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INTERSTITIAL LUNG DISEASE (A HAJARI CASE, SECTION EDITOR)

The Spectrum of Drug-Induced Interstitial Lung Disease

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Abstract

Purpose of Review Drug-induced interstitial lung disease (DI-ILD) is a very challenging topic both clinically and academically. With the advent of new immunotherapy and ever-growing arsenal of chemotherapeutic and biologic agents for a variety of conditions, it is paramount for the clinician to assess for the development of pulmonary toxicity before irreversible lung damage occurs. In this review, we have summarized the literature and describe the most commonly implicated agents and also describe new and rare causes of DI-ILD.

Recent Findings Bleomycin and amiodarone remain the most frequent culprits of DI-ILD. Proteasome inhibitors have been observed to cause pulmonary toxicity in some patients. GM-CSF has also emerged as a cause of DI-ILD in recent years. Nitrofurantoin is commonly associated with DI-ILD in the class of antimicrobial agents, with both acute and chronic toxicity described. Anti-TNF drugs, in particular, etanercept and infliximab, are the overwhelming offenders among the biologic agents. In addition, methotrexate has been widely associated with lung injury, especially in those with underlying rheumatoid arthritis.

Summary Over 300 drugs are known to be associated with DI-ILD, and risk factors for the development of DI-ILD are not well understood. Radiographic patterns and histological patterns do not correlate well, and the data on treatment response to glucocorticoid therapy remains variable. Early identification, removal of the offending agent, and elimination of other causes of lung injury remain paramount in the approach to DI-ILD.

Keywords Interstitial lung disease · Drug-induced ILD · DI-ILD · Immunotherapy · Chemotherapy

Introduction

Drug-induced interstitial lung disease (DI-ILD) is a very challenging topic both clinically and academically. Broadly, certain drug classes tend to cause similar, overlapping patterns of pulmonary involvement [1]. Most histological changes for most drug reactions are nonspecific, but a limited number of drugs (e.g., amiodarone) produce a characteristic histopathological pattern of involvement enabling almost instant recognition of the drug etiology [1]. Most of the other 350 drugs that have been known to have pulmonary toxicity have varying clinical phenotypes, as well as varying histopathological patterns, even with the same offending drug.

In the evaluation of DI-ILD, it is important to have a consistent clinical, radiologic, and pathologic approach that is comprehensive, yet efficient. In 2002, the American Thoracic Society/European Respiratory Society (ATS/ERS) attempted to standardize the classification of the idiopathic interstitial pneumonias (IIPs), which are a subset of interstitial lung disease (ILD) sometimes difficult to distinguish from DI-ILD. Briefly, IIPs are a heterogeneous group of non-neoplastic disorders resulting from damage to the lung parenchyma with varying patterns of inflammation and fibrosis. By default, if an identifiable cause of ILD can be isolated such as an offending drug, the disease is not idiopathic and the approach can be tailored. However, this distinction is often very difficult and relies heavily on thorough clinical history and high index of suspicion.

We hope to shed light on this often under-recognized form of ILD. We will discuss the most common culprits identified and elaborate on what is well known about

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the presentation of each in the literature. We also hope to provide a diagnostic framework with which to approach possible DI-ILD. The fundamental components in the diagnosis of DI-ILD include comprehensive medical history including current and past medications, environmental exposures, signs of connective tissue disease, serologic evaluation, high-resolution computed tomography (CT) chest, and histopathology of transbronchial or surgical lung biopsies, where appropriate. Figure 1 depicts a proposed diagnostic algorithm. Indeed, a multimodal approach is essential in the diagnosis of DI-ILD, with a heavy emphasis on high-resolution CT (HRCT) scan imaging.

Clinical Presentation and Diagnosis

Clinical Signs and Symptoms

Symptoms of DI-ILD tend to be nonspecific including cough, fever, dyspnea, hemoptysis, wheezing, and pleuritic chest pain [2•]. Clinical presentation is often confounded by the suspicion or presence of respiratory infection and is often initially treated with antibiotics for that reason. DI-ILD is often considered more serious when there is no significant improvement with empiric treatment of infection.

The timing of symptom onset is largely dependent on the underlying offending drug. Some agents lead to symptoms

