Respiratory Disease Series:
Diagnostic Tools and Disease Managements

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Editors

Drug-Induced Lung Injury

Springer

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Preface

Why is the disorder of drug-induced lung injury important currently?

Drug-induced lung injury refers to drug-related respiratory disorder that occurs during administration of drugs in the treatment of original diseases. The reasons for which drug-induced lung injury is noted and considered important are summarized as below:

1. The number of clinical reports about drug-induced lung injury is increasing.
   In recent years, new drugs, such as biological products, molecular-targeted drugs, and immune checkpoint inhibitors, are presented successively on pharmacy markets. Consequently, the cases of occurrence of drug-induced lung injury are increasingly reported.
2. According to studies worldwide, the incidence of drug-induced lung injury is different among human ethnicities.
   For example, the incidences of drug-induced lung injury due to bleomycin or gefitinib through the mechanism of cytotoxicity are a high trend in the Japanese population.
3. Cases may manifest clinically severe with diffuse alveolar damage (DAD).
   The drug-induced lung injury with DAD responds insufficiently to treatment bringing about poor prognosis.
4. The drug-induced lung injury shows a diversity of clinical types.
   For example, the drug-induced lung injury due to methotrexate may manifest different clinical types depending on cases.
5. The new pathological state of drug-induced lung injury is identified recently.
   For example, the incidence of interstitial pneumonia due to mTOR inhibitor is relatively high. However, if the disorder is clinically mild, the administration of mTOR inhibitor can be continued or readministered after a while of withdrawal of mTOR inhibitor.
6. The drug-induced lung injury is involved with various medical fields.
   Drug-induced lung injury is an unavoidable circumstance for all medical doctors who do the administration of drugs to their patients in disease treatment.

In the diagnosis of drug-induced lung injury, it is important to always keep in mind the principle that all drugs may cause lung injury, giving a suspicious impression of drug-induced lung injury. Clinicians have to differentiate the abnormal lung shadows appearing on the chest images during drug administration. However, it is often quite difficult to distinguish it from other diseases, such as the deterioration of original lung lesions or infectious diseases, because of the diversity and nonspecificity of clinical types of drug-induced lung injury.

Japan is in leading positions on many of the research fields regarding clinical epidemiology, serum markers, and CT diagnostic images of drug-induced lung injury in the world. The authors of this book are the researchers and clinicians who work in the first line of defense against drug-induced lung injury in Japan. Specifically, it's not an exaggeration to say that this book is a culmination of knowledge of what has been achieved on drug-induced lung injury. Needless to say, this book will be very helpful for clinicians in their daily medical practice; at the same time, it will serve as a compass in the basic and clinical researches for elucidation of the unknowns of drug-induced lung injury. I hope this book will be fully and widely used by many doctors and researchers for their aims.

Matsumoto, Japan — Masayuki Hanaoka
Ibaraki, Japan — Hiroyuki Nakamura
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Contents

Part I
Definition, Pathogenesis, and Epidemiology

Chapter 1
Definition and Pathogenesis of Drug-Induced Lung Injury: What Is DLI?

Hidetoshi Nakamura and Minoru Kanazawa

Abstract Drug-induced lung injury (DLI) results from the specific use of a drug, including prescription drugs, over-the-counter drugs, and supplements. A DLI is an adverse drug reaction that occurs in the pulmonary system including the lungs, bronchi, and pulmonary vessels. The following diagnostic criteria are generally used: (1) history of ingestion of a drug known to induce lung injury, (2) the clinical manifestation reported to be induced by a drug, (3) exclusion of other causes of the clinical manifestation, (4) improvement of the clinical manifestations after drug discontinuation, and (5) exacerbation of the clinical manifestations after resuming the drug. Pathogenetic mechanisms of DLI have not been precisely elucidated, but two possible mechanisms have been suggested. First, there are cytotoxic effects of drugs on alveolar type II and airway epithelial cells or vascular endothelial cells. The cytotoxic effects may be mediated by reactive oxygen species, proteases, and cytokines. Second, activation of immune cells may promote the development of DLI through acquisition of immunogenicity by binding of a drug or its metabolite to cytoplasmic proteins as a hapten. These two mechanisms may be involved in the pathogenesis of DLI independently or in combination, and they may be modified by a variety of host and environmental factors, such as genetic predisposition, age, underlying lung diseases, and interactions with concomitant drugs.

Keywords Adverse drug reaction • Adverse event • Cytotoxic • Reactive oxygen species • Hapten

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1.1 Definition and Concept of Drug-Induced Lung Injury

Drug-induced lung injury (DLI) is defined as a lung injury that results from the specific use of a drug, including not only a prescription drug but also an over-the-counter drug, herbal medicine, supplement, and illegal narcotics. DLI is therefore an adverse drug reaction (ADR) that specifically occurs in the pulmonary system, which includes the lungs, bronchi, pulmonary vessels, and pleura.

In general, an adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

In the case of clinical investigations, AEs may occur that, if suspected to be medical product-related ADRs or DLIs, might be significant enough to lead to important changes in the way the medical product is developed. This is true for reactions that, in their most severe forms, threaten life or function, as, for example, acute lung injury (ALI), due to the tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib.

Among these AEs, any noxious and unintended response to a medical product related to any dose should be considered an ADR. DLI is not limited to a typical interstitial lung disease or ALI due to an antineoplastic drugs, but it also refers to asthma attacks due to β-blockers in asthma patients, chronic nonproductive cough due to angiotensin-converting enzyme inhibitors (ACEIs), and CO_2 narcosis due to sedatives administered to patients with chronic obstructive pulmonary disease (COPD).

The phrase "responses to a medical product" means that a causal relationship between a medical product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. Definitions and terminology are summarized in Table 1.1 [1].

DLIs often show a close temporal relationship between exposure and the onset of lung disease. Generally, DLIs develop after a few weeks to a few months, but

Table 1.1 Definitions and terminology of event or response associated with administration of a drug or a pharmaceutical product

Drug-induced lung injury (DLI): A lung injury that results from the specific use of a drug, including not only prescription drugs but also over-the-counter drugs, herbal medicine, supplements, and illegal narcotics. A DLI is therefore an adverse drug reaction (ADR) that occurs specifically in the pulmonary system, which includes the lungs, bronchi, pulmonary vessels, and pleura
Adverse drug reaction (ADR): All noxious and unintended responses to a medical product related to any dose should be considered adverse drug reactions. The phrase "responses to a medical product" means that a causal relationship between a medical product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out
Adverse event (AE): Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have to have a causal relationship with this treatment

some may develop within an hour, such as transfusion-related ALI (TRALI), or they may take several years in the case of a DLI induced by amiodarone or methotrexate (MTX). Some drugs induce a distinctive pattern, making the recognition of DLIs in patients receiving the drug easy. In these cases, a causal relationship can be suspected easily, but many atypical cases or very rare cases may occur as well. Table 1.2 shows points of assessment for evaluating the causal relationship. However, even if these four points are met, it is still difficult to prove a causal relationship. In fact, there have never been established methods to prove a causal relationship between a medical product and an adverse event scientifically.

Based on these evaluation points, Camus proposed five diagnostic criteria for DLI, shown in Table 1.3 [2]. In these criteria, four of the five points are used to prove the causal relationship, and the fifth point is the clinical manifestation of lung diseases that have been reported as DLIs. In actual practice, the differential diagnosis of infection, cardiogenic pulmonary edema, pulmonary involvement of connective tissue diseases, and idiopathic interstitial lung diseases is difficult to perform, because there are no choices for clear-cut diagnostic criteria. The Japanese Respiratory Society adopted these diagnostic criteria in the guideline or consensus statement for the diagnosis and treatment of drug-induced lung injuries and firstly published it in 2006, then in 2012 in Japanese, and its English short version in 2013 [3–5].

The diagnosis of DLI can be made by starting to suspect a temporal relationship but more importantly by excluding other causes. Being cognizant of DLI enables the diagnosis to be suspected early and the causative medicine to be withdrawn timely, which should improve the outcome. Although discontinuation of an offending drug often positively affects the clinical prognosis, it may impact negatively on the underlying disease. Based on a patient's clinical status, corticosteroids may

Table 1.2 Points of assessment to evaluate a causal relationship between a drug and an adverse event

1. Exacerbation or recurrence of the adverse event after resuming the drug (rechallenge)
2. Improvement of the adverse event after drug discontinuation (de-challenge)
3. The adverse event occurs within a reasonable period of time
4. Other causes of the adverse event could be ruled out

Table 1.3 Diagnostic criteria for drug-induced lung injury

1. History of ingestion of a drug that is known to induce lung injury
2. The clinical manifestation has been reported to be induced by a drug
3. Other causes of the clinical manifestation could be ruled out
4. Improvement of the clinical manifestations after drug discontinuation
5. Exacerbation of the clinical manifestations after resuming drug administration

sometimes be avoided, and this will allow more accurate determination of the specific effects of drug withdrawal.

Mammalian target of rapamycin (mTOR) inhibitors induce drug-induced allergic hypersensitivity pneumonitis frequently, with a reported incidence of 11.7–53.9% [6]. Because of a good response to corticosteroid and its effect as antineoplastic drugs, mTOR inhibitors are used continuously after DLI develops, especially when patients are asymptomatic. In addition, even readministration of mTOR inhibitors may be considered when symptoms of DLI are absent. The positioning of diagnostic criteria and behavior in clinical practice may be exceptional in the case of DLIs due to mTOR inhibitors.

1.2 Clinical and Epidemiological Features of DLI

DLI is an increasingly frequent problem in clinical respiratory medicine as more, newer, more effective, and expensive pharmaceutical products are being used in the treatment of diseases. From clinical and epidemiological perspectives, DLI has two distinct features.

First, DLI manifests most frequently as interstitial lung disease or ALI. Several other clinical manifestations, such as airway diseases, pulmonary hypertension, and pleural disease, have been documented, but the number of cases is very limited. The term drug-induced interstitial pneumonia is then used synonymously with DLI. Among various drug-induced interstitial pneumonias or DLIs, it is most important to specifically diagnose acute interstitial pneumonia with a pathological background of diffuse alveolar damage (DAD) pattern. The diagnosis and treatment strategies must be determined by clinical, radiological, and pathological (CRP) multidisciplinary discussion. Early diagnosis, withdrawal of the offending drug, and corticosteroid pulse therapy should be considered. Antineoplastic drugs, molecularly targeted antineoplastic drugs such as gefitinib and erlotinib, monoclonal agents such as rituximab and bevacizumab, amiodarone, and methotrexate may be the causative drugs [7]. Other forms of interstitial pneumonia, such as hypersensitivity pneumonia pattern, organizing pneumonia pattern, and eosinophilic pneumonia pattern, show generally favorable responses to corticosteroids, and better prognosis can be expected than the DAD pattern. The diagnosis and treatment of these types of interstitial pneumonia should also be determined through CRP discussion. In any case, the possibility of DLI should be considered early during the clinical course, and early therapeutic intervention may be beneficial to patients.

Second, the categories of drugs that induce DLI are limited. From 2004 to July 2007, a number of DLI cases reported to the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) were investigated [8]. In this report, cases with diagnoses of interstitial lung disease, ALI, and eosinophilic pneumonia were collected. The category of antineoplastic drugs was most common (52.4%), followed by antirheumatic drugs (27.4%), blood products (6.8%) inducing TRALI, the antiarrhythmic

amiodarone (4.6%), antibacterial drugs (4.3%), and analgesics or antipyretics (2.2%). In other words, about 80% of the reported DLIs were due to either antineoplastic drugs or antirheumatic drugs. The leading cause in this investigation was gefitinib, followed by MTX and gemcitabine. The offending drugs have been changing, but it is always said that new drugs with new mechanisms of action may be accompanied by new adverse drug reactions or DLIs. Recently, many DLIs have been reported with the use of new epidermal growth factor receptor (EGFR)-TKIs, mTOR inhibitors, new biologics for rheumatoid arthritis, and the immune checkpoint blocker nivolumab. These products have common features of high cost and high effectiveness, although they also have a high risk for DLI.

1.3 Pathogenetic Mechanisms

Pathogenetic mechanisms of DLI have not been precisely elucidated except for a few drugs, but two possible major mechanisms have been postulated [5, 9]. First, there are cytotoxic effects of drugs on alveolar type II epithelial cells, airway epithelial cells, or vascular endothelial cells. Second, activation of immune cells by drugs acting as a hapten or mimicking an antigen may be responsible. These two mechanisms may be involved in the pathogenesis of DLI independently or in combination, and they may be modified by a variety of host and environmental factors, including genetic predisposition through the expression of drug metabolism- or immune-related genes; age; underlying lung diseases, particularly pulmonary fibrosis or chronic inflammatory lung diseases; and interactions with concomitant drugs.

There are several reasons why certain drugs cause toxicity specifically in the lungs [10]. Some drugs reach higher concentrations in cells or tissues of the lungs than other organs. Bioactivation of certain agents may occur in the lungs, and the consequences of bioactivation may also cause lung-specific injury. In general, DLIs induced by cytotoxic agents give rise to alveolitis and pulmonary edema. In response to the injury, tissue repair to restore the barrier function is immediately initiated. The injury may progress to chronic inflammation, which eventually leads to fibrotic change. In contrast, immune cell-mediated DLI typically manifests as eosinophilic pneumonia or hypersensitivity pneumonitis and responds well to steroid therapy.

1.3.1 Cytotoxic Effects

Direct cytotoxic effects are mediated by harmful molecules such as reactive oxygen species (ROS), proteases, and cytokines. Cytotoxic pulmonary injury can also be promoted by reduced deactivation of metabolites in the lungs and impairment of alveolar repair mechanisms. In addition to cytotoxic drugs including bleomycin (BLM), MTX, and cyclophosphamide, noncytotoxic drugs such as nitrofurantoin, sulfasalazine, and amiodarone may be toxic to the lungs.

DLI is mediated mainly by ROS, which is known to promote BLM-induced lung injury [11]. BLM forms a complex with Fe^{2+} or Cu^{2+}. When reducing agents are present, an electron is given from Fe^{2+} to an oxygen molecule of the reducer, and ROS are generated. ROS injure deoxyribonucleic acid (DNA) of the cells, which results in cell death. Adverse effects of BLM are observed in the lungs and skin, in which high concentrations of BLM can be detected. However, the severities of BLM-induced lung injury differed among distinct mice strains presumably associated with human leukocyte antigen (HLA)-DRA [12], which implies that immune systems are involved in BLM-induced lung injury, in addition to its direct cytotoxicity. The toxic mechanism of amiodarone is also mediated by oxygen radicals and reduced deactivation of toxic metabolites of the drug. Similar to other cationic amphiphilic drugs, amiodarone has also been demonstrated to induce phospholipidosis in alveolar macrophages and type II epithelial cells leading to impaired functions of these cells.

There are many granulocytes and monocytes in the pulmonary circulation that are activated by certain drugs leading to the production of ROS from the inflammatory cells. Although these cells essentially produce ROS as defense tools against microorganisms or foreign bodies, pulmonary vascular endothelial cells are injured by ROS released from accumulated inflammatory cells, especially in the lungs of elderly patients. These processes are related to the pathogenesis of acute respiratory distress syndrome (ARDS) and multiple organ failure progressing from systemic inflammatory response syndrome.

Meanwhile, most antineoplastic drugs themselves have cytotoxicity, and they may directly injure alveolar type II epithelial cells. These cells are resistant to these agents during G0 phase, but they are susceptible to the antineoplastic drugs during proliferating phases, and the cell injury may gradually spread in the lungs, leading to DAD [13]. Such chemotherapy lung is a representative of cytotoxic lung injury, and the risk is increased by concurrent radiation or oxygen therapy. Antineoplastic drugs such as gemcitabine also induce the systemic release of cytokines, resulting in capillary leakage and pulmonary edema. MTX-induced pulmonary toxicity may be mediated by the release of free oxygen radicals and cytokines, including interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and transforming growth factor (TGF)-β through the p38MAPK signaling pathway [14]. MTX has also been reported to inhibit cysteine protease inhibitors, possibly leading to protease-induced tissue injury [15].

Recently, molecularly targeted agents, which exert their effects on tumor cells by turning on the death signal, have been widely used. Antibodies against EGFR and its TKI are representative molecularly targeted agents. It has been suggested that EGFR-TKIs may act on normal alveolar epithelial cells in addition to tumor cells and induce epithelial cell injury. EGFR-TKIs are supposed to promote the vulnerability of epithelial cells by inhibiting the expression of heat shock protein 70 (HSP70) [16], and they may induce DLI through the same mechanism.

