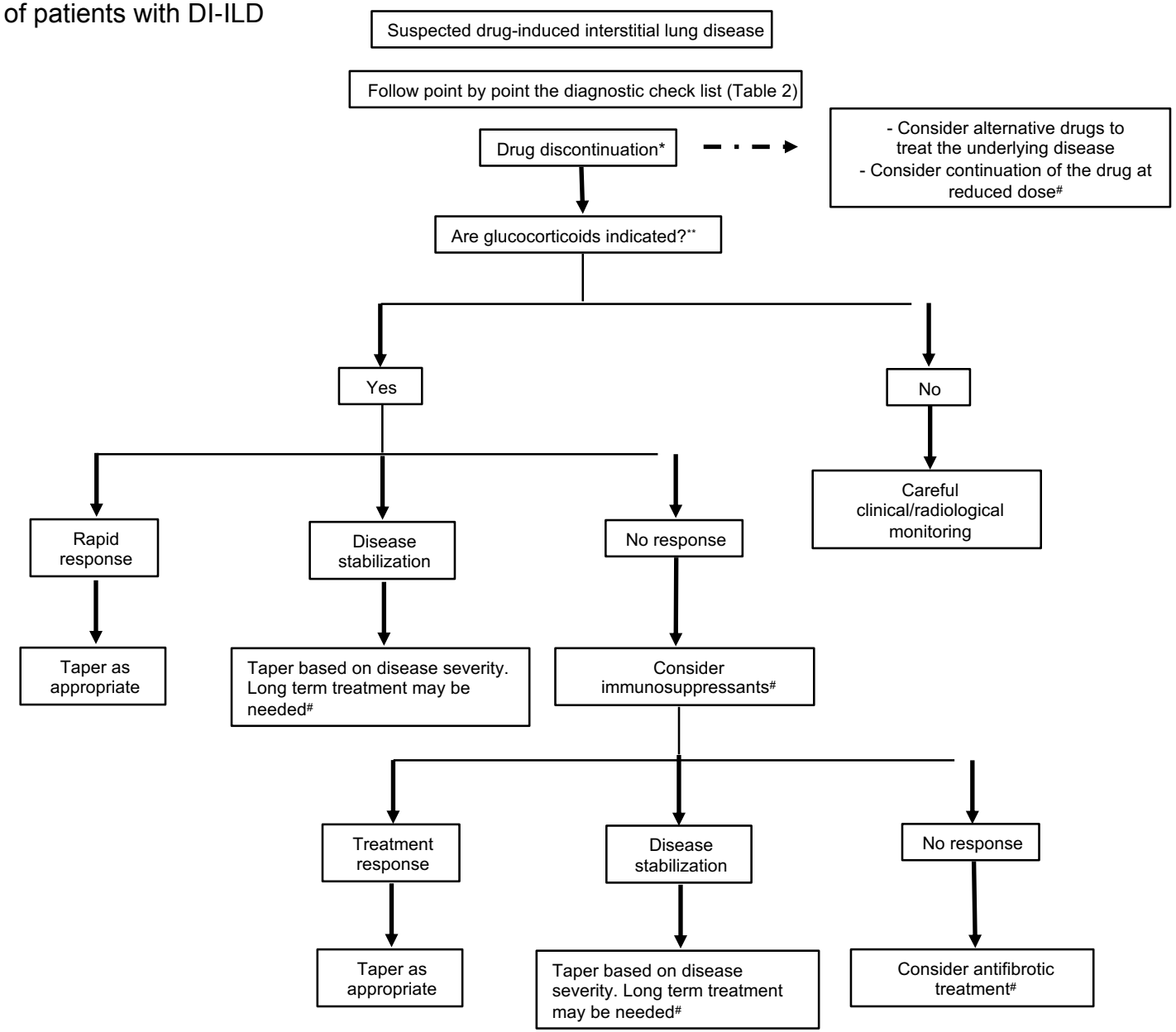


Figure 6B. Amiodarone-induced interstitial lung disease. 77-year-old man with atrial fibrillation. High-resolution CT before (A) and one month after initiation of amiodarone (B). Axial CT shows extensive ground glass opacities and increased interstitial markings.

Figure 7. Management of patients with DI-ILD



*Careful continuation of antineoplastic drugs/immunotherapy may be considered (Grade 1 and grade 2 toxicities), particularly in the absence of valid alternative treatment options; ** Depending on disease severity; # Multidisciplinary discussion in a reference center highly recommended