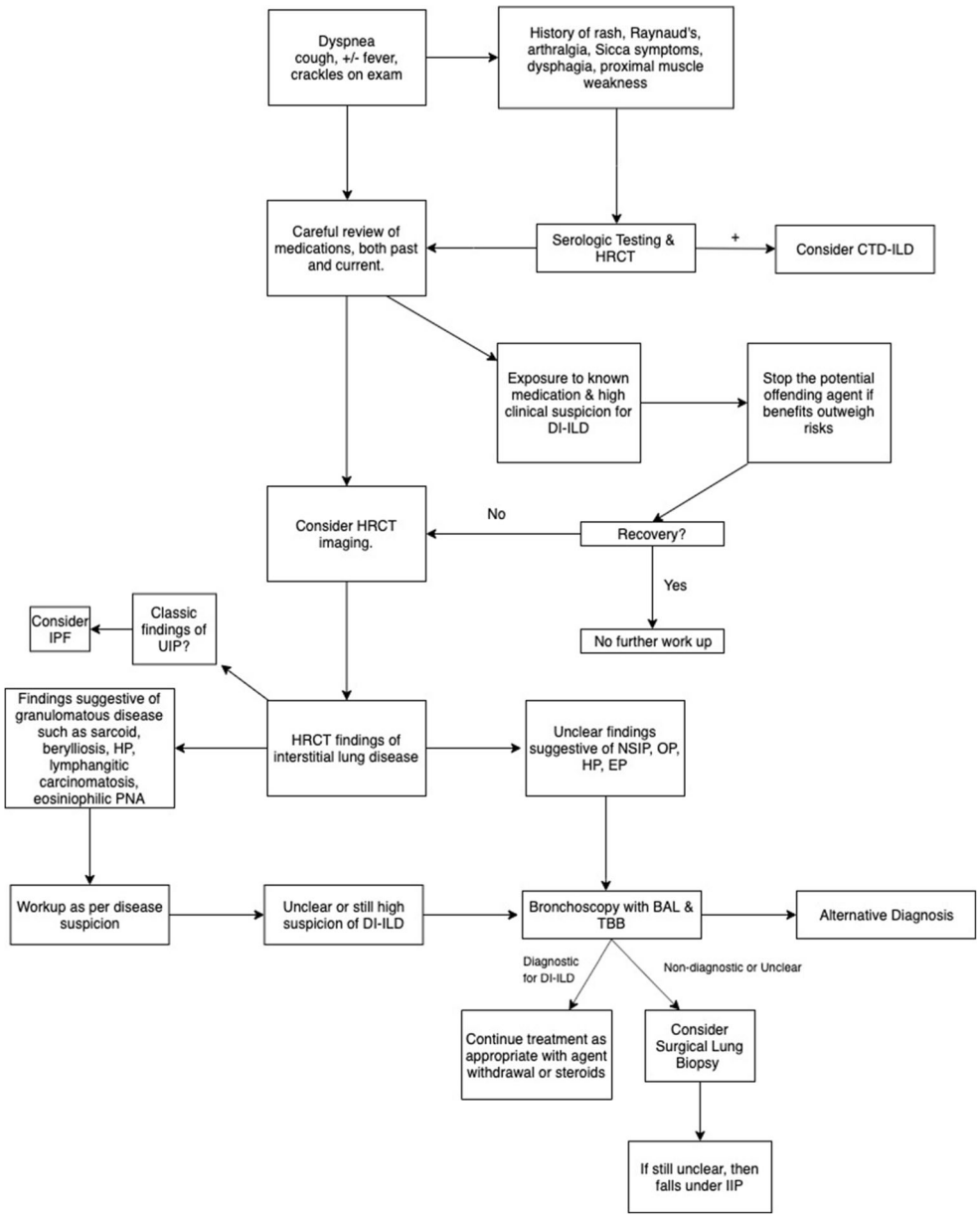

Fig. 1 Diagnostic algorithm

within days, while others such as cytotoxic chemotherapeutic agents can take weeks to months, even years depending on dose accumulation [1]. Physical examination findings are also nonspecific and can vary depending on the underlying histopathology. Common findings include dry "Velcro" crackles on respiratory examination, sometimes with digital clubbing. Signs of right ventricular dysfunction may also be appreciated including jugular venous distension and lower extremity edema [1]. Stigmata of autoimmune disorders should be evaluated for on physical exam as connective tissue disease (ILD) is in the differential diagnosis.

Diagnostic Testing

Serologic tests are largely used to rule out other causes of interstitial lung disease, as DI-ILD is often a diagnosis of exclusion. Autoimmune disorders and subclinical connective tissue diseases must be evaluated for with common nuclear antibodies: antinuclear antibodies (ANAs), rheumatoid factor (RF), cyclic citrullinated peptide (CCP) antibodies, anti-synthetase antibodies, and myositis-related antibodies (creatine kinase and aldolase). This is usually not necessary or helpful in those with an already established underlying connective tissue disease, such as someone with RA receiving methotrexate (MTX). Peripheral eosinophilia can be seen in those with eosinophilic pneumonia and hypersensitivity pneumonitis [1, 2•, 3]. However, it is also nonspecific and can be seen in less than 40% of patients [3].

Pulmonary function testing (PFT) can guide clinicians to the diagnosis of interstitial lung disease; however, it is nonspecific for DI-ILD. A restrictive pattern with an impaired gas exchange is usually present. Reductions in diffusion capacity and forced vital capacity (FVC) for diagnostic accuracy have been studied in amiodarone and nitrofurantoin–associated ILD [4, 5]. Both studies showed poor sensitivity and specificity.

Bronchoscopy is often an important component of the diagnostic evaluation for DI-ILD, with microbiologic evaluation as a critical component, particularly in immunocompromised hosts. Bronchoalveolar lavage (BAL) with cytology may be useful to suggest certain histopathological manifestations of DI-ILD such as eosinophilic pneumonia (EP) but is generally not diagnostic. Lymphocytic alveolitis is commonly associated with DI-ILD and characteristically is comprised by neutrophils or eosinophils with a predominance of T lymphocytes [6].

Radiographic Manifestations

The radiographic manifestations of DI-ILD are variable and nonspecific. Patients in early forms of drug-induced injury may have normal imaging. The advent of HRCT has allowed for a more precise evaluation of parenchymal changes, showing superiority over chest radiograph [7–9]. Some radiographic patterns closely correlate with underlying histopathologic patterns, while others do not. A small retrospective chart review [10•] evaluated the correlation between HRCT and histopathologic patterns in biopsy-confirmed DI-ILD. The most commonly reported abnormalities noted on HRCT in their cohort were ground glass opacities (GGOs), consolidation, septal thickening, and centrilobular nodules. They found concordance of HRCT and histological diagnosis including nonspecific interstitial pneumonia (NSIP), diffuse alveolar damage (DAD), organizing pneumonia (OP), hypersensitivity pneumonitis (HP), and EP in 45% of patients [7]. Further, they found limited prognostic value in the pattern, distribution, and extent of fibrosis on HRCT.