One of the risk factors for lung injury by gefitinib is underlying interstitial pneumonia/pulmonary fibrosis, in which impaired regulation of HSP70 expression is among the host factors responsible for the vulnerability of the lungs [17]. In addition,

gefitinib may augment underlying pulmonary fibrosis through a decrease in EGFR phosphorylation with coincident regenerative epithelial proliferation [18]. Epithelial to mesenchymal transition (EMT) is also suggested to be a mechanism involved in leflunomide-induced lung injury [19]. These observations imply that various target molecules are associated with the mechanisms in DLI and further investigation of the distinct mechanism for each drug is needed.

1.3.2 Activation of Immune Cells

Lung injury by cytotoxic drugs is associated with the doses and duration of the administration of causative drugs. When lung injury is induced by a small dose or the first administration of the drug, DLI may be mediated by the activation of immune cells. Most of the reactions in immune-mediated DLI may be T cell mediated.

Drug hypersensitivity is caused by the recognition of drugs via T cells, and the processes are usually accounted for by the hapten concept. Most drugs have low molecular weights (<1000 kDa) and must be covalently bound to high-molecular-weight carrier proteins as haptens to become immunogens [20]. A drug or its metabolite may bind to an immunogenic peptide presented by a major histocompatibility complex (MHC) molecule. Another possibility is a pharmacological interaction between drugs and immune receptors. If the drugs happen to bear T cell receptors, they could activate T cells. Matzinger proposed an alternative explanation: certain drugs may cause cell injury and act as immunologic triggers by releasing endogenous danger signals derived from undergoing stress, damage, or abnormal death and induce the activation of dendritic cells [21].

DLI related to immune cell activation often presents as eosinophilic pneumonia. Eosinophils originally play roles in defending against relatively large pathogenic microorganisms, such as parasites. Precise mechanisms by which drugs induce eosinophil accumulation to the lung tissues are to be elucidated. IL-5 contributes to proliferation, maturation, and release to the circulation of immature eosinophils in bone marrow. As observed in immediate allergic responses, Th2 lymphocytes produce IL-5 shortly after antigen presentation by antigen-presenting cells (APCs). In alveoli, eosinophil chemoattractant eotaxin is produced by alveolar macrophages, epithelial cells, and endothelial cells. Recruitment of large numbers of eosinophils to alveolar spaces may partly be mediated by such mechanisms. Eosinophils contain various defensive molecules, such as eosinophil cationic protein in the granules, which can lead to tissue injury. However, clinically severe cases are rare, because eosinophilic pneumonia is usually responsive to corticosteroid therapy.

Amiodarone induces lung injury by immune-mediated mechanisms in addition to direct toxicity. Kuruma et al. reported that the Th1/Th2 balance may influence the metabolism and toxicity of this drug [22]. Amiodarone is also reported to be involved in the angiotensin enzyme system activation related to apoptosis of alveolar epithelial cells [23]. The number of cases of lung injury triggered by anti-TNF-α

agents is increasing. TNF-α has both pro- and anti-fibrotic effects, and it can promote lung tissue repair by inducing apoptosis of inflammatory cells. Anti-TNF-α therapy may result in impaired apoptosis of inflammatory cells, which release proteolytic enzymes enhancing the potential pulmonary toxicity of MTX when both drugs are administered [24]. Anti-TNF-α agents may also increase anti-inflammatory cytokines, such as TGF-β1, promoting pro-fibrotic effects. The exacerbation of pulmonary fibrosis may be mediated by these processes during treatment with anti-TNF-α agents. Rituximab, an anti-CD20 antibody, can induce cell destruction. Cell-derived peptides may stimulate dendritic cells and induce the activation of cytotoxic T lymphocytes [25]. Rituximab may induce lung injury through complement activation and the release of cytokines such as TNF-α and IL-6.

Interestingly, even oral and intravenous drugs can cause granuloma formation in the lungs [26]. Theoretically, it has been speculated that hapten effects by drugs or the existence of individuals with the specific MHC reactive to the hapten effects may be responsible for the development of DLI. However, the mechanisms have not been clarified in most drugs. Therefore, DLI cannot be diagnosed solely by the results of the drug lymphocyte stimulation test (DLST), and more careful evaluation is required for the assessment of DLI.

1.3.3 Underlying Pulmonary Disorder and Host Susceptibility in DLI

Various lung injuries are induced by medical procedures besides drugs, e.g., ALI after radiation therapy and major operations. The risk of ALI is increased by comorbid infections, hypoxia by blocked circulation and subsequent reoxygenation, and exposure to high concentrations of oxygen during anesthesia in major operations. It has been reported that avoiding high concentrations of oxygen supply can reduce the risk of ALI [13]. Epidemiological studies have demonstrated that underlying interstitial pneumonia/pulmonary fibrosis and smoking history are major risk factors for the development of DLI caused by EGFR-TKIs including gefitinib and erlotinib.

Smoking-induced lung parenchymal destruction (pulmonary emphysema) and tissue remodeling with epithelial cell injury (pulmonary fibrosis) may be consequences of the vulnerability of lung tissues caused by the failure in the host defense systems, in addition to the extrinsic factors. Such mechanisms include a decrease in antioxidants such as growth-stimulating hormone (GSH) and superoxide dismutase (SOD) in environments with oxidative stress in inflamed lungs. Recovery of lung injury has been reported with the administration of antioxidants. Therefore, impaired defensive systems (SOD, glutathione, catalase, etc.) against the ROS generated in the processes of cytotoxicity and a decrease in HSP70 and HSP90 may contribute to increased risks of DLI [27]. Furthermore, “aging and senescence” themselves are risk factors for DLI.

Promotion of cessation of smoking and improvement of working environments reduce exposure to noxious gases and dusts, but environmental problems related to

Table 1.4 Pathogenetic mechanisms of drug-induced lung injury

1. Cytotoxic effects
• Direct injury to alveolar epithelial and endothelial cells • Mediated by reactive oxygen species, proteases, and cytokines • Increased vascular permeability, inflammation, and tissue injury, resulting in pulmonary fibrosis (extent of injury generally correlated with total dose and duration)
2. Activation of immune cells (allergic reaction)
• Acquisition of immunogenicity by binding of a drug or its metabolite to cytoplasmic proteins (hapten effects) • Eosinophil infiltration in the alveolar wall and airspaces (eosinophilic pneumonia) • Interstitial pneumonia mediated by lymphocyte infiltration and granuloma formation in the alveolar wall (involved in most cases of DLI and usually not related to the dose or duration)
3. Host factors
• Aging, smoking, environmental chemicals/dusts, and genetic factors • Underlying pulmonary diseases: fibrosis and emphysema • Iatrogenic: radiation, surgery, exposure to high concentrations of oxygen

chemical substances and fine particles are still critical worldwide due to ongoing globalization. As for factors related to host susceptibility in DLI, the HLA complex plays a role in antigen presentation for T cell recognition. Patients with rheumatoid arthritis positive for HLA-B40 have a higher risk of developing gold-induced pneumonitis [28]. In addition, CYP single nucleotide polymorphisms are among the key factors causing variations in drug responses among individuals [29].

As described above, the pathogenesis of DLI is complex and needs to be further studied on an individual basis. It is, however, obvious that DLI is caused by multiple factors, including cytotoxic effects of the drugs, immune cell activation by the drugs, and host factors such as smoking, underlying pulmonary diseases, and genetic predisposition (Table 1.4).

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Chapter 2
Epidemiology and Risk Factors of Drug-Induced Lung Disease: What Are the Prevalence and Risk Factors of DILD?

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Abstract The precise frequency of drug-induced lung disease (DILD) is unclear, but the reported number of cases of DILD has been increasing, especially after reports of severe DILD caused by gefitinib in Japan. General risk factors for DILD include current smoking, old age, preexisting lung disease (especially interstitial pneumonia), history of thoracic surgery or irradiation of the lung, and renal failure. There are ethnic differences in the frequency of DILD caused by certain drugs, and genetic factors may partially contribute to this. In addition to classic antineoplastic agents, antirheumatic drugs, interferon, herbal medicine, and molecularly targeted drugs frequently cause DILD. Checkpoint inhibitors can also cause severe interstitial lung disease (ILD) as one of a variety of side effects associated with their immunomodulatory function.

Keywords Disease susceptibility • Epidemiology • Risk factor

2.1 Epidemiology

The precise frequency of drug-induced lung disease (DILD) is unclear, but it has been stated that DILD accounts for 3% of all ILD cases [1, 2]. The number of published cases increases exponentially [2]. In Japan, urgent safety information was issued for gold in 1988, Sho-saiko-to in 1996, and gefitinib in 2002. After the reporting of severe DILD caused by gefitinib, reports of DILD have been increasing in Japan [3, 4] (Table 2.1).

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Table 2.1 Numbers of case reports of all suspected drug-induced adverse events and ILD from 2004 to 2015

Year	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
All adverse events	24,403	24,185	24,301	25,636	28,592	29,293	32,976	36,226	40,848	37,970	48,793	51,222
ILD	1239	1194	1161	1159	1486	1451	1628	1727	1624	1493	1995	2075
Death with drug-induced ILD	272	245	249	272	330	300	284	332	300	275	310	271

The numbers of cases filed with the PMDA were extracted from the Japanese Adverse Drug Event Report database. *ILD* interstitial lung disease

The epidemiology of DILD has changed with time. For instance, ILD from methotrexate and antitumor necrosis factor alpha (anti-TNF-α) antibody therapy is increasing, whereas cases of gold- and penicillamine-induced pulmonary reactions have vanished [2]. When literature cases are referred to, it should be taken into account that reporting bias may increase the incidence of DILD caused by a specific drug shortly after the approval of that drug. The incidence of DILD also depends on which test is used to diagnose it. In Japan, high-resolution computed tomography (HRCT) is more widely used in daily clinical practice than in other countries, which may increase the incidence of mild cases.

In Japan, DILD is reported by pharmaceutical companies, doctors, and pharmacists to the Pharmaceuticals and Medical Devices Agency (PMDA). The data are aggregated and published on the agency's website [5]. In this chapter, the epidemiology of DILD and its risk factors will be reviewed based on data from the PMDA in Japan and literature on DILD from other countries.

2.2 Risk Factors

Risk factors have been identified for only a few patients with DILD, making it difficult to predict occurrence in most patients [2]. General risk factors for DILD include the following: current smoking, age above 60 years, preexisting lung disease (especially interstitial pneumonia), post-thoracic surgery, subnormal baseline physiology (particularly carbon monoxide diffusing capacity), oxygen use, history of irradiation of the lung, and renal failure. The risk of DILD is also influenced by a variety of host and environmental factors including genetic susceptibility (genes involved in drug metabolism, immune regulation, etc.) [2, 4]. However, it remains unclear if the risk factors listed above actually increase the frequency of DILD or just lower the threshold of symptomatic presentation. Asthma and atopy may expose patients to the risk of drug-induced eosinophilic pneumonia. Elevated daily or cumulative doses and/or plasma levels of some drugs increase the risk of developing ILD [2], and threshold values have been identified for some drugs.

2.3 Ethnic Differences in Drug-Induced Lung Disease

It has been shown that the incidence of DILD caused by some drugs is higher in Japanese patients than in people with other ethnic backgrounds. This difference may be related to differences in medical or health insurance systems, individual body constitution, or availability of diagnostic tools such as HRCT. However, even after allowing for these possible differences, the incidence of fatal ILDs appears to be higher in Japan than in other countries [4].

DILD caused by epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) is much more frequent in Japanese patients than in those from other countries. To investigate the genetic background of these Japanese patients, Hagiwara

et al. performed whole-exome sequencing in 36 Japanese patients with ILD caused by EGFR-TKIs and 45 patients with acute exacerbation of idiopathic pulmonary fibrosis. Whole-exome sequence data from 70 healthy Japanese subjects were used as control. Hagiwara et al. detected 180,215 gene mutations which caused amino acid substitutions. After narrowing down the number of candidate genes based on the information of epidemiology, genetic function, and organ localization, *mucin 4* (*MUC4*) was the only gene identified that was considered to be associated with ILD. Homozygous mutation of the *MUC4* gene was associated with a high frequency of EGFR-TKI ILD, idiopathic pulmonary fibrosis, and antineoplastic drugs-induced ILD [6].

2.4 Epidemiology and Risk Factors for DILD Caused by Different Groups of Drugs

The number of reported cases of DILD caused by different groups of drugs in Japan is shown in Tables 2.2, 2.3, 2.4, and 2.5. Cases of DILD caused by interferon and herbal medicine are decreasing in number (Table 2.3), whereas cases of DILD caused by antineoplastic drugs, especially molecularly targeted drugs and immune checkpoint inhibitors, are increasing (Table 2.4). In addition, ILD is one of a variety of adverse events caused by immune checkpoint inhibitors including nivolumab.

Table 2.2 Anti-cancer drug-induced ILD

Anti-cancer drugs	Incidence	Onset pattern	Numbers of case reports				
			2005	2010	2013	2014	2015
Fluorouracil	Unknown	G,K	38	151	76	94	75
Irinotecan	0.9%	B	32	66	28	63	41
Gemcitabine	1.0%	B	88	62	56	46	89
Cyclophosphamide	Unknown	E,J	29	32	18	25	22
Docetaxel	0.6%	A,B,I,J,K,L	43	94	72	92	83
Paclitaxel	0.5%	B,C,G,I	56	44	34	55	147
Cisplatin	<0.1%	G	13	16	16	16	13
Oxaliplatin	0.3%	B,G	14	61	44	59	55
Bleomycin	10%	B,E,G,H,K,M	9	5	6	5	7
Doxorubicin	1.4%	A,J	14	21	5	9	21
Methotrexate (i.v.)	<0.1%	A,B,C,D,G,L,N	3	11	11	52	29

The numbers of cases filed with the PMDA were extracted from the Japanese Adverse Drug Event Report database. The incidence was described in the label information of Japan. The onset pattern was cited from Pneumotox.com. A: acute ILD/NSIP (interstitial lung disease/non-specific interstitial pneumonia); B: subacute ILD/NSIP (interstitial lung disease/non-specific interstitial pneumonia); C: PIE (pulmonary infiltration with eosinophilia); D: granulomatous ILD (interstitial lung disease); E: OP (organizing pneumonia); F: DIP (desquamative interstitial pneumonia); G: pulmonary fibrosis; H: lung nodules; I: transient infiltrates; J: pulmonary edema; K: ARDS (acute respiratory distress syndrome); L: DAH (diffuse alveolar hemorrhage); M: PVOD (pulmonary veno-occlusive disease); N: opportunistic infections

Table 2.3 Antirheumatic and other drug-induced ILDs

Drugs	Incidence	Numbers of case reports				
		2005	2010	2013	2014	2015
Methotrexate (p.o.)	0.1–5%	136	106	123	106	112
Salazosulfapyridine	0.03%	6	6	8	10	15
Auranofin	Unknown	1	1	0	0	0
Aurothiomalate	<0.1%	4	5	1	0	1
Bucillamine	0.03%	21	19	14	21	12
Leflunomide	1.0%	4	5	2	1	0
Amiodarone	1.9%	35	52	55	43	53
Interferon	0.1–5%	69	56	21	29	16
Sho-saiko-to	<0.1%	10	7	2	2	4

The numbers of cases filed with the PMDA were extracted from the Japanese Adverse Drug Event Report database. The incidence was described in the label information of Japan

2.4.1 Antineoplastic Drugs (Other Than Molecularly Targeted Drugs)

It is widely known that antineoplastic drugs can cause DILD (Table 2.2). The incidence of lung toxicity caused by antineoplastic drugs is estimated to be 10–20%. In Japan, some drugs are contraindicated for use in patients with symptomatic ILD such as irinotecan and gemcitabine [5].

2.4.1.1 Bleomycin

It is recognized that fatal pulmonary toxicity is relatively frequent in bleomycin-induced lung injury. Pulmonary toxicity is predominantly fibrotic, but hypersensitivity to bleomycin has also been recognized [7]. It has been reported that the frequency of lung toxicity is approximately 20% (0–46%), and mortality is 1–27% with the bleomycin administration [8, 9]. The number of reported cases of DILD caused by bleomycin was much higher before the 1980s, but it has decreased in recent years (Table 2.2). The frequency of bleomycin-induced pulmonary fibrosis largely depends on the cumulative dose. It is reported that there is a definite risk of pulmonary toxicity at about the same rate at all dose levels below a total dose of 450 mg; however, there has been a significant increase in the overall incidence of pulmonary toxicity at total doses greater than 450 mg [10]. Other risk factors include being older than 70 years, cigarette smoking, renal dysfunction, severity of underlying malignancy at presentation, concomitant use of oxygen, radiation therapy, other chemotherapeutic agents, and the use of hematopoietic colony-stimulating factors [7, 9]. Therefore, alternative drugs should be considered in elderly patients or those with decreased renal function.