Chemotherapeutic-induced ILD has better radiographic and histological pattern correlation, particularly in the case of bleomycin [8]. An example of severe bleomycin toxicity is shown in Fig. 2 following treatment with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) for Hodgkin's lymphoma.

DAD, one of the most common histological manifestations in DI-ILD, mimics that of adult respiratory distress syndrome (ARDS) on HRCT. As the underlying mechanisms are attributed to alveolar damage, imaging illustrates bilateral airspace consolidation with ground glass opacities in the dependent lung regions [11]. During the organizing phase, architectural distortion, septal thickening, and traction bronchiectasis can occur. Diffuse alveolar hemorrhage (DAH) also may present with nonspecific extensive bilateral ground glass opacities. Drug-induced HP presents with a radiographic pattern that is indistinguishable from that induced by inhaled organic antigens [9]. HRCT findings consist of diffuse bilateral ground glass opacities with or without poorly defined centrilobular nodules. Imaging should ideally include expiratory images, obtained at end of expiration, to assess for lobular areas of air trapping which is typical of HP.

Drug-induced NSIP is also difficult to distinguish from idiopathic NSIP on imaging. Radiological abnormalities consist of patchy bilateral diffuse ground glass opacities with reticular opacities, and traction bronchiectasis favoring the lower lung zones. An example of amiodarone-induced lung disease in an NSIP-like pattern following long-term amiodarone exposure is shown in Fig. 3. OP tends to favor a more disorganized pattern with an asymmetric bilateral distribution of airspace consolidation. Amiodarone-induced OP has been reported in the literature [12, 13]. Radiographic manifestations of drug-induced EP can take many forms, especially with those similar to OP [14]. A UIP pattern is uncommon with drug-induced injury and can be suggestive of an alternative diagnosis.

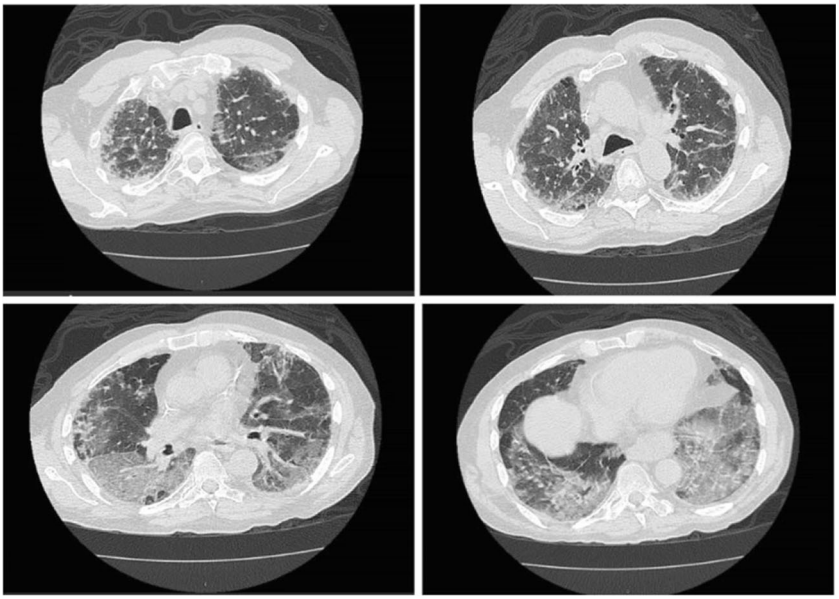

Fig. 2 Bleomycin-induced interstitial lung disease. HRCT shows diffuse bilateral ground glass opacities and reticulation, but no clear honeycombing

Histopathology

Drug toxicity is inconsistent in its histopathologic manifestations and can manifest as any form of acute or chronic non-neoplastic lung disease. Although any given drug may be associated with multiple different histologic patterns of lung injury, there are certain well-documented associations. The reader is referred to the website www.pneumotox.com for a comprehensive and regularly updated resource for pulmonary drug toxicities. The histologic manifestations include acute lung injury (DAD and OP), chronic interstitial lung disease (cellular and fibrosing (nonspecific) interstitial pneumonia patterns), eosinophilic pneumonia, granulomatous pneumonitis, and other specific morphologic patterns. Table 1 lists drugs associated with these common histologic patterns. The list is not comprehensive but reflects both traditional wisdom and strength of association based on published literature. Select examples are shown Fig. 4.

The histopathological pattern of the most severe pattern of DI-ILD, DAD, is defined by the phase of disease which ranges from the acute (exudative) and organizing (proliferative) phase to the final fibrotic phase. The acute phase exhibits the presence of eosinophilic hyaline membranes with intra-alveolar capillary congestion. The later fibrotic phase is

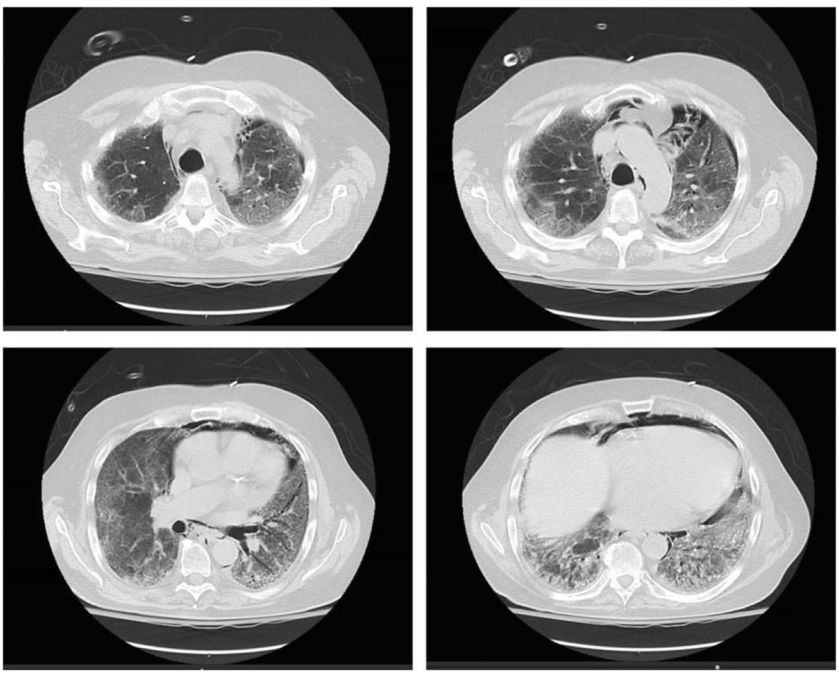

Fig. 3 Amiodarone-induced lung disease in a patient on long-term treatment. CT images demonstrate an NSIP-like pattern with ground glass opacities, traction bronchiectasis, and no clear honeycombing. Bilateral pneumothoraces are present as well

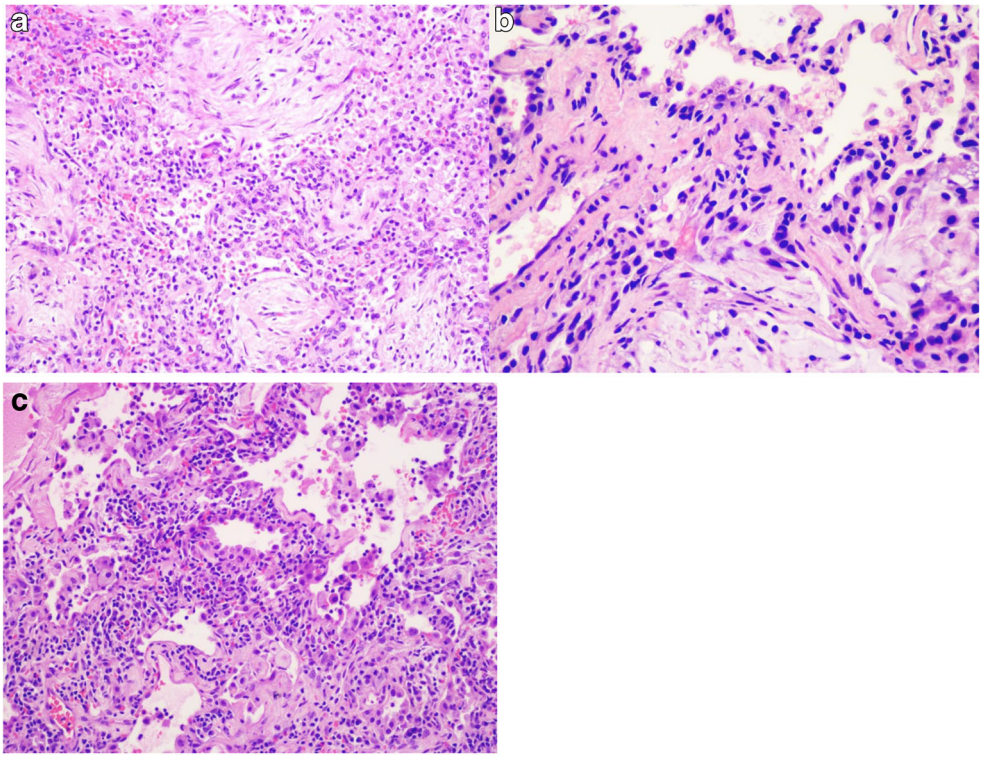

Fig. 4 **a** Organizing pneumonia (H&E, × 200). There are prominent intra-alveolar fibromyxoid plugs as well as marked chronic inflammation. The patient received immune checkpoint inhibitor therapy for renal cell cancer and presented with this lung mass-like consolidation. **b** Amiodarone toxicity (H&E, × 400). Characteristic finely vacuolated pneumocytes and histiocytes. The background lung (lower half) shows alveolar and interstitial edema. **c** Cellular NSIP (H&E, × 200). The interstitium is uniformly widened by a dense chronic inflammatory infiltrate. This is an example of methotrexate toxicity

characterized as interstitial expansion with loose, myxoid fibroblastic tissue with dense collagen fibers. Bleomycin incites this histopathologic finding by causing direct pneumocyte apoptosis with resulting cellular atypia. Continued use of the drug, particularly at high doses, can result in irreversible fibrosis. OP is histologically characterized by patchy interstitial inflammation along with occlusion of terminal bronchioles and alveoli by fibromyxoid plugs known as Masson bodies.

NSIP may be the most common manifestation of DI-ILD. Histologically, there is relatively uniform and homogeneous interstitial involvement by inflammation and/or fibrosis. Eosinophilic pneumonia is described histologically by prominent tissue, alveolar, and interstitial eosinophilia with preserved architecture. It can also present with a chronic interstitial and fibrosing pneumonitis, or a leukocytoclastic vasculitis as seen in Montelukast-associated Churg-Strauss syndrome [15]. Granulomatous DI-ILD can mimic other forms of granulomatous lung disease such as sarcoidosis, tuberculosis, nontuberculous mycobacterial disease, and hypersensitivity pneumonitis from inhalation exposures found in the environment.

Risk Factors

Risk factors for the development of DI-ILD remain elusive, and its occurrence is unpredictable. Extrinsic factors such as genetics and environment play a role in affecting the genetic disposition of a certain drug. Certain risk factors exist for the development of DI-ILD, but largely, the studies are limited to a few specific drugs. For example, bleomycin pulmonary toxicity has been known since early clinical trials in the 1960s. Of the studied risk factors, cumulative dose and reduced renal function are the most well-established risk factors [16] (refer to Table 2).