Table 2.4 Molecularly targeted drug- and immune checkpoint inhibitor-induced ILD

Drugs	Mechanism	Incidence		Numbers of case reports				
		Japan	US	2005	2010	2013	2014	2015
Gefitinib	EGFR inhibitor	5.8%	1.3%	188	60	45	17	35
Erlotinib	EGFR inhibitor	4.4%	1.1%		88	48	50	39
Sorafenib	Multi-kinase inhibitor	0.34%	–		25	17	15	7
Sunitinib	Multi-kinase inhibitor	2.2%	–		10	6	10	7
Everolimus	mTOR inhibitor	15%	–		110	42	178	169
Temsirolimus	mTOR inhibitor	17.1%	–		14	29	30	25
Imatinib	Bcr-Abl inhibitor	<5%	–	16	24	18	123	22
Crizotinib	ALK inhibitor	1.7%	2.9%			36	32	26
Alectinib	ALK inhibitor	1.7%	–				14	25
Bevacizumab	Anti-VEGF antibody	0.4%	–		44	56	51	52
Trastuzumab	Anti-Her2 antibody	Unknown	–	11	11	29	50	68
Cetuximab	Anti-EGFR antibody	0.5–10%	<0.5%		18	34	67	75
Infliximab	Anti-TNF-α antibody	Unknown	–	22	23	28	19	19
Adalimumab	Anti-TNF-α antibody	0.70%	–		34	19	14	11
Nivolumab	Anti-PD-1 antibody	5.30%	1.8% (melanoma) 3.4% (NSCLC)				5	75
Ipilimumab	Anti-PD-1 antibody	<0.1%	–					8

The numbers of cases filed with the PMDA were extracted from the Japanese Adverse Drug Event Report database. *EGFR* epidermal growth factor receptor, *mTOR* mammalian target of rapamycin, *ALK* anaplastic lymphoma kinase, *VEGF* vascular endothelial growth factor, *TNF* tumor necrosis factor, *PD-1* programed cell death-1, *NSCLC* non-small cell lung cancer. The incidence was described in the label information of Japan and the United States. "–" means that the incidence of interstitial pulmonary diseases was not described

Table 2.5 Characteristics of patients with nivolumab-induced ILD

Total		80
Sex	Men	62
	Women	17
	Unknown	1
Cancer type	Melanoma	22
	NSCLC	57
	Gastric	1
Age	40s	5
	50s	16
	60s	23
	70s	30
	80s	5
	Unknown	1
Period of treatment at the episode	1 week	15
	2 weeks	18
	4 weeks	19
	12 weeks	14
	24 weeks	8
	Unknown	6
Outcome	Remission	32
	Recovery	19
	No recovery	12
	Death	11
	Aftereffects	2
	Unknown	4

Cases filed with the PMDA were extracted from the Japanese Adverse Drug Event Report database

2.4.1.2 Cyclophosphamide

Cyclophosphamide is classified as an alkylating agent and is widely used for malignant and nonmalignant diseases. The incidence of cyclophosphamide-induced ILD is reported to be 0.1–5% [5], and it can cause a variety of ILDs including subacute pneumonia, organizing pneumonia, and acute respiratory distress syndrome. Some patients develop ILD within 1–6 months of starting treatment with cyclophosphamide, whereas others develop progressive ILD several months or years after starting the drug. The latter form is sometimes histologically characterized by pleuroparenchymal fibroelastosis [11].

2.4.2 Antineoplastic Drugs (Molecularly Targeted Drugs)

Gefitinib is an anti-EGFR agent used in patients with non-small cell lung cancer (NSCLC). The frequency with which it causes lung toxicity differs in different ethnic groups. The incidence of gefitinib-induced DILD is 2–6% in Japanese, whereas

it is between a tenth and a sixth of this figure in Caucasians [3, 12]. Mortality resulting from DILD caused by this drug is reported to be 31.6% in Japanese patients [13]. DILD frequently develops 2–3 weeks after the start of therapy. Risk factors for gefitinib-induced acute lung injury (ALI) and interstitial pneumonia include an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or higher, a history of smoking, the presence of a comorbid interstitial pulmonary disease at the time of drug initiation, and a history of chemotherapy [4]. The reported number of DILDs caused by gefitinib was the highest soon after its launch and has decreased in recent years (Table 2.4).

Erlotinib is also an anti-EGFR agent used for NSCLC. In the post-marketing surveillance of erlotinib used for second-line or later therapy in Japan, ILD was observed in 429 (4.3%) of 9909 patients, and the mortality of those who developed ILD was 35.7% (153/429). In Western countries, the frequency of DILD is less than 1% [14, 15], although two out of seven patients died according to one report [15]. When erlotinib was used in combination with paclitaxel plus carboplatin, there were five severe ILD-like events in the erlotinib arm (1.0%), versus one event in the placebo arm (0.2%). All ILD-like events in the erlotinib arm were fatal [16].

Osimertinib is a third-generation EGFR-TKI that is indicated for EGFR T790 M mutation-positive, inoperable, or relapsed NSCLC. In a phase II clinical trial, ILD was reported in 11 (2.7%) of 411 patients and 5 (6.3%) of 80 Japanese patients.

Bevacizumab is a recombinant humanized monoclonal antibody that blocks angiogenesis by inhibiting vascular endothelial growth factor (VEGF). It is used to treat colorectal cancer, NSCLC other than squamous cell carcinoma, ovarian cancer, and malignant glioma. Pulmonary complications with bevacizumab include hemorrhage, tracheoesophageal fistula, and thromboembolic disease. The incidence of interstitial pneumonia is reported to be 0.4% [5].

Sunitinib is used to treat gastrointestinal stromal tumors, renal cell carcinomas, and pancreatic neuroendocrine tumors. The frequency of interstitial pneumonia is relatively high in Japan, with a reported incidence of 2.2% [5]. However, sunitinib-induced pneumonitis is rare in other countries [17].

Sorafenib is a multi-kinase inhibitor which interacts with multiple intracellular (CRAF, BRAF, and mutant BRAF) and cell surface (KIT, FLT-3, VEGFR-2, VEGFR-3, and platelet-derived growth factor receptor-B (PDGFR-B) kinases. Sorafenib has been approved for the treatment of renal cell carcinoma, hepatocellular carcinoma, and thyroid cancer. Clinical trials are ongoing to investigate the efficacy of sorafenib in other types of tumors. In a post-marketing surveillance in Japan, the frequency of lung toxicity associated with sorafenib was only 0.46% (62/13,600), but its mortality was as high as 41% (25 of 62) [18]. In this report, CT evaluation was possible in 33 patients, and 18 out of the 33 patients showed diffuse alveolar damage. Twelve of the 18 patients had a fatal outcome [18].

Trastuzumab is a monoclonal antibody that interferes with the human epidermal growth factor receptor 2 (HER2). It is used for the treatment of breast cancer and gastric cancer. The frequency of lung toxicity is reported to be less than 1% [19], but in Japan the reported number has recently been increasing (Table 2.4). Although the incidence is low, there are occasional fatalities. Acute respiratory distress syndrome,

interstitial pneumonia, and organizing pneumonia have been reported to be associated with trastuzumab therapy.

Patients with symptomatic lung disease, or with extensive tumor involvement of the lungs, resulting in dyspnea at rest, appear to experience more severe toxicity [19].

Crizotinib, ceritinib, and alectinib are inhibitors of anaplastic lymphoma kinase (ALK), and they are used for ALK-positive NSCLC. The incidences of interstitial pneumonia caused by crizotinib, ceritinib, and alectinib are reported to be 1.7, 1.4, and 1.7%, respectively [5]. One report showed that ILD developed in 5 out of 29 patients who underwent crizotinib treatment, and there were two types of ILD: one was a severe, usually fatal type of ILD that occurs during the first month of treatment, and another was a less severe ILD, occurring later [20].

Mammalian target of rapamycin (mTOR) inhibitors are known to be associated with a high incidence of DILD (Table 2.4). One report showed that patients who developed pneumonitis during treatment with mTOR inhibitor had more favorable response to the treatment than those without pneumonitis, supporting the hypothesis that the emergence of pneumonitis might be a marker of therapeutic benefit [21].

Temsirolimus is an mTOR inhibitor approved for the treatment of renal cell carcinoma. Pneumonitis associated with temsirolimus is seen in 5–30% of patients [5, 21, 22]. Although it can be fatal, ILD caused by temsirolimus is generally mild, and some patients can continue to use the drug even after the development of ILD [21].

The frequency of lung injury caused by everolimus is 13–23%, and many of the cases are reversible, as is seen with temsirolimus [23, 24].

2.4.3 Immune Checkpoint Inhibitors

Checkpoint inhibitors are immunomodulatory antibodies. Drugs targeting programed cell death-1 (PD-1) receptor (pembrolizumab, nivolumab) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) (ipilimumab) are used clinically. These agents have been approved for melanoma, and nivolumab and pembrolizumab have also been approved for use in NSCLC. Checkpoint inhibitors can cause a variety of harmful events associated with their immunomodulatory function.

Clinical trials revealed that immune-related pneumonia developed in 0.4–4% of patients with advanced malignant melanoma following treatment with nivolumab. According to data from the PMDA, ILD caused by nivolumab is seen in 5.3% of patients [5] (Table 2.4).

A total of 80 patients given nivolumab were reported to develop DILD (57 had NSCLC, 22 had melanoma, and 1 had gastric cancer). Recovery or remission was seen in 51 out of the 80 patients, and 11 patients died (Table 2.5).

Gettinger et al. reported clinical, radiographic, and pathological features of pneumonitis in 24 affected patients with NSCLC receiving a PD-1 axis (anti-PD-1 and anti-PD-L1) inhibitor [25]. Median time to onset of the pneumonitis was 75 days (range, 8–549 days). Nineteen patients were treated with steroids, and pneumonitis resolved to grade 1 or 0 in all cases. There were three types of chest CT findings:

organizing pneumonia was the most frequent pattern (52%), followed by ground glass type (28%), nodular type (8%), and their combinations (12%). Six patients were re-challenged with a PD-1 axis inhibitor, and four patients developed recurrent pneumonitis. Although DILD due to PD-1 axis inhibitors is generally corticosteroid responsive, re-challenge might be associated with a high risk of recurrence. Limited data show that anti-TNF-α drugs may be effective in some patients who have a poor response to corticosteroids. Further information is necessary on the characteristics and optimal treatment for DILD caused by nivolumab. Severe myasthenia gravis leading to death has also been reported.

The frequency of ILD caused by ipilimumab is reported to be 0.4–1.6% in clinical trials and less than 1% of patients in Japan [5]. DILD caused by ipilimumab can sometimes be fatal. Developments of sarcoidosis [26] and organizing inflammatory pneumonia [27] have also been reported.

In a phase Ib trial of osimertinib (a EGFR-TKIs agent) combined with durvalumab (an anti-PD-L1 antibody) in EGFR-mutant NSCLC (TATTON trial), DILD was seen in 13 out of 34 patients (38%) in the combination regimen group [28]. In addition, a case of fatal DILD was reported in Japan, when osimertinib was started 29 days after nivolumab was discontinued. Further data accumulation is necessary to elucidate if combining EGFR-TKIs and checkpoint inhibitors may increase the risk of DILD. It is important to have knowledge about specific complications when using checkpoint inhibitors.

2.4.4 Antirheumatic Drugs

During the clinical course of rheumatoid arthritis (RA), a variety of lung diseases can occur including ILD associated with RA and pulmonary infections. In addition, DILD caused by disease-modifying antirheumatic drugs (DMARDs) represented by methotrexate is not infrequent. Occasional cases of penicillamine-induced bronchiolitis, gold lung, and sulfasalazine-induced pneumonitis have long been reported, followed recently by lung injury caused by leflunomide and anti-TNF agents, which has sparked concerns over the safety of these drugs.

2.4.4.1 Methotrexate

As it is often used in combination with other drugs and because of the influence of RA itself, it is not clear how often lung injury is caused by methotrexate. In the 1990s, incidences of 1–5% were reported in Japan [4], and the reported number of cases of methotrexate-induced DILD in Japan is constantly high (Table 2.3). However, it is speculated that DILD that is definitely caused by methotrexate may be rare. Mortality estimates from methotrexate-induced pneumonitis vary but are around 20% in most series [29].

The risk factors for methotrexate-induced lung injury during the treatment of RA include being older than 60 years, rheumatoid pleuropulmonary involvement,

previous use of DMARDs, hypoalbuminemia (either before or during therapy), and diabetes mellitus [30].

Hyperinsulinemia may increase the risk of ILD by increased polyglutamation of methotrexate [31]. Hypoalbuminemia can also increase the risk of DILD by lowering the degree of protein binding and increasing free levels of methotrexate. Other risk factors include higher weekly doses of methotrexate, abnormal pulmonary function tests prior to therapy, and decreased elimination of methotrexate by renal insufficiency or ascites.

2.4.4.2 Leflunomide

Leflunomide is one of the drugs, the lung toxicity of which differs between patients from Western countries and Japan. A survey from Japan reported acute pneumonitis in leflunomide-treated patients with a national incidence of 0.5%, which is five times greater than that encountered in Western countries [29, 32]. Another study from Japan showed that 61 (1.2%) of 5054 RA patients who received leflunomide were reported to have developed and/or had an exacerbation of ILD [33]. Risk factors associated with lung injury include preexisting interstitial pneumonia, use of a loading dose, cigarette smoking, and low body weight [33]. It is pointed out that leflunomide was frequently used in combination with methotrexate, or in patients with preexisting lung disease, which may be the reason for this high frequency of complications.

2.4.5 Interferon

Interferon is used for the treatment of kidney cancer, myeloma, and leukemia and nonmalignant diseases such as type B and type C hepatitis. A variety of lung toxicities have been reported in association with interferon use, including interstitial pneumonitis, pleural effusion, bronchiolitis obliterans-organizing pneumonia, and exacerbation of sarcoidosis. The incidences of interstitial pneumonia and pulmonary fibrosis are reported to be less than 5% and less than 0.1%, respectively [5]. The reported number of interferon-induced DILD cases in Japan has decreased over time (Table 2.3). Combination treatment with Sho-saiko-to increases the risk of DILD, and so it is contraindicated to use this combination. A literature search revealed that the mortality rate was 7% in patients who developed pneumonitis during treatment with peginterferon alfa-2b [34].

2.4.6 Amiodarone

Amiodarone is a representative anti-arrhythmic agent which can cause DILD (Table 2.3). Its long half-life causes long-lasting major adverse effects including pulmonary toxicity.

Although the precise incidence of ILD caused by amiodarone is unclear, it is reported to be 1–11% [35–37]. The risk factors for DILD caused by amiodarone include a higher daily dose (≥400 mg/day), higher total cumulative dose, increasing age, male gender, preexisting lung disease, renal disease, and lower pretreatment diffusing capacity of the lungs for carbon monoxide [4, 35, 36]. It occurs most commonly during the first 12 months of therapy, but DILD can also develop later in the clinical course [36–38].

One study showed that there were no cases of pulmonary toxicity when the maintenance dose was below 305 mg/day [36], whereas a retrospective series of 500 Japanese patients found that an average daily maintenance dose of 141 mg was associated with an incidence of amiodarone lung toxicity of 11% at 5 years [37].

2.4.7 Herbal Medicine

In Japan, about 140 kinds of herbal medicine are approved by health insurance, and all of these drugs contain several components. Sho-saiko-to, used for type C hepatitis, is the most widely known herbal medicine which causes severe ILD (Table 2.3). Ogon is one of the components of Sho-saiko-to, and it is also contained in many herbal medicines which cause DILD. Therefore, it is speculated that ogon may be the component that is responsible for causing DILD. In 1996, 10 cases of DILD considered to be caused by Sho-saiko-to were reported, and urgent safety information was issued. Nationwide surveillance was conducted in response to the report, and the results found 100 patients who experienced a Sho-saiko-to-induced lung injury. Although 90 patients recovered quickly, the other 10 died [4].

Due to the spreading recognition of the fact that herbal medicine can cause DILD and the decreased in use of herbal medicine, cases of DILD caused by herbal medicine have decreased in number.

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Chapter 3
Clinical Characteristics of DLI: What Are the Clinical Features of DLI?

Atsuhito Ushiki and Masayuki Hanaoka

Abstract While DLIs can have a variety of clinical manifestations, drug-induced interstitial pneumonia has been found to occur at the highest frequency. The clinical feature of 165 cases of drug-induced interstitial pneumonia occurring in medical institutions across Japan was as follows. Common subjective symptoms included difficulty breathing, fever, and coughing, but there were also 17 cases that were asymptomatic. The most frequent causative drug was drug for malignant neoplasms in 92 cases. The period from the start of drug administration to the development of symptoms ranged from 2 to 8280 days, with a median of 69. The median serum KL-6 were elevated at 623 U/mL. With a normal upper limit for KL-6 of 400 U/mL, the number of cases exhibiting an elevated value was 138 cases. As treatment, the suspected drug was discontinued in 159 cases, and corticosteroids including pulse therapy were used in 132. The outcomes were relatively favorable, ranging from a complete cure to an improved condition in 142 cases, but there were 5 fatalities.