Common Causative Drugs by Class

This section shows an outline of the most common classes of drugs that may lead to DI-ILD. It is not an exhaustive list, and certainly, any drug should be considered a potential culprit of DI-ILD in the right clinical scenario when all other etiologies have been ruled out.

Chemotherapeutic Agents

Adverse drug reactions (ADRs) to antineoplastic chemotherapy drugs are common, with 10–20% of patients developing pulmonary toxicity [17]. These antineoplastic agents targeting cancer often suppress the immune system, and it, therefore, becomes particularly difficult clinically to distinguish DI-ILD from infectious complications [17, 19]. Once an infection has been excluded or treated without expected improvement, other causes of pulmonary symptoms should be considered. Early-onset chemotherapy-induced lung injury patterns include not only inflammatory interstitial pneumonitis (DI-ILD) but also pulmonary edema, bronchospasm, as well as pleural disease (effusions and pleurisy). The time course is

Table 1 Drugs associated with common histologic patterns

Histologic injury pattern	Common/strong associations
Diffuse alveolar damage	Amiodarone (organizing DAD) Chemotherapeutics (busulfan, bleomycin, cyclophosphamide, 5-FU) Gefitinib Radiation therapy Illicit drugs of abuse Gemcitabine Transfusion-associated lung injury (TRALI) Oxygen toxicity
Organizing pneumonia	Amiodarone Hydralazine Chemotherapeutic agents Methotrexate Immune checkpoint inhibitors Radiation therapy Propylthiouracil
Cellular interstitial pneumonia/NSIP	Amiodarone Methotrexate Nitrofurantoin Organic dusts Anti-TNF alpha agents
Eosinophilic pneumonia	Antibiotics (beta-lactams, sulfa drugs) Azathioprine Cisplatin Minocycline NSAIDs Leukotriene inhibitors Cigarette smoke
ILD with granulomas	Illicit drugs of abuse BCG therapy (intravesical) Interferon Methotrexate Sirolimus Nitrofurantoin Anti-TNF agents
Pulmonary fibrosis	Alkylating agents Amiodarone Chemotherapeutic agents Nitrofurantoin Organic dust Radiation therapy Stem cell/bone marrow transplantation
Lung nodules (may represent OP, granulomas, vasculitis, necrosis, or lipoid pneumonia)	Amiodarone Paraffin/mineral oils Radiation therapy
Pleuroparenchymal fibroelastosis	Alkylating agents Statins Radiation therapy
Pulmonary edema	Aspirin-containing drugs Beta-blockers Beta-2 agonists Ara-C Drug overdose Epoprostenol Inhaled gases Gastric banding Transfusion products Heroin abuse Hydrochlorothiazide Tocolytic therapy
Diffuse alveolar hemorrhage	Abciximab Anticoagulants Amphotericin Erlotinib Bone marrow/stem cell transplantation
Obliterative bronchiolitis	Bone marrow/stem cell transplantation Herbal products
Intravascular emboli	Hydrophilic polymer embolization (used as a coating for catheter-based interventions) Therapeutic polyamide microspheres (used for uterine and liver tumors) Silicone (used in plastic surgery implants) Illicit drugs of abuse
Pleuropericarditis	Hydralazine Isoniazid Methyldopa

DAD diffuse alveolar hemorrhage, *5-FU* fluorouracil, *TNF* tumor necrosis factor, *NSAIDS* nonsteroidal anti-inflammatory drugs, *BCG* Bacillus Calmette-Guerin, *Ara-C* cytarabine

important as there should be a high index of suspicion for DI-ILD in any patient on a new chemotherapeutic regimen with a new onset of respiratory symptoms [20]. The majority of chemotherapy-induced pulmonary diseases present after at least 2 months of completion of therapy, with radiographic pulmonary fibrosis being the most common pattern of DI-ILD.

Bleomycin, one of the most heavily studied drugs, is attractive as a component of combination chemotherapy regimens because of its broad activity and low myelotoxicity [16]. It is most commonly used in Hodgkin's lymphoma and germ cell tumors, with reported pulmonary toxicity rates between 6.8 and 27% [16, 21]. Toxicity is mostly due to free radical promoting ability, which also leads to a suggested increased risk of bleomycin-induced pulmonary injury with the administration of supplemental oxygen [22]. Johnson et al. [23] tested interim PET-CT as a measure of early response to chemotherapy in patients with Hodgkin's lymphoma and found that the omission of bleomycin from the ABVD regimen (doxorubicin, bleomycin, vinblastine, and dacarbazine) resulted in a lower incidence of pulmonary toxic effects than with conventional ABVD but did not significantly lower the efficacy [23], suggesting that a careful risk-benefit ratio

Table 2 Risk factors for drug-induced interstitial lung disease

Risk factor	Points to consider
Age	• Risk of bleomycin-induced lung injury is increased up to 2.3-fold in patients > 40. • Age and cumulative dose are risk factors for amiodarone toxicity. • Age > 60 has been proven to be a risk factor for MTX-associated toxicity
Preexisting lung conditions	Gefitinib-induced pneumonitis is fatal in one third of cases, and one of the risk factors includes the presence of previous lung damage from smoking, chemotherapy, irradiation, infection, or pulmonary fibrosis
Dose of drug	Dosage (high or cumulative dosing) may increase the risk of DI-ILD, particularly with amiodarone, bleomycin, and BCNU
Gender	Male sex has been a reported risk factor for DI-ILD in some studies following treatment with amiodarone, methotrexate, and EGFR inhibitors
Genetics/pharmacogenomics	The presence of certain variant cytochrome P-450 (CYP) alleles was strongly associated with the development of DI-ILD in a Dutch study, suggesting the potential utility of pharmacogenomic testing to guide therapy and improve efficacy, tolerability, and drug safety

References: [17, 18, 52, 53]

MTX methotrexate, *DI-ILD* drug-induced interstitial lung disease, *BCNU* carmustine, *EGFR* epidermal growth factor receptor

can and should be considered prior to its inclusion in chemotherapeutic treatment regimens.

Proteasome inhibitors, bortezomib, farfilzomib, and ixazomib, used mainly in the treatment of hematologic malignancies, have been observed to cause pulmonary toxicity and ILD in some patients. In a recent Japanese study evaluating 1010 patients with multiple myeloma, 26 (2.6%) patients were diagnosed with bortezomib-induced ILD. Of those 26 patients, the majority of cases (18/26) were categorized as NSIP, with overlapping DAD and granulomatous subtypes [24]. A recent correspondence by Murashige et al. reviewed data on adverse events from the Pharmaceuticals and Medical Devices Agency and found 839 cases of ILD among patients receiving gefitinib from April 2004 through December 2009, with 31.6% all-cause mortality rate [25]. Another recent clinical trial of first-line gefitinib for elderly patients (75 years of age or older) who had EGFR-mutated non-small cell lung cancer (NSCLC) cited 1/31 (3.2%) treatment-related deaths due to ILD [26].

Granulocyte-macrophage colony-stimulating factor (GM-CSF) has become increasingly recognized as a potential culprit for pulmonary toxicity. Adachi et al. [27] reported that the mechanism of ILD due to GM-CSF was the enhancement of the infiltration of the alveoli by alkaline phosphatase-positive neutrophils. Yokose et al. [28] reported that pulmonary toxicity had occurred in 6 out of 52 patients with non-Hodgkin's lymphoma who received G-CSF with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) therapy. The study demonstrated that the mean peak leukocyte count with each therapy cycle was associated with the development of pulmonary toxicity and concluded that lowering the G-CSF dose appeared to be useful in the prevention of this toxicity. We describe a case of acute hypoxemic respiratory failure just days after initiation of filgrastim therapy. Figure 5 shows a non-contrast CT of the chest demonstrating diffuse bilateral ground glass opacities in this case. A graphical representation of the fraction of inspired oxygen and leukemoid response over time demonstrates the temporal relationship between response to drug administration and development of respiratory failure. Fortunately, there was significant improvement of hypoxemia after cessation of the drug and initiation of steroids [29].

Antibiotics

Nitrofurantoin is the most common antimicrobial agent associated with DI-ILD, with both acute and chronic toxicity described. Acute toxicity is more common, occurring within 2 weeks of administration with most patients recovering after discontinuation of the drug [14]. Chronic nitrofurantoin-induced lung disease is usually seen in older women who present with respiratory symptoms after greater than 1 year of therapy, usually for recurrent UTIs [30].

There have been few cases reports on DI-ILD related to trimethoprim and sulfamethoxazole (TMP/SMX). Yuzurio et al. [11] looked at ten patients with underlying lung disease who had received additional glucocorticoids for treatment of worsening disease within 14 days after introduction of TMP/SMX. Radiographically and clinically, the pulmonary infiltrates were felt not likely to be due to infection or exacerbation of underlying disease, and after detection of the infiltrates, TMP/SMX was discontinued in 3 out of 10 cases and continued in the rest. Interestingly, in 9 of 10 cases, the pulmonary infiltrates resolved between 26 days and 90 days after the

introduction of TMP/SMX, suggesting its effects were transient in nature in most cases [11].

High-dose daptomycin for treatment of infective endocarditis has been associated with a 2.9% incidence of eosinophilic ILD in an observational study of 102 patients [31].

Antiarrhythmics

The antiarrhythmic drug most commonly associated with DI-ILD is amiodarone, affecting as many as 6% of patients receiving the drug. There are a variety of clinical presentations, the most severe of which is ARDS with or without rapidly progressive pulmonary fibrosis [32]. The most common presentation is a subacute illness consisting of non-productive cough or progressive dyspnea on exertion in a patient with underlying heart disease receiving amiodarone [18, 32].

With amiodarone toxicity, chest radiographs and CT scans show recognizable patterns in the majority of patients. Chest radiographs usually reveal bilateral patchy or diffuse infiltrates. HRCT almost invariably reveals more extensive disease than seen on chest radiographs. Bilateral interstitial or alveolar infiltrates are typical and can be either peripheral or diffuse in nature [33, 34]. A recent study on amiodarone-induced pulmonary toxicity reported universal HRCT findings of bilateral, diffuse ground glass opacities with alveolar consolidation [18].

The half-life of amiodarone is close to 53 days, during which time it reaches higher concentrations in the lung parenchyma than in the heart. Early studies on amiodarone-induced pulmonary toxicity suggested that only high daily dosages were associated with toxicity; however, recent studies have found that the duration of therapy and the cumulative dose increase the risk. A study of 1196 patients found a 10% incidence of pulmonary toxicity [35]. The risk was highest between 6 and 12 months of therapy, and a cumulative dose between 101 and 150 g over 4 years [34].

After discontinuation of the drug, most patients experience gradual improvement if the disease is limited. In more advanced cases, corticosteroid therapy is advised. The mortality related to severe amiodarone pulmonary toxicity can be as high as 40–50%, despite the withdrawal of the agent and corticosteroid therapy, which makes early recognition critical.