Keywords Drug-induced interstitial pneumonia • Drug for malignant neoplasms • Molecularly targeted drug • Corticosteroids

3.1 Introduction

Drugs for molecularly targeted therapy and biological drugs have recently been developed and marketed. There has also been an increase in drug-induced lung injuries (DLIs) [1]. The following standard has been proposed for the diagnosis of DLIs [2]: (1) history of taking a drug that is known to be a causative factor; (2) having clinical manifestations reported to be caused by the drug; (3) other causative conditions can be ruled out; (4) clinical condition improves after discontinuing the drug;

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(5) exacerbation by resuming drug. However, in the actual clinical setting, it is often difficult to determine whether or not each of those items is applicable because the clinical picture for drug-induced interstitial pneumonia is varied. In addition, since there are no specific test procedures for diagnosing DLIs, it is ultimately necessary to perform a comprehensive diagnosis based on the medical history, physical findings, blood tests, and imaging examinations.

In terms of the prognosis of DLIs, there are many cases that resolve solely by discontinuing the causative drug, but there have also been more than a few fatal cases. Japan is considered to have a relatively high DLI incidence and mortality compared to other countries [1, 3, 4], and it is necessary to clarify this clinical picture. However, DLIs are relatively uncommon, and it is considered necessary to gather cases on a national scale.

While DLIs can have a variety of clinical manifestations, including interstitial pneumonia, airway lesions, and vascular lesions, this paper considers drug-induced interstitial pneumonia, which has been found to occur at the highest frequency.

3.2 Collecting Cases of Drug-Induced Interstitial Pneumonia

As part of a health and labor sciences research grant program from 2009 to 2011, we collected cases of drug-induced interstitial pneumonia jointly with Chiba University, Hiroshima University, and the Chuo General Hospital (now the Tokyo Yamate Medical Center). Furthermore, the Nippon Medical School and the National Institute of Health Sciences (NIHS) participated in the case collection from 2012 under a similar research program, building a system for gathering cases from hospitals across the country. In order to collect the cases efficiently and sufficiently, the pharmaceutical companies were requested to cooperate with this project by the Ministry of Health, Labour, and Welfare through the Federation of Pharmaceutical Manufacturers' Association of Japan. The medical institution that jointed with the case-collection project informed the event of drug-induced interstitial pneumonia to the pharmaceutical company through the Pharmaceuticals and Medical Devices Agency of Japan. At the same time, this information also reported to the NIHS. Then, the NIHS mailed a case card to the medical institution for recording of the clinical event of the patient. A physician of the medical institution obtained the consent of the patient, completed the case card, and mailed it back to the NIHS. All the case cards finally gathered in the Shinshu University, where the clinical feature of drug-induced interstitial pneumonia was analyzed.

3.3 The Clinical Feature of Drug-Induced Interstitial Pneumonia

The clinical picture of 165 cases of drug-induced interstitial pneumonia occurring in medical institutions across Japan was as follows. Note that absent special indication, the numbers given are the numbers of cases (percentage) or the median (minimum

value to maximum value). There were 115 (69.7%) men and 50 (30.3%) women aged 69 (25–97) years. Common subjective symptoms included difficulty breathing in 70 cases (42.4%), fever in 57 (34.5%), and coughing in 56 (33.9%), but there were also 17 (10.3%) that were asymptomatic (Table 3.1). There were 60 cases (36.7%) with a primary disorder, complication, or history of respiratory disease. There were 94 cases (57.0%) with a history of smoking, of whom 8 cases (4.8%) were current smokers and 86 (52.2%) were former smokers. The quantity of cigarette smoking was 40 pack-years (0.05–180 pack-years).

The causative drugs were indicated antineoplastic drugs in 92 cases (55.9%), antirheumatic drugs in 22 cases (13.3%), herbal medicine in 17 cases (10.3%), antiarrhythmic drugs in 8 cases (4.8%), antimicrobial drugs in 7 cases (4.2%), interferon in 3 cases (1.8%), and other drugs in 16 cases (9.7%). Thus, antineoplastic drugs constituted a majority of the causative drugs (Fig. 3.1). There were 40 cases (24.2%) in which a drug classified as molecularly targeted drug was the cause of drug-induced interstitial pneumonia. The period from the start of drug administration to the development of symptoms ranged from 2 to 8280 days, with a median of 69 days. Thirty-nine patients (24.5%) developed the drug-induced interstitial pneumonia within 30 days of drug administration, 72 patients (45.2%) developed it within 60 days, and 92 patients (57.9%) developed it within 90 days. In addition, 26 cases (16.4%) developed the drug-induced interstitial pneumonia after 360 days following the start of drug administration (Fig. 3.2).

Table 3.1 Symptoms of drug-induced interstitial pneumonia (with overlaps)

Symptoms	Number of cases (percentage)
Difficulty breathing	70 (42.4%)
Fever	57 (34.5%)
Coughing	56 (33.9%)
Expectoration	9 (5.4%)
Reduced appetite	6 (3.6%)
None	17 (10.3%)

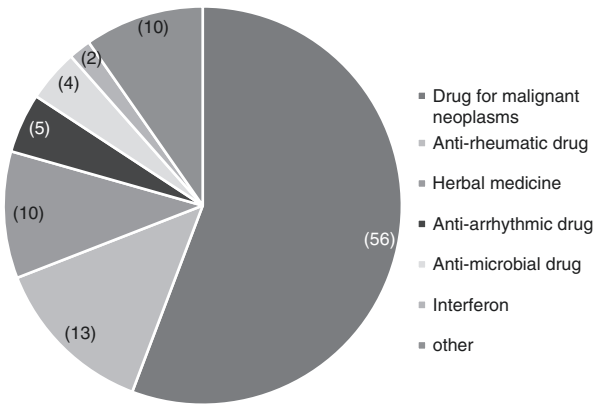

Fig. 3.1 Number of cases (percentage) by causative drug

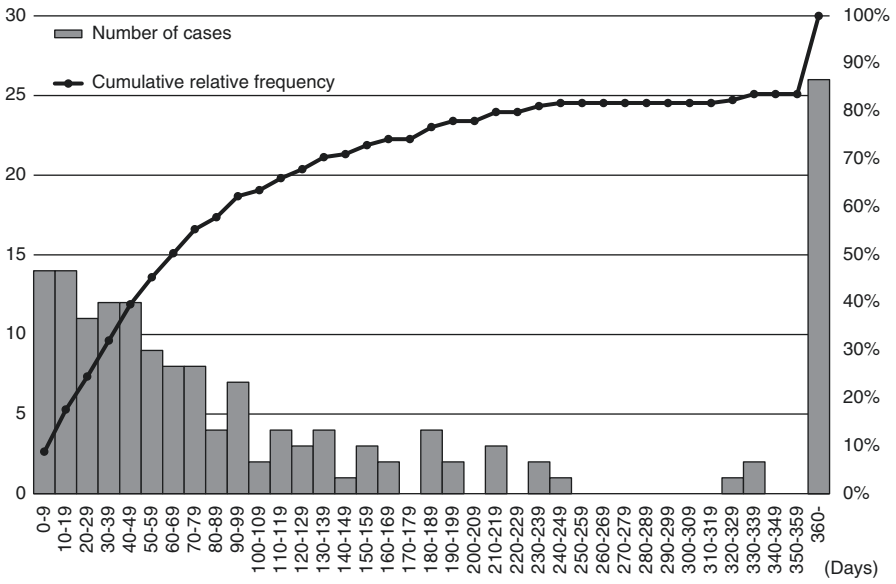

Fig. 3.2 Number of days from drug administration to development of symptoms

In the physical findings, percutaneous oxygen saturation (SpO_2) was at least 90% in 72 cases (43.6%), less than 90% in 35 cases (21.2%), and no data of SpO_2 in 58 cases (35.2%). Chest auscultation findings included fine crackles in 65 cases (35.2%), coarse crackles in 6 cases (3.6%), wheeze in 3 cases (1.8%), and rhonchi in 2 cases (1.2%). There were 30 cases (16.4%) in which rales were not heard during chest auscultation. However, there were also 59 cases (58.2%) in which the chest auscultation findings were no data.

In the blood tests, the white blood cell (WBC) count was measured in 162 cases. With a normal value of 7035/μL, there was a significant variation of the WBC count, ranging from a minimum of 1800/μL to a maximum of 31,480/μL. The C-reactive protein (CRP) was measured in 150 cases, which showed slight elevation at 4.51 mg/dL (0–29.6 mg/dL). The lactate dehydrogenase (LDH) that commonly increases in interstitial pneumonia was measured in 157 cases, which showed an elevation at 284 IU/L (120–984 IU/L) as well in this study. The serum Krebs von den Lungen-6 (KL-6), surfactant protein-D (SP-D), and surfactant protein-A (SP-A), those that are thought to be relatively specific to interstitial pneumonia, were measured in 146, 86, and 31 cases, respectively, with elevation at 623 U/mL (145–11,280 U/mL), 124 ng/mL (13.2–1080 ng/mL), and 67.4 ng/mL (32.6–161 ng/mL) correspondingly (Table 3.2). With the normal upper limits for KL-6, SP-D, and SP-A of 400 U/mL, 110 ng/mL, and 43.8 ng/mL, respectively, the number of cases exhibiting elevated values were 138 (94.5%), 48 (55.8%), and 24 (77.4%), respectively.

In imaging examinations using high-resolution chest computed tomography (CT), 138 cases (83.6%) exhibited bilateral ground-glass opacity or infiltrative shadows, while there were 23 cases (13.9%) with unilateral shadows.

In tests of respiratory function, the percentage of the predicted values for vital capacity was 88.6% (43.2–119.8%) (21 cases measured), while the forced expiratory

volume in one second (FEV_1) was 91% (48.2–123.7%) of the predicted value (23 cases measured), which was in the normal range. The FEV_1/forced vital capacity (FVC) ratio was measured in 23 cases, and 4 cases (17.4% of those measured) showed the value of less than 70%. Diffusing capacity was measured in 15 cases and decreased to 56.3% (28.0–103.3%) of the predicted value.

Bronchoscopic examinations were performed in 67 cases, and cell fractionation from bronchoalveolar lavage fluid yielded diverse results with dominance of lymphocyte (at least 15%) in 52 cases (77.6%), dominance of eosinophil (at least 1%) in 48 cases (71.6%), and dominance of neutrophil (at least 3%) in 35 cases (52.2%).

The drug lymphocyte stimulation test (DLST) was performed in 69 cases, yielding a positive result in 30 (43.5%).

As treatment, the suspected drugs were discontinued in 159 cases (96.4%), and corticosteroids including pulse therapy were used in 132 cases (80.0%). Furthermore, for severe cases, sivelestat was used in seven cases (4.2%), cyclosporine was used in two cases (1.2%), and endotoxin adsorption therapy was used in one case (0.6%). Respiratory management involved six cases (3.6%) requiring noninvasive positive-pressure ventilation and three cases (1.8%) using intratracheal intubation and artificial respiration management.

The prognosis was relatively favorable, ranging from complete cure to improved condition in 142 cases (86.1%), but there were five (3.0%) fatalities (Fig. 3.3).

Table 3.2 Blood test findings for drug-induced interstitial pneumonia

Test	Number of measured cases	Median	Range
WBC (/μL)	162	7035	1800–31,480
CRP (mg/dL)	150	4.51	0–29.6
LDH (IU/L)	157	284	120–984
KL-6 (U/mL)	146	623	145–11,280
SP-D (ng/mL)	86	124	13.2–1080
SP-A (ng/mL)	31	67.4	32.6–161

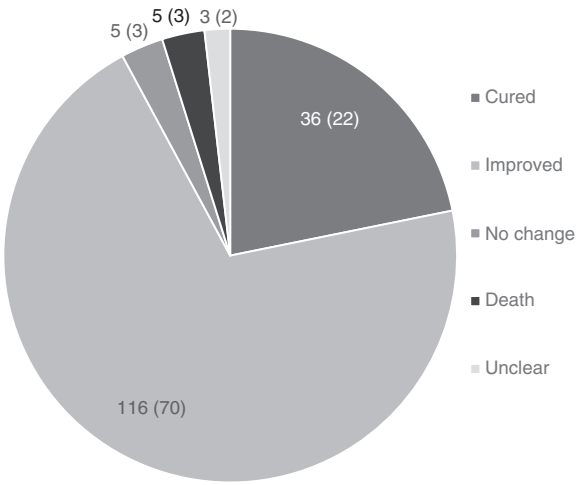

Fig. 3.3 Prognosis. The data were shown number of cases (percentage)

3.4 Summary of Clinical Feature

In other words, the clinical feature for drug-induced interstitial pneumonia is varied, and a final diagnosis is not easy to achieve. Nevertheless, our investigation suggests that it is essential to promptly evaluate the related symptoms in patients who are administered a drug that is known to induce drug-induced interstitial pneumonia with high frequency, such as a drug for malignant neoplasms, within the past 3 months, with exhibitions of bilateral shadows in chest CT and elevations of serum KL-6, SP-D, or SP-A levels.

Among the cases of current study, approximately 40% of the cases showed SpO_2 of at least 90%, and approximately 35% of cases were not measured SpO_2. The cases in which SpO_2 were not measured were likely to have relatively mild symptoms without respiratory complaints, such as difficulty breathing or coughing. Therefore, it is believed that most of the cases had relatively mild symptoms, including cases with an SpO_2 of at least 90%, in this study.

On chest auscultation, many cases had fine crackles. This can be heard in early stage of interstitial pneumonia, even without findings on chest radiographs, and is an extremely useful indicator for early detection of interstitial pneumonia. In the current study, there were some cases without chest auscultation, but auscultation is a useful examination for the detection of drug-induced interstitial pneumonia, which can be performed with just a stethoscope, and should be performed as a part of routine clinical care.

DLST is not covered by medical insurance for DLIs in Japan but is commonly performed, and a positive rate of 66.9% is reported for drug-induced pneumonia [5]. However, as in the case of the herbal medicine, Sho-Saiko-To has the ability to stimulate lymphocytes, and false positive were reported [6]. Conversely, dugs that suppress lymphocyte function such as minocycline hydrochloride can cause false negatives [7]. Thus, it is not recommended to diagnose DLIs or identify the causative drug with DLST alone. The results of DLST should merely serve as a reference.

Discontinuation of the causative drug was performed as a part of the treatment in nearly all cases, but there were also many cases that improved DLIs with this measure alone. The molecularly targeted drug everolimus caused drug-induced interstitial pneumonia at the very high frequency of approximately half of the treated patients. On the other hand, continuing or resuming administration after cessation is possible in mild cases, a situation differing greatly from the treatment of conventional drug-induced interstitial pneumonia, for which drug resumption is contraindicated.

3.5 Conclusion

The clinical feature of drug-induced interstitial pneumonia obtained from the current study is summarized as follows:

1. Symptoms of difficulty in breathing, fever, and coughing developed after administration of the causative drugs (approximately 60% of cases occurring within 3 months).

2. The causative drugs were quite varied but were most commonly indicating for malignant neoplasms.
3. Serum levels of KL-6, SP-D, or SP-A were elevated in a large majority of cases.
4. In chest CT, bilateral infiltrative shadows or ground-glass opacity were common.
5. There were no specific features in the cell fractionation of bronchoalveolar lavage fluid.
6. The DLST-positive rate was 43.5%.
7. Most cases were improved by discontinuing the causative drug and administering corticosteroids, but there were five5 (3.0%) fatalities.

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Part II
Diagnosis

Chapter 4
Diagnostic Approach for DLI: How is DLI Diagnosed?

Shu Hashimoto, Mari Hikichi, Mai Takahashi, and Yasuhiro Gon

Abstract When diagnosing drug-induced lung injuries, one must always remember that lung injuries can be caused by any drug and that the injuries occur not only during treatment but also after completing a course of treatment. When a new lung lesion emerges, the onset of drug-induced lung injury should be considered, while also differentiating it from the worsening of a pulmonary/pleural lesion that a patient may have already had as an underlying disease and from the opportunistic infections—particularly when the patient has reduced immunity and defense against such infections.

Keywords Diagnostic procedure • Differential diagnosis • Diagnostic criteria • Diagnostic step

4.1 Diagnostic Criteria

Figure 4.1 shows points that are suggestive of drug-induced lung injury. If drug-induced lung injury is suspected, the diagnosis should be made according to the diagnostic criteria for the injury [1] (Table 4.1). Steps should be taken to reach a diagnosis based on the procedure, while also identifying the likely causative drug [1, 2] (Table 4.2) and discontinuing any drug thought to have been involved in the onset.

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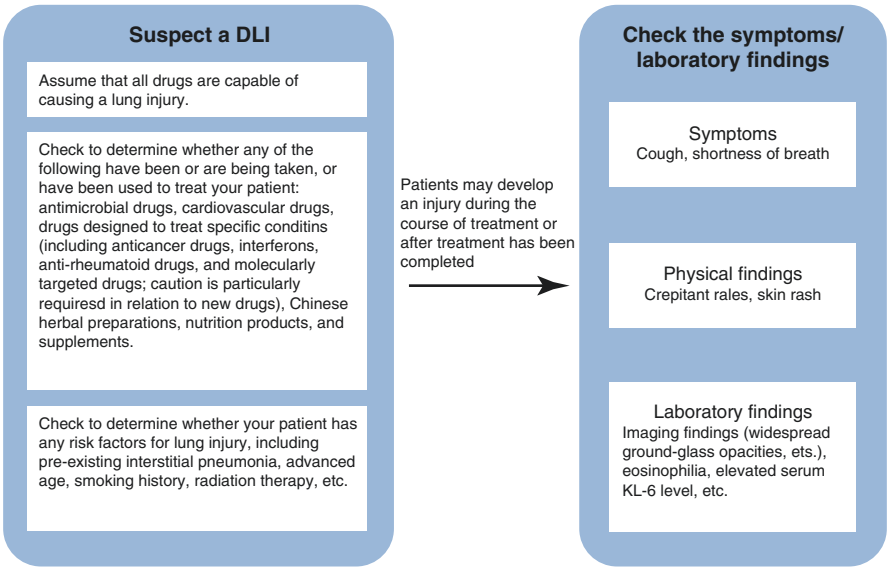

Fig. 4.1 Approach for diagnosing DLIs in daily medical practice [2]

Table 4.1 Diagnostic criteria for DLIs [2]

1.	History of ingestion of a drug that is known to induce lung injury	Specifically inquire about the following when taking the patient's history: over-the- counter (OTC) drugs, health foods, and illegal narcotic drugs/antihypnotic drugs
2.	The clinical manifestations have been reported to be induced by a drug	The clinical manifestations include clinical findings, imaging findings, and pathological features
3.	Other causes of the clinical manifestations could be ruled out	Differentiation from infection, cardiogenic pulmonary edema, exacerbation of an underlying disease, etc
4.	Improvement of the clinical manifestations after drug discontinuation	Spontaneous remission or remission in response to an adrenocorticosteroid
5.	Exacerbation of the clinical manifestations after resuming drug administration	Resuming drug administration to identify the causative drug is not generally recommended, but is acceptable if the patient requires the drug and safety is assured

Table 4.2 Diagnostic steps for DLIs [2]

Identification of the causative drug
(1) Detailed medical history To investigate the possibility that a drug, health food, supplement, home-made food, illegal substance, additive, or radiation therapy may have caused the injury
(2) Focus on a single drug If the patient is using several different drugs, the possibility that any one of the drugs caused the lung injury should be assessed by checking the side effects pulmonary reaction patterns to each drug
(3) Identification of the responsible drug a. As DLIs may develop at any time during or after drug administration, all past and currently administered drugs are candidates. It should be noted that the interval between drug use and symptom onset differ from patient to patient b. All symptoms of DLIs, except pulmonary fibrosis, should ideally resolve after discontinuation of the suspected drug. Thus, to be certain that the symptoms have resolved as a result of discontinuing the suspected drug, whenever possible, adrenocortical steroids should not be used c. Recurrence of the injury after resumption of drug administration may provide validation for the suspected drug being the causative agent. However, resumption of drug administration may risk symptom exacerbation or death of the patient. Adequate informed consent is required before resuming administration
The characteristic clinical features, BALF findings, and pathological findings of DLIs are needed to make a differential diagnosis between DLIs and infections/pulmonary lesions of underlying diseases
(1) Clinical manifestations Identification of causes of respiratory symptoms, such as cough and dyspnea a. DLI b. Pulmonary and pleural lesions of underlying diseases c. Pathological conditions of underlying diseases (heart failure, renal failure, etc.) d. Concomitant infection
(2) Physical findings Skin rash, rales, etc
(3) Clinical laboratory findings Blood tests: eosinophil count, liver function test values, serum KL-6, SP-A, SP-D, LDH, and β-D glucan levels
(4) Chest X-ray and chest CT findings Imaging findings corresponding to the clinical manifestations and pathological findings of DLIs can be obtained
(5) Respiratory function tests Restrictive ventilatory impairment and diffusion impairment
(6) Bronchoalveolar lavage fluid (BALF) a. Exclusion diagnosis Diagnosis of malignant diseases: evidence of malignant cells Diagnosis of infection: bacteriological diagnosis and gene diagnosis of pathogens b. Suspected case of DLI: an increase in total cell count; increases in the numbers of eosinophils, lymphocytes, and neutrophils, depending on the pathology
(7) Histopathological examination of lung biopsy specimens Diffuse alveolar damage, non-specific interstitial pneumonitis, eosinophilic pneumonia, bronchiolitis obliterans, organizing pneumonia, hypersensitivity pneumonia, etc., are diagnosed histopathologically
(8) Drug lymphocyte stimulation test Positive rate is high in patients who developed the injuries due to a type IV allergic reaction
(9) Resumption of administration to identify the causative drug Informed consent is necessary

4.2 Diagnostic Procedures and Differential Diagnosis

4.2.1 Symptoms, Medical Interview, Physical Findings, and History of Drug Use

4.2.1.1 Symptoms

Subjective symptoms form important evidence for diagnosing drug-induced lung injuries. Relationships between subjective symptoms such as cough, sputum, and dyspnea and the timing of drug initiation and switching, dosage, and duration are factors on which suspicion of drug-induced lung injuries can be based. In addition, the course of development of respiratory symptoms such as dyspnea is important in determining the severity of drug-induced lung injuries and, in particular, acute-onset respiratory failure, which requires differential diagnosis and prompt treatment. Major respiratory symptoms include dyspnea, dry cough, chest pain (pleurisy or pleural effusion), wheezing (airway lesion), and bloody sputum (alveolar hemorrhage). Particular attention should be paid to differentiation from pulmonary infections and edema. Even in the absence of major subjective symptoms, the suspicion of drug-induced lung injury may be aroused by reduced percutaneous oxygen saturation, the emergence of a new abnormal shadow in the chest X-ray, or pleural effusion. Important systemic symptoms associated with dyspnea include fever, rash, and fatigue. Drug-induced hypersensitivity syndrome typified by hypersensitivity to antiepileptic drugs, which involves rash and increased eosinophils in the peripheral blood, is classified as drug-induced generalized disorders, and a case with accompanying lung injury has been reported [3].

4.2.1.2 Medical Interview

The diagnosis of drug-induced lung injury is made based on the temporal relationship between drug intake and onset and by ruling out other causes. Thus, it is important to collect information through interviews. The core of the diagnosis is entirely formed from pieces of information collected through interviews, such as the history of using a suspected causative drug, relationships between drug administration and exacerbation/remission of clinical findings, consistency with the reported clinical disease type, and the presence or absence of worsening when drug use is resumed. The clinical application of Camus' diagnostic criteria shown in Table 4.1 requires knowledge of drugs that can cause drug-induced lung injuries and clinical disease types associated with individual drugs. Knowledge of infections, cardiogenic pulmonary edema, and underlying diseases is also necessary to make a differential diagnoses. Adequate information on risk and prognostic factors of drug-induced lung injuries can be obtained by means of interviews.

4.2.1.3 Physical Findings

Examinations should include vital signs, percutaneous arterial blood oxygen saturation (SpO_2), and visual inspections of and palpation for rash, oral mucosa, and superficial lymph node enlargement. To assess the respiratory status, a patient should be checked for increased respiratory rate and reduced percutaneous arterial oxygen saturation after exertion. On chest auscultation, a patient should be checked for asymmetry and any crackling breath sounds and for airway diseases during deep inspiration and forced expiration. As abnormalities are not always noticeable on auscultation in the early stages of lung damage, obstructive bronchiolitis, and some other lung conditions, assessments should be complemented with information on symptoms, imaging findings, and respiratory function results.

4.2.1.4 History of Drug Use

Drugs that can cause lung damage are not only limited to those administered by medical institutions as insurance-covered medical care but also include over-the-counter drugs, illegal narcotics/stimulants, and remedies and food products used in folk medicine. With respect to the modes of inducing respiratory symptoms, some drugs cause symptoms similar to adverse reactions that are predictable from the original drug actions, such as bronchospasm induced by β-blockers and respiratory suppression induced by sedatives, while symptoms induced by other drugs are unpredictable adverse reactions related to allergic or idiosyncratic drug reactions. The latter type of symptoms can be further divided into dose-dependent direct cell-damaging or cytotoxic effects of, for example, anticancer agents and drug reactions due to hypersensitivity or immune reactions. In either case, the diagnosis of drug-induced lung injury cannot be established without information on the history of drug use. Therefore, a patient's history of drug use should be carefully recorded, particularly when there is no other likely cause and drug-induced lung injury is suspected.

4.2.2 Flowchart of the Diagnosis/Differential Diagnosis

Figure 4.2 shows a flowchart for the diagnosis.

4.2.3 Significance of Different Tests

4.2.3.1 Chest Imaging

Before drug administration, the presence of any preexisting pulmonary or pleural lesion should be confirmed. In particular, findings of interstitial pneumonia and pulmonary fibrosis are risk factors for drug-induced lung injury and are contraindications

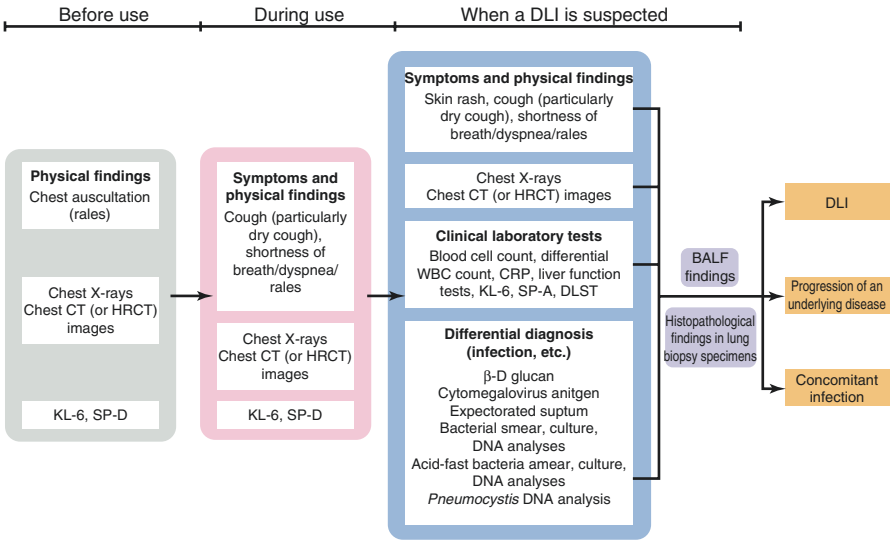

Fig. 4.2 Flowchart for diagnosing a DLI [2]

for some drugs. Drugs required for disease treatment, such as antirheumatic drugs, should be selected from those that rarely damage the lung and should be used with adequate caution. As subtle early changes are difficult to detect on chest plain radiography, chest computed tomography (CT) is an essential modality for the early detection of lung injuries. When a new respiratory symptom emerges, decisions should only be made after comparison with imaging findings from pre-administration examinations. Worsening of a preexisting lung lesion and infection should be explored using various methods in combination, such as drug serum markers and respiratory function tests, while keeping the onset of drug-induced lung injury in mind. The involvement of a drug should be suspected in cases of pneumonia that are refractory to antibiotics or are not accompanied by appreciable infection symptoms. Imaging findings collected over time, such as those collected over the course of treatment for a pulmonary lesion and those following improvement of the lesion after discontinuing the drug, are useful for diagnosing drug-induced lung injuries and assessing the therapeutic response.

4.2.3.2 Respiratory Function Tests

Tests corresponding to abnormal shadows observed on images over time are arterial blood gas analysis and SpO_2 measurement. Reduced DL_{CO} (carbon monoxide diffusing capacity: lung diffusing capacity) is recognized as an aberrance from the early stage. Conventional lung volume measurement is not always performed as an

index in the acute phase. Because hyperventilation often accompanies and makes unnoticeable the reduced PaO_2 (oxygen partial pressure: arterial oxygen partial pressure), attention should also be paid to changes in $PaCO_2$ (carbon dioxide partial pressure: arterial carbon dioxide partial pressure). A-aDO_2 (alveolar-arterial gradient of oxygen pressure) and PaO_2/FIO_2 (fraction of inspired O_2 concentration: inspired oxygen concentration) under room air intake are useful for the evaluation of the gas exchange capacity.

4.2.3.3 Blood Biochemistry/Immunological Tests

A finding of increased peripheral blood eosinophils is suggestive of an allergic mechanism. Some drugs may cause systemic organ damage, and hepatic, renal, and coagulation functions should be examined. KL-6 and SP-D are important markers that reflect drug-induced lung injuries [4, 5]. SP-D levels are often elevated to reflect the onset of lung injury. KL-6 is recommended as a marker over time, with the pre-administration value as a reference, and any change, even within the range of standard values, should arouse the suspicion of the onset of drug-induced lung injury. Elevated KL-6 levels also reflect existing interstitial pneumonia, exacerbation of pulmonary fibrosis, progression of lung cancer, and opportunistic infection and are thus used to narrow the differential diagnoses for lung lesions related to the underlying disease.

4.2.3.4 Bronchoscopy

Bronchoalveolar lavage (BAL) is a meaningful procedure for the differentiation of opportunistic infections, eosinophilic pneumonia, alveolar hemorrhage, and interstitial pneumonia during the diagnosis at the time of the onset of drug-induced lung injury. Increased eosinophils and lymphocytes in the cell fraction of BAL fluid in the confirmed absence of an infection constitute a basis for steroid therapy as well as the diagnosis.

Transbronchial lung biopsy (TBLB) is meaningful in making the differential diagnosis, including interstitial pneumonia of organizing pneumonia pattern, fungal infections such as pulmonary cryptococcosis, and lymphangitis carcinomatosa.

4.3 Summary

Any drugs can cause drug-induced lung injury. The injuries occur not only during treatment but also after completing a course of treatment. When a new lung lesion emerges, the onset of drug-induced lung injury should be considered, and diagnosis can be made following the diagnostic procedure.

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Chapter 5
Blood Tests for the Diagnosis and/or Management of DLI: What Are the Clinical Significances of KL-6, SP-A, SP-D, and DLST in DLI?

Yasushi Horimasu and Noboru Hattori

Abstract Blood tests can be used for the diagnosis or management of DLI, and those currently applicable for this purpose are as follows: (1) measurement of biomarkers reflecting non-specific systemic inflammatory response or tissue damage, (2) measurement of biomarkers derived from type II pneumocytes, and (3) drug-induced lymphocyte stimulation test. The biomarkers reflecting non-specific systemic inflammatory response, such as C-reactive protein, lactate dehydrogenase, and eosinophil count, can help monitor the disease activity and/or predict the treatment response. Previous Japanese studies suggest that type II pneumocyte-derived serum biomarkers such as KL-6, SP-A, and SP-D have the potential to aid the diagnosis, monitor the severity, and predict the efficacy of the treatment or the outcome in patients with DLI. Additionally, the drug-induced lymphocyte stimulation test can in part provide supportive information about the causative agents of DLI.

Keywords KL-6 • SP-A • SP-D • Drug-induced lymphocyte stimulation test

5.1 Introduction

Blood test, a laboratory analysis of a blood sample, helps to assess the general state of health, to detect the presence of diseases, to evaluate potential risk for developing a certain disease, to measure the efficacy of a certain treatment, and to predict the outcome. In the clinical management of DLI, blood tests, such as measurement of biomarkers reflecting non-specific systemic inflammatory response or tissue damage,

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measurement of biomarkers derived from type II pneumocytes, and the T lymphocyte stimulation test, have been reported to be useful in the diagnosis, identification of the causative agent, monitoring the severity, and predicting the efficacy of the treatment or the outcome. Although DLI cannot be diagnosed or managed only on the basis of such blood tests alone, they should be considered because they are cost effective, noninvasive, and more reproducible in comparison to other clinical examinations used to assess DLI, including high-resolution computed tomography (HRCT), pulmonary function tests, and bronchoscopy.

In this chapter, the usefulness of blood tests in diagnosing and/or managing DLI is discussed, focusing on the biomarkers derived from type II pneumocytes and the lymphocyte stimulation test.