Dronedarone, which was designed without iodine in an attempt to reduce pulmonary toxicity, has an unknown incidence of DI-ILD due to less cumulative experience with the drug. A cross-sectional study of 186 patients taking dronedarone 400 mg twice daily for an average duration of 9.2 months found 18 patients with the development of respiratory symptoms after initiation of dronedarone. After the application of the Naranjo algorithm, 4 patients (2.2%) were classified as having dronedarone-induced pulmonary toxicity, 3 as "possible" and 1 as "probable" [36].

Biologic Agents

Over the last decade, biological therapies have moved into the forefront of medicine. However, they have also emerged as a new cause of drug-related pulmonary injury. Commonly implicated agents include anti-TNF inhibitors to include rituximab, cetuximab, alemtuzumab, bevacizumab, and trastuzumab [1, 37, 38]. Mechanistically, cytokines including TNF-alpha play a large role in the pathogenesis of ILD [39]. In a systematic review of 122 reported cases of biological agents associated with ILD, anti-TNF drugs were the overwhelming agent associated with the development of ILD [30]. Specifically, they found etanercept (58 cases) and

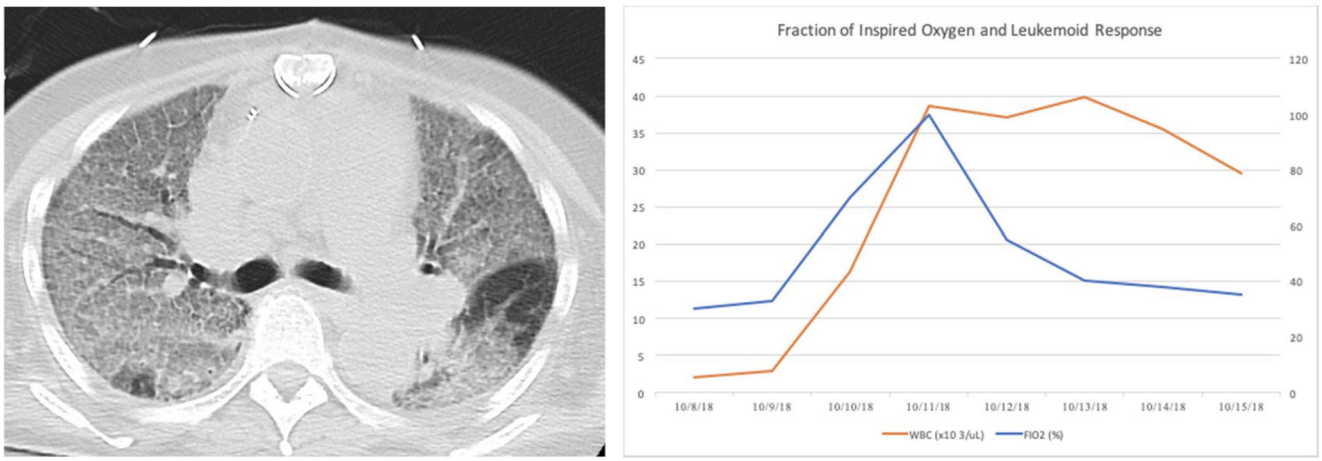

Fig. 5 (Left) non-contrast chest CT demonstrating diffuse bilateral ground glass opacities and septal thickening 7 days after initiation of filgrastim for medication-induced neutropenia. (Right) a graphical representation of the clinical course of respiratory failure with fraction of inspired oxygen (blue line, right axis) and leukocyte count (orange line, left axis) after treatment with filgrastim. Clinical improvement began after cessation of the drug and initiation glucocorticoid treatment on October 11, 2018 [29]

infliximab (56 cases) to be highly causative agents in the rheumatoid arthritis population. DI-ILD developed at a mean of 26 weeks after initiation. Histopathology showed a mix of usual interstitial pneumonia (UIP), NSIP, and organizing pneumonia. They reported a resolution of 40% of cases when the drug was withdrawn.

The incidence of rituximab-induced-ILD (RTX-ILD) remains low at 0.01–0.03% [40]. Naqibullah and colleagues [40] reported a case series of 5 of RTX-ILD. They found similarities in the affected cases including onset within several weeks of initiation and nonspecific pulmonary symptoms. CT chest typically demonstrates diffuse bilateral consolidations and GGOs. Discontinuation of treatment, supportive care, and glucocorticoid therapy is the normal treatment course [40].

Trastuzumab-induced ILD appears to be rare, with little reported on the subject. Three cases of trastuzumab monotherapy–associated ILD were reported in the *Journal of Molecular and Clinical Oncology* in late 2017 by Sugaya and colleagues [41]. One patient developed ILD after 5 courses of therapy, while the other 2 patients developed ILD after the first administration [41]. Previous treatment with chemotherapy was present in 2/3 of the patients, making causality difficult to confirm.

Anti-inflammatories

In a recent large systematic review by Skeoch et al. [42••] in the *Journal of Clinical Medicine*, they identified six single-center studies on DI-ILD. While cancer drugs were the leading cause, NSAIDS and disease-modifying antirheumatic drugs (DMARDs) made up a significant portion (0–23% and 6–72%, respectively) [42••]. Among the DMARDs, MTX has been most commonly associated with DI-ILD. The incidence of MTX-induced lung disease has been estimated to be 3.5–7.6% with a prevalence of 5% [10•]. Imokawa and colleagues [43] did a review of methotrexate pneumonitis in the literature and found 123 reported cases as of the year 2000. HP is the most common pulmonary toxicity associated with MTX. Similar to HP that develops from the inhaled organic antigen, MTX presents with mononuclear lymphocytic infiltration with granulomatous inflammation and eosinophils. Acute and organizing DAD can also be appreciated [43]. CT scan findings are often nonspecific and hard to differentiate from ILD associated with the underlying connective tissue disease for which the MTX is being used to treat. BAL may aid in the diagnosis, while nonspecific, it may show an increase in both CD4+ count and CD4/CD8 ratio [43, 44].