5.2 Biomarkers for Non-Specific Systemic Inflammatory Response or Tissue Damage

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are representative biomarkers for a systemic inflammatory response. Lactate dehydrogenase (LDH) reflects the degree of tissue damage, and peripheral blood eosinophil count serves as a biomarker for allergic reaction. These biomarkers are not useful in diagnosing DLI but can be used for monitoring the disease activity and/or predicting the treatment response.

5.2.1 Biomarkers for Non-Specific Systemic Inflammation

ESR has been reported to be a useful biomarker for predicting clinical deteriorations and radiological changes in patients with pulmonary toxicity induced by bleomycin or gemcitabine [1, 2]. ESR levels have been reported to be higher than 100 mm/h prior to radiological change and to decrease after corticosteroid treatment. CRP, the classic acute phase reactant, inhibits chemoattractant-induced neutrophil inflammation [3]. Patients with amiodarone-induced pulmonary toxicity have been reported to show an abnormal elevation in serum CRP level [4] and high serum CRP levels were associated with poor outcome among the patients with leflunomide-induced lung injury [5].

5.2.2 Biomarkers for Tissue Damage

LDH reflects the damage of lung parenchyma, which contains abundant LDH activity under normal conditions and releases it into the circulation when damaged [6].

Its usefulness for assessing the disease activity and/or treatment response has been reported in various diffuse lung diseases including amiodarone-induced DLI [7, 8].

5.2.3 Biomarkers for Allergic Reactions

More than 160 drugs cause eosinophil infiltrations in the lung. Although the lung eosinophilia, confirmed by bronchoalveolar lavage (BAL) and/or lung biopsy, indicates eosinophilic pneumonia, the detection of peripheral blood eosinophilia may be helpful for diagnosing DLI with eosinophilic lung inflammation. Additionally, peripheral blood eosinophil count drops immediately after cessation of an offending drug and/or treatment with corticosteroids [9].

5.3 Biomarkers Derived from Type II Pneumocytes: KL-6, SP-A, and SP-D

5.3.1 Conceptual Background of Biomarkers Derived from Type II Pneumocytes

Under normal conditions, a tight and thin barrier is present between alveolar airspace and capillary bloodstream, comprising the alveolar epithelium and capillary endothelium with their adherent basement membrane to maintain effective gas exchange. This blood-air barrier prohibits the transfer of alveolar protein into the capillary, under normal conditions. However, in severe forms of lung injury, various inflammatory mediators including tumor necrosis factor (TNF)-α, matrix metalloproteinases, and transforming growth factor-β1 induce a marked increase in blood-air barrier permeability and significant alveolar epithelial damage [10]. Although detailed mechanism of increased alveolar protein leakage into the capillary is poorly understood, we can speculate that apoptotic cell death of type I pneumocytes and proliferative reaction of regenerative type II pneumocytes may increase paracellular permeability [10]. Additionally, hyperplasia of regenerative type II pneumocytes may induce a significant alteration in production and/or metabolism of type II pneumocyte-derived proteins [11]. Furthermore, decreased numbers of lymphatic vessels in the interlobular septa and visceral pleura may cause defects in the drainage framework, resulting in the abnormal accumulation of alveolar protein [12]. Therefore, type II pneumocyte-derived proteins directly represent peripheral lung damage, potentially indicating the presence or absence of interstitial lung diseases (ILDs), reflecting the disease activity, and predicting the outcome of the patients with ILDs. In the rest of this subchapter, we will discuss the three representative biomarkers derived from type II pneumocytes: Krebs von den Lungen-6 (KL-6), surfactant protein-A (SP-A), and SP-D in detail.

5.3.2 *Molecular Background of Biomarkers Derived from Type II Pneumocytes*

5.3.2.1 Molecular Basis of KL-6

In 1988, Kohno et al. developed a novel monoclonal antibody, named anti KL-6 antibody, by immunizing mice with human lung adenocarcinoma cells [13, 14]. Anti KL-6 antibody recognizes a sialylated sugar chain of mucin-1 (MUC1), a transmembrane high-molecular weight glycoprotein [13, 15]. Recently, Seko et al. identified three *O*-linked carbohydrates, which demonstrated high affinity to anti KL-6 antibody, as the putative epitope for anti KL-6 antibody (Fig. 5.1) [16].

Immunohistochemical analysis revealed that KL-6 is expressed at the apical membrane of type II pneumocytes and respiratory bronchiolar epithelial cells under normal conditions [14]. In lung tissues of interstitial pneumonias regenerative type II pneumocytes and the alveolar macrophages expressed KL-6 strongly [14]. Therefore, high serum KL-6 levels in patients with interstitial pneumonias can be explained by the increased amount of KL-6 expressed by regenerative type II pneu-

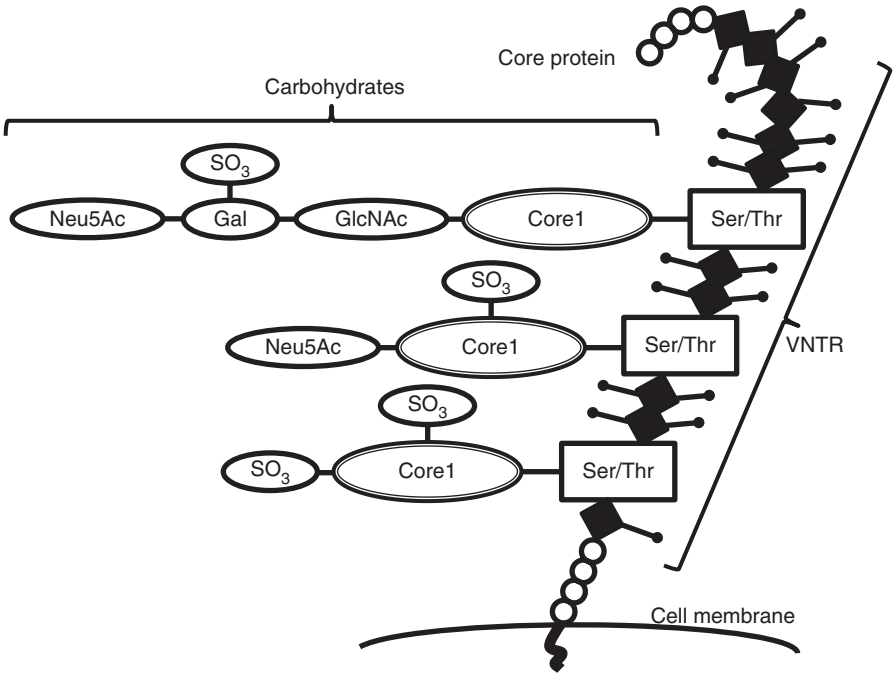

Fig. 5.1 A schematic drawing of MUC1 molecule and the putative epitopes of anti KL-6 antibody. The variable number of tandem repeat (VNTR) which covers mostly of the extracellular domain of MUC1 core protein contains a lot of serine (Ser) and threonine (Thr) residues. These residues are highly glycosylated by *O*-linked glycosylation and anti KL-6 antibody shows especially high affinity to the three core 1 glycans containing at least one sulfo group

mocytes and increased permeability of blood-air barrier. KL-6/MUC1 has been reported to possess chemoattractant, proliferative, and apoptosis-suppressing activity for the lung fibroblasts, suggesting the possibility of increased expression of KL-6/MUC1 in the lung being involved in the pathogenesis of ILDs by promoting fibroblast recruitment [17, 18].

5.3.2.2 Molecular Basis of SP-A and SP-D

In 1985, Kuroki et al. developed monoclonal antibodies against SP-A isolated from the lung lavage fluids of patients with alveolar proteinosis [19] and human recombinant SP-D derived from amniotic fluid [20].

SP-A and SP-D, the hydrophilic proteins in pulmonary surfactant, belong to the collectin subgroup of the C-type lectin superfamily and are synthesized mostly by type II pneumocytes and Clara cells within the lung. SP-A and SP-D molecules comprise trimeric polypeptide chains assembled into oligomers (Fig. 5.2). Each polypeptide chain contains an N-terminal domain (NTD), a collagen domain, an α-helical

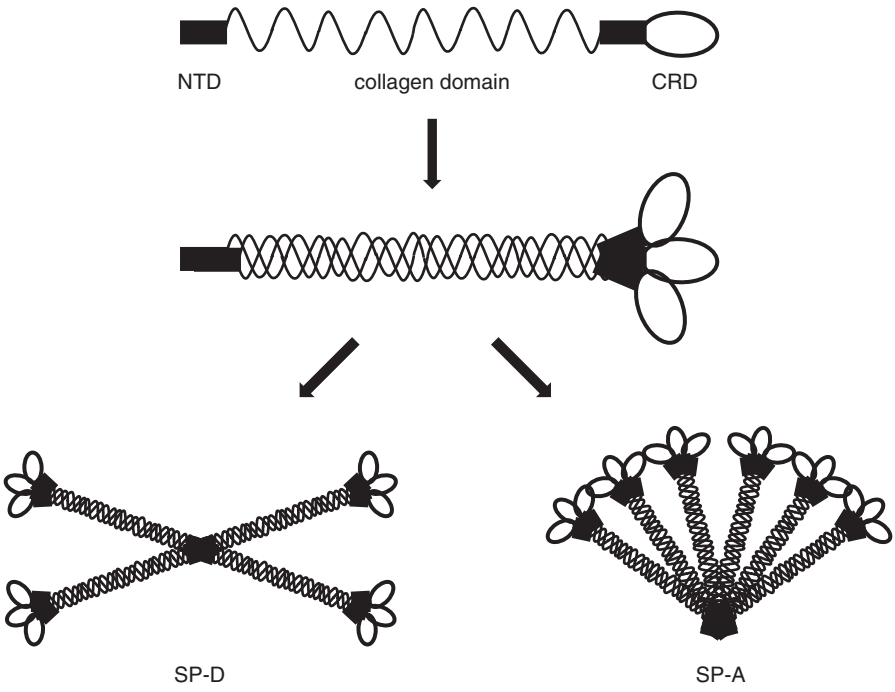

Fig. 5.2 Schematic drawings of SP-A and SP-D molecules. SP-A and SP-D molecules are comprised of trimeric polypeptide chains that are formed by the folding of the collagen domains into triple helices and coiled-coil bundling of α-helical neck region. The trimeric polypeptide subunits of SP-A assemble into a "flower bouquet" octadecamer, while the trimer of SP-D assemble into a cruciform dodecamer

neck region, and a carbohydrate recognition domain (CRD). SP-A and SP-D play important roles in the pulmonary innate immune systems; the CRD in both these molecules recognize and bind to pathogen-associated molecules, thus acting as agglutinins, opsonins, and immunomodulators [21]. Furthermore, they interact with various cell surface ligands on inflammatory cells including macrophages, thereby regulating phagocytosis and cellular inflammatory responses [22]. Although their direct role in the pathogenesis of interstitial lung diseases is still unclear, several studies have demonstrated the role of SP-A and SP-D in bleomycin-induced lung inflammation and/or fibrotic lung remodeling, indicating their important role in modulating inflammation or lung fibrosis induced by noninfectious challenges [23, 24].

5.3.3 Diagnostic Utilities of Biomarkers Derived from Type II Pneumocytes for DLI

5.3.3.1 Utility of Serum KL-6 for DLI Diagnosis

In Japan, the optimal cutoff value of serum KL-6 to distinguish patients with interstitial lung diseases from healthy subjects and from patients with other lung diseases has been set as 500 U/mL. Serum KL-6 levels higher than this cutoff value were observed in more than 70% of the patients with DLI [25]. Interestingly, differences in serum KL-6 levels based on the HRCT patterns of DLI have been observed. The number of cases identified as positive for serum KL-6 (higher than 500 U/ml) was relatively higher for DLI displaying diffuse alveolar damage (DAD) or chronic interstitial pneumonia (CIP) pattern, than that identified in DLI displaying organizing pneumonia (OP)/eosinophilic pneumonia (EP) pattern or hypersensitivity pneumonia (HP) pattern [26]. In patients with non-small cell lung cancer (NSCLC), receiving epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), the ratio of serum KL-6 level at the onset of DLI to that at baseline (before treatment with EGFR-TKIs) greater than 1.5 was shown to indicate a high possibility of developing the DAD pattern of DLI [27].

Recently, we reported that the optimal cutoff value of serum KL-6 to distinguish patients with idiopathic pulmonary fibrosis (IPF) from healthy subjects was higher in the German-Caucasian population than that in the Japanese [28]. Although further studies are warranted, we have to consider the possible differences in the serum KL-6 levels between the Japanese and the Caucasians, when suggesting the occurrence of DLI.

5.3.3.2 Utility of Serum SP-A and SP-D for DLI Diagnosis

Previous reports have demonstrated the utility of serum SP-A and SP-D for the detection of DLI caused by amiodarone, pegylated interferon, or EGFR-TKIs [29–31]. In DLI caused by pegylated interferon, the elevation of serum SP-D

levels likely occurs earlier than that of serum KL-6 levels and the appearance of abnormal change in chest X-ray film [29]. Additionally, serum SP-A levels in DAD pattern of DLI are significantly higher than those in other patterns of DLI [32].

The approved cutoff values of serum SP-A and SP-D to distinguish patients with interstitial lung diseases from healthy subjects are set as 110 and 43.8 ng/mL in Japan, respectively. For convenience, these values have been used to detect the occurrence of DLI. Interestingly, a difference in serum SP-D levels, but not in serum SP-A levels, has been observed between German and Japanese healthy subjects [33]. We have to consider this ethnic difference in serum SP-D levels when using this biomarker for the detection of DLI in non-Japanese populations.

5.3.4 Possible Roles of Biomarkers Derived from Type II Pneumocytes in Assessing Disease Activity of DLI

5.3.4.1 Association Between Serum KL-6 and the Disease Activity of Interstitial Lung Diseases

Serum KL-6 reportedly correlates with the degree of pulmonary uptake of radioisotope in gallium 67 scintigraphy which reflects disease activity of interstitial lung diseases [14]. Additionally, serial changes in serum KL-6 levels also correlated with changes in clinically assessed disease activity of interstitial lung diseases [14]. Similar association has been observed between serum KL-6 levels and disease activity in patients with DLI caused by EGFR-TKIs, methotrexate, and amiodarone [27, 34, 35]. Interestingly, serum KL-6 levels also correlated with the degree of opacity on HRCT in patients with DLI [26]. On the basis of these observations, serial measurements of serum KL-6 in DLI patients can be considered useful for assessing disease activity and, probably, for treatment decisions.

5.3.4.2 Association Between Serum SP-A or SP-D and the Disease Activity of Interstitial Lung Diseases

In patients with IPF, both serum levels of SP-A and SP-D have been reported to correlate with the degree of ground-glass opacity (GGO) but not with the extent of honeycombing on HRCT [36]. This suggests that serum levels of SP-A and SP-D reflect the extent of interstitial inflammation but not that of the fibrotic changes in the lung. Although not well studied, we can speculate that serum levels of these biomarkers also correlate with the extent of interstitial inflammation in patients with DLI. In addition, serial changes in serum SP-A and SP-D have been reported to reflect changes in clinically assessed disease activity in patients with DLI caused by methotrexate or EGFR-TKI [31, 34].

5.3.5 Utility of Biomarkers Derived from Type II Pneumocytes for Predicting the Outcome of DLI

5.3.5.1 Utility of Serum KL-6 for Predicting the Outcome of Patients with DLI

The serum KL-6 value recorded at diagnosis has been reported to be able to predict the outcome in the patients with DLI; the mortality rate was significantly higher in patients with serum KL-6 levels higher than 500 U/mL than that in patients with serum KL-6 levels below 500 U/mL (31.3% vs. 0%, $p < 0.05$) [26]. Furthermore, the serum KL-6 levels of the patients who died from DLI were found to be unchanged or increased even after the cessation of the causative agents [26]. Similar trend between a change in serum KL-6 level and mortality was observed in patients with NSCLC, who developed DLI caused by EGFR-TKI [27].

5.3.5.2 Serum SP-A and/or SP-D as Possible Biomarkers for Predicting the Outcome of DLI

Higher levels of serum SP-D at the initial visit were reported to be associated with poorer prognoses in patients with IPF [37]. Additionally, serum SP-A was indicated to be a strong and independent predictor of early mortality in patients with IPF [38]. Although not conclusive yet, these findings indicate that serum SP-A and SP-D can be potential biomarkers for predicting the outcome of patients with DLI.

5.4 Lymphocyte Stimulating Tests

T lymphocyte, an important player in organizing the immune defense system, is involved in the pathogenesis of drug hypersensitivity reactions [39]. Sensitized T lymphocytes secrete various cytokines, such as interleukin (IL)-4 and IL-13 to promote IgE-mediated reactions, IL-5 to promote eosinophilic inflammation, IL-8, and granulocyte-macrophage colony-stimulating factor (GM-CSF) to promote neutrophilic inflammation and interferon (IFN) γ and TNF-α to promote monocyte-mediated inflammation [40].