Penicillamine, an alpha amino acid metabolite to penicillin, has been implicated in various forms of DI-ILD. Its use in treating rheumatoid arthritis has largely been restricted because of adverse side effect profile. The most common pulmonary toxicity pattern is OP, with few reported cases of diffuse miliary lung ILD pattern, acute pneumonitis, EP, DAD, and DAH [45, 46]. Camus and colleagues [45] report a case of penicillamine-induced severe pneumonitis associated with the treatment of RA. Autopsy findings demonstrated marked pulmonary interstitial fibrosis and edema, with numerous lymphocytes and plasma cells scattered throughout the interstitial space [45].

NSAIDs may cause an acute hypersensitivity reaction that results in bilateral interstitial infiltrates [47]. A review of NSAID-induced pulmonary syndromes with eosinophilia attributed 6 cases to naproxen. The onset of symptoms was within 2 weeks to 6 weeks after initiation. Chest radiography showed diffuse bilateral infiltrates that resolved with discontinuation of therapy [48]. Diffuse parenchymal lung disease is less commonly seen with NSAIDs, and extensive literature review shows a paucity of cases.

Treatment

The most critical course of action in DI-ILD is the withdrawal of the suspected causative agent. Documentation of reaction, as well as avoidance of re-challenging with the agent in the future, is also important.

Although most patients with DI-ILD that is severe or does not improve after the withdrawal of offending drug are treated with steroids, there is a lack of randomized data on the impact of glucocorticoid (GC) therapy on the resolution of DI-ILD or survival. Most published experience is in the form of case series with small sample sizes and variable GC dosing strategies. A recent systematic review pooled 15 studies where GC dosing information and/or outcomes were available. They found efficacy to vary widely within each observational study and also between studies. The authors conclude that GCs may be most useful in severe disease [42••]. GC dosing and duration vary widely and tend to follow common practices based on the radiographic pattern present. No guidelines exist on dosing, duration, or route of GCs (e.g., oral steroids, intravenous steroids, or high-dose pulse steroids). Response rates show minimal to no improvement in those with a DAD pattern, and equivocal response with OP, HP, and NSIP patterns. If identified, removing the offending agent remains the cornerstone of treatment.

Prognosis

Due to the vast array of drugs causing DI-ILD, outcomes are quite heterogeneous between drugs and between

individuals. Clearly, discontinuation of the implicated drug and possibly glucocorticoid use improve chances for complete recovery. In some cases, it is difficult to assess prognosis as discontinuation of certain drugs, such as antineoplastic agents, can have a detrimental impact on the treatment of their underlying disease. For example, 85% of metastatic germ cell tumors are cured with bleomycin as a part of the treatment regimen, and studies investigating omission of bleomycin from the regimen without a compensatory increase in the dose or number of courses of platinum-containing chemotherapy show reduced efficacy [16, 49].

The prognosis of DI-ILD also depends upon the time of recognition. It is such a difficult, and oftentimes, diagnosis of exclusion that delayed recognition of a drug-induced process may lead to adverse outcomes. Typical complications of DI-ILD are pulmonary fibrosis and respiratory failure requiring mechanical ventilation. From studies of amiodarone, the prognosis is generally favorable when diagnosed early, but mortality is difficult to quantify as it differs widely in published series depending on the setting. Clearly, mortality is significant (~ 20–30%) for patients requiring hospitalization and even higher (~ 50%) for those who develop ARDS. However, in the majority of cases, outcomes are favorable with early diagnosis and treatment [32].

Biomarkers

There are no widely accepted biomarkers in the diagnosis or treatment of DI-ILD. Several investigational serum biomarkers have been studied including Kerbs von Lungren (KL-6), surfactant protein A and B (SP-A, SP-B), and monocyte chemoattractant protein 1 (MCP-1) [50]. KL-6 shows the highest sensitivity, specificity, and diagnostic accuracy for the presence of ILD in general [50]. Ohnishi and colleagues [50] examined KL-6 in 30 patients with DI-ILD, and finding the overall sensitivity of detecting DI-ILD was 53.3%. Further, KL-6 levels were higher in those with DAD and chronic interstitial pneumonia (CIP), then those with OP, EP, and HP [50]. Although a promising concept for the future, biomarkers for DI-ILD remain nonspecific and not of broad clinical application at this time.

Conclusion

DI-ILD remains a diagnosis of exclusion and is associated with a myriad of causative agents. Although some characteristic radiographic and histological patterns exist, the clinical presentation can be heterogeneous and a high index of suspicion of DI-ILD is paramount. Knowledge of commonly associated agents and a diagnostic framework to exclude other etiologies of ILD is helpful in making a diagnosis. Many confounding factors may exist, particularly in the setting of polypharmacy and underlying diseases that could themselves be associated with pulmonary disease, and often diagnosis is provisional. Cessation of the inciting agent may result in partial or full resolution of DI-ILD. However, glucocorticoid therapy may be necessary in severe or persistent cases. Irreversible parenchymal changes may result from DI-ILD; thus, prompt identification and removal of the potential culprit is a key to reduce the likelihood of permanent damage.

Compliance with Ethical Standards

Conflict of Interest Ankush Ratwani, Bhavik Gupta, Brian Stephenson, Haresh Mani, and A. Whitney Brown declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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