The drug-induced lymphocyte stimulation test (DLST) is an in vitro examination that can detect T lymphocytes sensitized in vivo to a causative drug [41]. This test measures the proliferation of T lymphocytes, following an exposure to the causative drug. Although the result of this test is not necessarily linked to the diagnosis of DLI, DLST has a number of advantages, including safety and simultaneous assessment of T lymphocyte sensitization to multiple drugs.

5.4.1 The Basic Principles of DLST

5.4.1.1 T Lymphocyte Sensitization by Drugs

Sensitization of T lymphocytes by drugs is considered to be caused by some different mechanisms. A protein or polypeptide drugs, such as insulin or therapeutic antibodies, are strong immunogens and can directly sensitize T lymphocytes to stimulate B lymphocytes to produce specific antibodies. However, most drugs are structurally too small to be immunogenic; alternatively, they act as a hapten, which binds covalently to a peptide or protein to gain immunogenicity [42]. Some drugs directly interact with the T-cell receptor without covalent bond to any other peptide [43].

5.4.1.2 Detection of T Lymphocyte Proliferation

The concept of detecting T lymphocyte sensitization to drugs is to evaluate proliferation of T lymphocytes following exposure to drugs by measuring ^{3}H-thymidine uptake into cells. Pure substance of a causative drug at appropriate concentrations stimulates the sensitized T lymphocyte to proliferate. The uptake of ^{3}H-thymidine added to the culture medium as a DNA precursor can reflect the increase in synthesis of nucleic acid. The amount of ^{3}H-thymidine incorporated in T lymphocytes is measured as counts per minutes (cpm), and the ratio of ^{3}H-thymidine uptake in the presence of a drug to that in the absence of a drug is calculated as stimulation index (SI). In general, SI > 3 and SI < 2 are regarded positive and negative, respectively, and SI between 2 and 3 is considered marginally positive [41].

5.4.2 Clinical Application of DLST for the Diagnosis of DLI

When interpreting the results of DLST, we have to consider that the result is just in vitro indicator of T lymphocyte sensitization by a drug and do not necessary conform to the clinical conditions of a patient with DLI. In other words, we cannot confirm or deny a diagnosis of DLI merely based on the results of DLST. The results of DLST may serve as supportive evidence when the occurrence of DLI is suspected.

5.4.2.1 Utility of DLST for the Diagnosis of DLI

Nyfeler et al. performed DLST for 923 patients with suspected drug allergy and identified 100 patients with a drug allergy and 102 patients without a drug allergy based on the history, clinical course, and provocation tests. They found that 78 of the 100 patients with drug allergy had positive DLST and 87 of the 102 patients

Table 5.1 Rate of positive DLST in cases with DLI based on the category of causative drugs

Drug category	Rate of positive DLST (%)
Anticancer drugs	33.3
Gold drugs	72.7
Chinese herbal drugs	67.6
Chinese herbal drugs plus interferon	25.0
Antituberculosis drugs	85.7
Antimicrobial drugs	58.0
Anti-inflammatory analgesics	89.5
Interferon	20.2
All causative drugs	66.9

without a drug allergy showed negative DLST [44]. These results of this single previous study suggest that the sensitivity and specificity of DLST to detect drug allergy are 78 and 85%, respectively. In cases with DLI, however, the rate of positive DLST was relatively lower (less than 50%) than that in cases with anaphylaxis or maculopapular skin rash [41]. Additionally, the rate of positive DLST in patients with DLI also differs according to the category of the causative drug (Table 5.1); in anti-tuberculosis drugs and anti-inflammatory analgesics, more than 85% of cases had positive DLST whereas only 20–30% of cases showed positive DLST in interferon and anticancer drugs [45].

5.4.2.2 Drugs that May Affect the Results of DLST

Some drugs potentially affect the process of DLST. For example, methotrexate can cause false positives for DLST by promoting the uptake of ^{3}H-thymidine into lymphocytes by depleting the intracellular thymidine pool [46]. Chinese herbal drugs can also induce false positives because of the contamination of plant-derived nonspecific mitogens, which promote T lymphocyte proliferation [47]. In contrast, minocycline itself has a suppressive effect on T-cell proliferation, and therefore it can lead to false-negative result for DLST [48].

5.5 Conclusion

Previous studies mainly reported from Japan suggest that type II pneumocyte-derived serum biomarkers, such as KL-6, SP-A, and SP-D, have the potential to aid the diagnosis, monitor the severity, and predict the efficacy of the treatment or the outcome in patients with DLI. Despite its advantages and disadvantages, DLST plays a crucial role in identifying the causative agent in DLI. For the clinical management of DLI, it would be beneficial to effectively use such blood tests because

they are cost effective, less invasive, and more reproducible compared to other clinical examinations used to assess DLI, including HRCT, pulmonary function tests, and bronchoscopy.

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Chapter 6
Imaging Features of Drug-Induced Interstitial Lung Disease: How HRCT of DLI Is Interpreted

Fumikazu Sakai

Abstract Since imaging finding of drug-induced lung injury (DLI) is varying and nonspecific, diagnosis of DLI must be performed by the integration of clinical, imaging, and pathologic findings, when available. The roles of imaging evaluation in the diagnosis and treatment of DLI include detection of preexisting chronic fibrosing interstitial pneumonia as risk of DLI, early detection of DLI, diagnosis of DAD-type DLI for the estimation of prognosis, aids to differential diagnosis, follow-up examination including evaluation of treatment effect, and so on.

Keywords Drug-induced lung injury • HRCT • Imaging

6.1 Introduction

Clinical signs and symptoms and imaging findings of drug-induced lung injury (DLI) are nonspecific; its diagnosis therefore must integrate clinical information and imaging, laboratory, and pathology findings, if available. We describe imaging findings and roles, values, and limitations of imaging findings in the diagnosis and treatment of DLI.

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6.2 Clinical Features of Drug-Induced Lung Injury

Clinical features of DLI are nonspecific, and there are no pathognomonic findings [1–3]. Imaging findings of DLI are also nonspecific and offer limited diagnostic capability when used alone. Diseases that might show similar clinical signs and symptoms must be ruled out. Diagnostic criteria [3] of drug induced lung injury include [1] the onset of lung disease after the administration of suspicious drug [2], improvement of lung injury after the cessation of the suspicious drug [3], recurrence or progression of lung injury after readministration, and [4] previous case of DLI of same clinicoradiological pattern have been described [5]. It is necessary to exclude diseases for which the suspicious drug administered, infection, and so on, as well as their progression.

Because there is no reliable noninvasive laboratory examination of DLI, the level of its diagnosis sometimes remains suspicious [3]. Only one reliable diagnostic test is challenge test; drug; a method to investigate exacerbation or relapse of signs and symptoms after the administration of small dose of the suspicious drug. However, challenge tests always cannot be performed due to ethical problems especially in severe DLI. Drug lymphocyte stimulation test (DLST);the test to check increased ^{3}H thymidine uptake in mixed culture of suspicious drug and patient lymphoctytes, culture shows relatively high false and negative rates and has limited value in the diagnosis of DLI [3].

DLI is more common in patients with preexisting chronic fibrosing interstitial pneumonia (CFIP) at computed tomography (CT), a major risk factor for the development of DLI, and DLI in these patients bears a poor life prognosis [4–7]. One major role of imaging in the diagnosis and treatment of drug-induced lung injury is the evaluation of risk before the administration of drugs. Other major risk factors reported are male and old patients, smoking history and poor performance status in DLI for lung cancer [4, 5], diabetes mellitus, and abnormal findings on chest X-ray (CXR) in rheumatoid arthritis (RA) patients [6].

Incidence of DLI, especially severe DLI, is more frequent in Japanese than in other countries including western countries and other northern and southern Asian countries [3]. Occurrence of DLI of antineoplastic drugs and antirheumatic drugs in Japan is ten to hundred times as frequent as compared to those in other countries [8]. Reasons of the high occurrence have not been solved, but some possible causes have been considered: genetic factors, dose of drug, difference of diagnostic approach to DLI, and so on.

Detailed correlation of severe DLI and specific gene mutation and ethnic difference of these gene mutations have not been reported yet. Dose of drug might be high for Japanese in international collaboration trial for Japanese patients.

6.3 Imaging Findings of DLI

CXR can detect DLI and show its clinical course, but the detection of DLI in its early stage and analysis of detailed imaging findings require high-resolution CT (HRCT).

In general, imaging findings of DLI include diffuse or multiple scattered foci of ground glass opacity (GGO)/consolidation, which usually demonstrate non-segmental distribution in bilateral lungs (Fig. 6.1). GGO sometimes includes intralobular reticular opacities and/or thickened interlobular septa [2, 9–14]. In DLI with diffuse alveolar damage (DAD) after late organizing phase, structural distortion, such as traction bronchiectasis, is evident (Fig. 6.2).

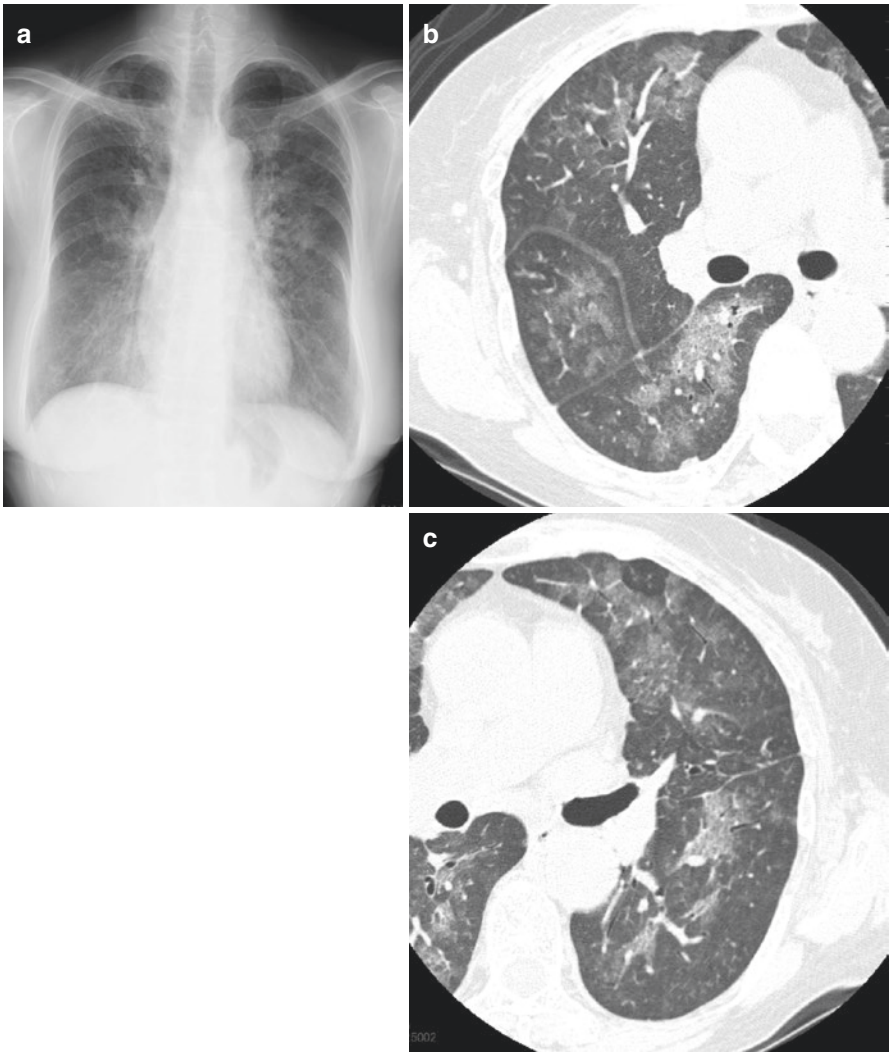

Fig. 6.1 Hypersensitivity pneumonia-like lung injury (methotrexate and infliximab for rheumatoid arthritis). (**a**) Chest X-ray shows diffuse ground glass opacity (GGO) obscuring pulmonary vascular markings in bilateral lungs. (**b**) High-resolution computed tomography (HRCT) shows widespread patchy panlobular GGO. (**c**) HRCT shows widespread patchy panlobular GGO

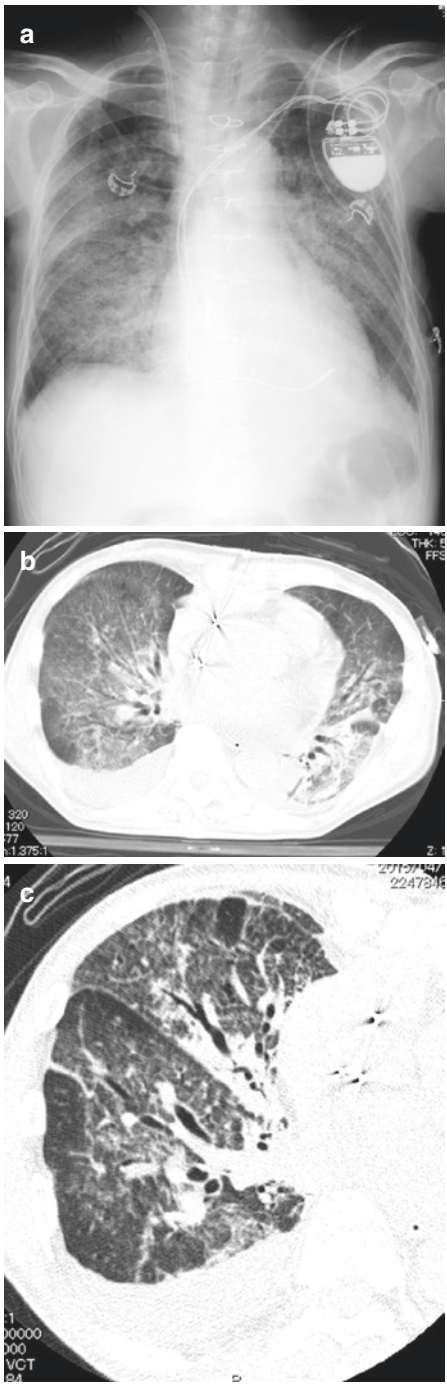

Fig. 6.2 DAD pattern drug-induced lung injury (amiodarone). (**a**) Chest X-ray shows cardiomegaly and perihilar abnormal opacity in bilateral lungs mimicking congestive cardiac failure and pulmonary edema. (**b**) CT shows perihilar ground glass opacity and consolidation. (**c**) HRCT shows ground glass opacity and intralobular reticular opacity/ peribronchovascular consolidation with structural distortion, and dilated bronchus is evident (traction bronchiectasis)

In drug-induced lung injury by amiodarone, important diagnostic information can be obtained by CT. In patients treated with amiodarone, high density of liver or consolidation of lung suggests the deposition of amiodarone within these tissues, since amiodarone includes iodine. Amiodarone deposition cannot be diagnosed with CT in normally aerated lung or ground glass opacity because air within the lung obscured high density of amiodarone molecules. Increased attenuation of consolidated lung or liver is one of the CT findings suggesting amiodarone lung injury (Fig. 6.3) [15, 16].

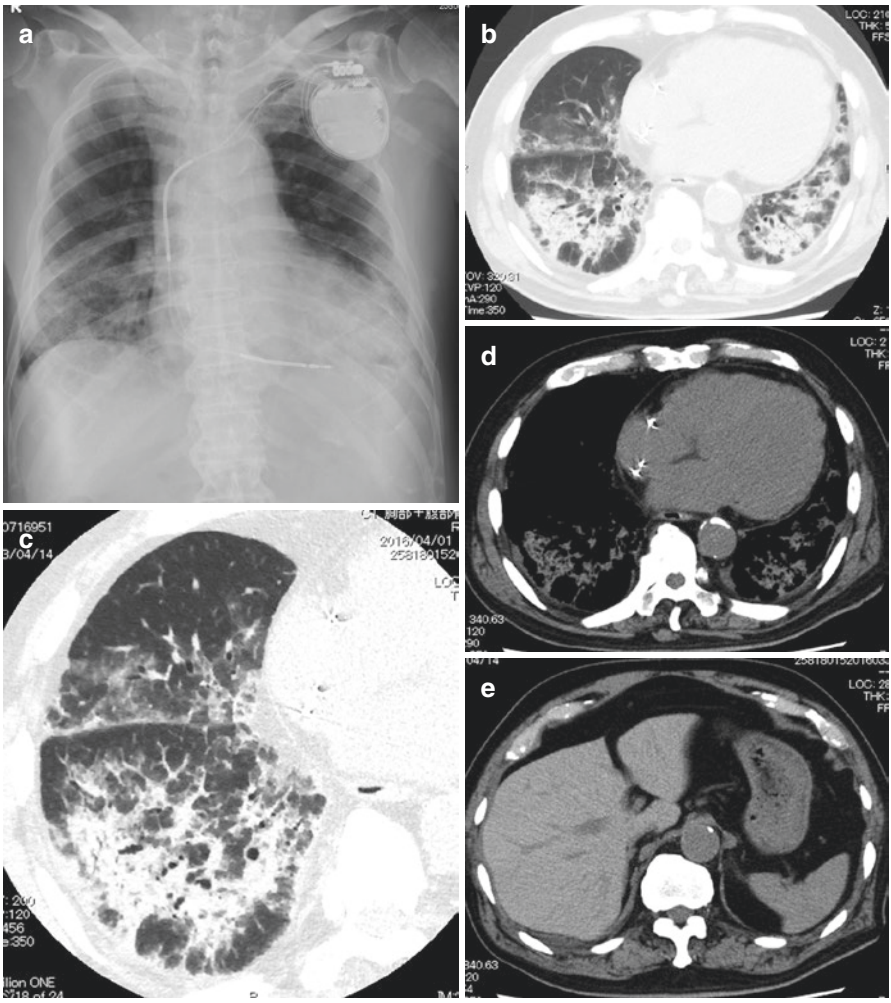

Fig. 6.3 Amiodarone lung injury. (**a**) CXR shows abnormal opacity in bilateral mid- to lower lung fields. Defibrillator was placed. (**b**) CT lung window setting: Conventional CT shows consolidation which shows ground glass opacity mixed with peribronchovascular consolidation in bilateral lower lobes, mimicked fibrosing OP pattern. (**c**) HRCT shows ground glass opacity mixed with peribronchovascular consolidation. (**d**) CT mediastinal window setting: Consolidation shows relatively high attenuation suggesting deposition of amiodarone. (**e**) Abdomen CT: Attenuation value of CT shows relatively high density suggesting amiodarone deposition in the liver

6.4 Imaging Patterns of DLI

6.4.1 Pattern Resembling Acute Interstitial Pneumonia (AIP-Like) or Diffuse Alveolar Damage (DAD Pattern)

HRCT findings of DLI that resemble findings of acute interstitial pneumonia. HRCT show diffuse/patchy GGO and/or consolidation that indicates structural distortion (Figs. 6.2 and 6.4) with ciatrization and traction bronchiectasis.

Diffuse alveolar damage is presumed to underlie a pattern resembling that of AIP. Pathologically, DAD demonstrates three phases—an early phase of intraluminal exudation with formation of a hyaline membrane (exudative phase) followed by a phase of organization of the intraluminal exudation (organizing phase) and then phase of incorporation of organized materials to alveolar septa and fibrosis (fibrotic phase). Changes are reversible in only the early exudative phase.

HRCT findings of the early exudative phase of DAD vary from normal to GGO/consolidation depending on the extent of intra-alveolar exudation. In the late organizing phase to the fibrotic phase, HRCT shows decreased volume of the lung parenchyma and GGO/consolidation with irregular cicatrization (structural distortion) that includes traction bronchiectasis [12].

HRCT does not permit the diagnosis of DAD in the exudative phase. In this early phase, DAD-type DLI may mimic non-DAD-type DLI, and non-DAD-type DLI

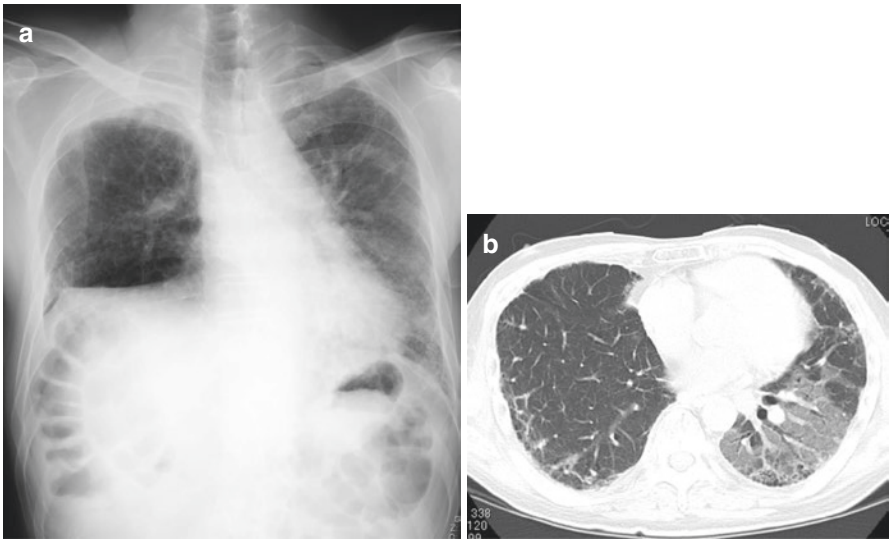

Fig. 6.4 DAD-type lung injury by chemotherapeutic agents after surgery for lung cancer. This patient had preexisting interstitial pneumonia. (**a**) CXR: Right upper lobectomy was performed for lung cancer. Following postoperative chemotherapy, abnormal opacity appeared abnormal opacity predominantly in the left lung. (**b**) HRCT: On HRCT, ground glass opacity including traction bronchiectasis is noted

may seem to progress to DAD-type DLI. However, DAD is evidenced only after the late organizing phase, when there is structural distortion that includes traction bronchiectasis.

Because of the poor life prognosis with DAD-type DLI, its differentiation from non-DAD-type DLI is very important [16–20]. One of the most important roles of imaging pattern recognition is the differential diagnosis of the DAD and non-DAD types.

A pattern of lung injury resembling that of acute interstitial pneumonia may be seen mainly in antineoplastic drugs, antirheumatic drugs, and so on; this pattern may represent acute exacerbation of chronic fibrosing interstitial pneumonia [21]. Differential diagnosis of AIP-like DLI includes DAD resulting from other causes, such as infection, acute exacerbation of preexisting CFIP, and non-DAD-type DLI.

6.4.2 Pattern Resembling Hypersensitivity Pneumonia (HP-Like Pattern)

HRCT findings of drug-induced lung injury that resemble hypersensitivity pneumonia show bilateral diffuse GGO or widespread patchy GGO without structural distortion (Figs. 6.1 and 6.5) and may show random or centrilobular distribution of fine nodular opacity. In some cases, intralobular fine reticular opacity may coexist. Lung injury with this pattern is caused by many kinds of durgs; antineoplastic drugs such as paclitaxel and gemcitabine, antirheumatic drugs such as MTX, and so on [22–24].

An HP-like imaging pattern of DLI shows infiltration of lymphocytes and plasma cells to alveolar wall and formation of small granulomata that mimic HP caused by inhalation of antigens, but the distribution of granulomata is not centered in the airway [25]. This type of DLI is typically caused by low-dose treatment with MTX for rheumatoid arthritis, but many other drugs can cause the HP-like pattern.

Distribution of fine nodular opacity is most frequently random and perilymphatic and less frequently centrilobular. At present, we do not know why disease without airway spread shows centrilobular distribution like that of hypersensitivity pneumonia caused by inhalation of antigens.

Clinically, the prognosis of HP-like DLI is favorable. However, HRCT findings of DAD in the early exudative phase may mimic those of HP-like DLI. It is important to recognize that imaging findings of the exudative phase of DAD-type DLI may mimic those of non-DAD-type DLI. Early-phase DAD cannot be excluded based solely on HRCT findings in these cases.

The differential diagnosis of hypersensitivity pneumonia-like DLI includes *Pneumocystis jirovecii* pneumonia, cytomegalovirus (CMV) pneumonia, pulmonary edema, alveolar hemorrhage, and other types of DLI. The most important of these is PCP [26–30] because HP-like DLI and PCP are not generally differentiated based solely on HRCT findings [26].

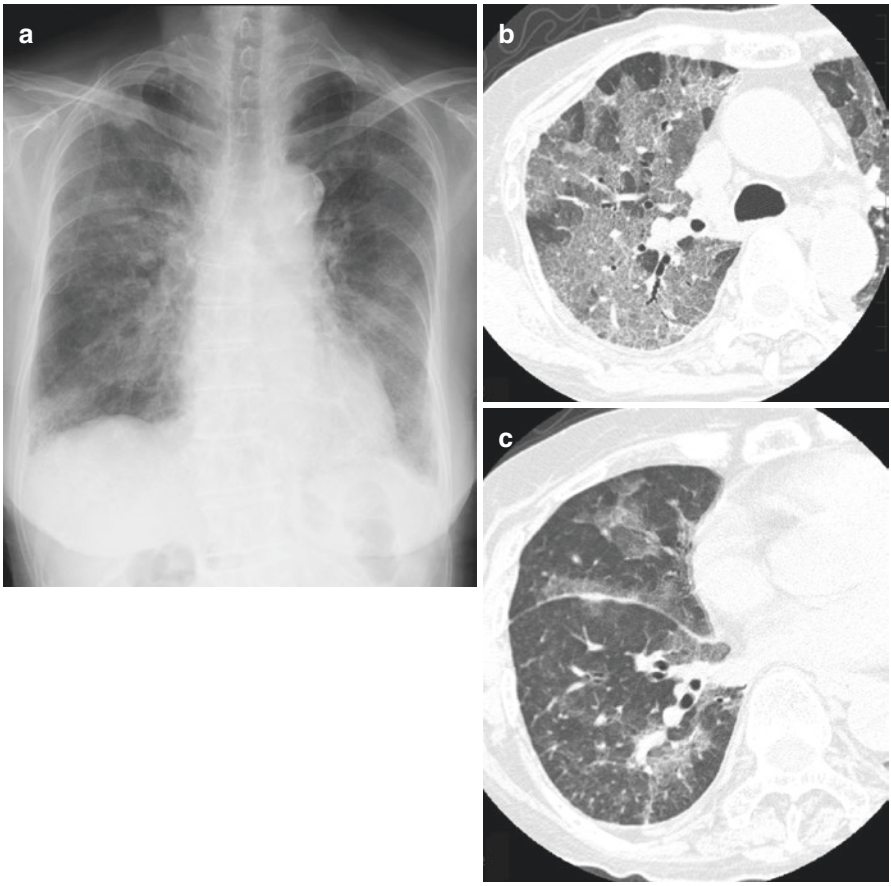

Fig. 6.5 HP-like drug-induced lung injury (MTX for rheumatoid arthritis). (**a**) Chest X-ray shows diffuse ground glass opacity (GGO) in bilateral lungs. (**b**) High-resolution computed tomography (HRCT) of the right upper lung shows panlobular/multilobular GGO including intralobular reticular opacity mimicking hypersensitivity pneumonia. Spared lobules are identified. (**c**) HRCT of the right lower lung shows patchy GGO less prominently than in the upper lung

6.4.3 Pattern Resembling Cryptogenic Organizing Pneumonia (OP-Like Pattern)

HRCT findings of drug-induced lung injury that resembles cryptogenic organizing pneumonia show multiple subpleural or peribronchovascular foci of consolidation with non-segmental distribution (Fig. 6.6). The pathology of OP generally shows intraluminal organization. Differential diagnosis includes bacterial pneumonia, chronic eosinophilic pneumonia, other types of DLI (early-phase DAD or nonspecific interstitial pneumonia (NSIP)-like DLI), and organizing pneumonia by other causes.

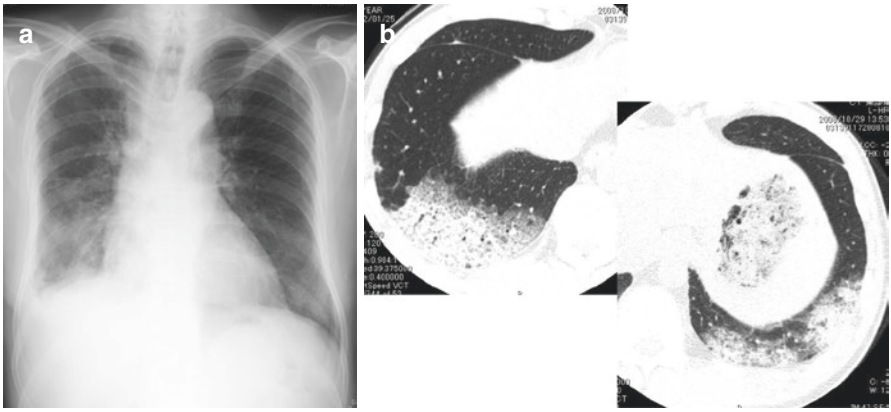

Fig. 6.6 OP-type drug-induced lung injury (docetaxel for lung cancer). (**a**) Chest X-ray film shows consolidation in bilateral lower lung fields. (**b**) HRCT of the right lower lung showed non-segmental consolidation in subpleural region mimicking cryptogenic organizing pneumonia

6.4.4 Pattern Resembling Acute Eosinophilic Pneumonia (AEP-Like Pattern)

The AEP-like pattern of drug-induced lung injury is one of the most problematic, and the pathology underlying this pattern is not clear. HRCT findings of patchy panlobular GGO and/or consolidation with thickened interlobular septa/bronchovascular bundles simulate findings of acute eosinophilic pneumonia (Fig. 6.7). Some AEP-like DLI shows hypereosinophilia, but others do not. Entities with this pattern might include non-cardiogenic edema, a mild form of DAD.

Patterns of DLI with hypereosinophilia vary and resemble those of AEP, fine nodular opacity, and OP. The pathology underlying AEP-like DLI must be further investigated [31, 32].

The differential diagnosis of DLI with an AEP-like pattern includes malignant lymphoma, lymphoproliferative disorders, carcinomatous lymphangitis, and others.

6.4.5 Pattern Resembling Nonspecific Interstitial Pneumonia (NSIP-Like Pattern)

Computed tomographic findings of NSIP-like DLI show peribronchovascular GGO and/or consolidation (Figs. 6.8 and 6.9). The imaging pattern may mimic that of interstitial pneumonia in patients with dermatomyositis or anti-aminoacyl tRNA synthetase (ARS) syndrome.

The underlying pathology is regarded as fibrosing OP (fOP), one form of unclassifiable interstitial pneumonia. Fibrosing OP is considered to be similar to cellular

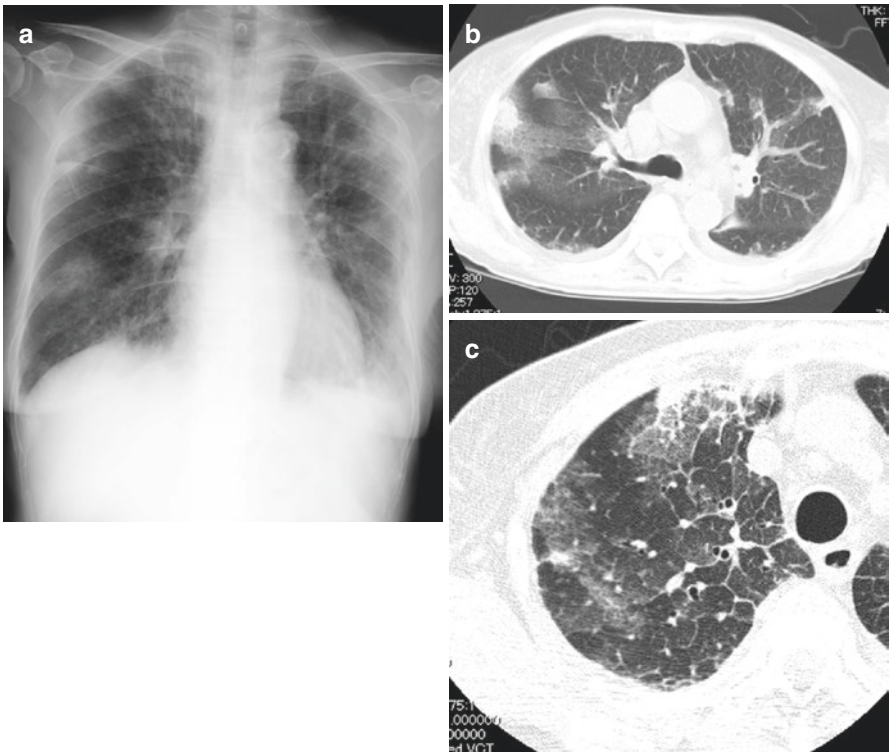

Fig. 6.7 Acute eosinophilic pneumonia-like pattern of lung injury (TKI for renal cell cancer). (**a**) Chest X-ray shows abnormal opacity in bilateral lungs. (**b**) CT shows widespread ground glass opacity and peripherally located consolidation. (**c**) HRCT: In addition to ground glass opacity and consolidation, interlobular septal thickening is noted

NSIP including wide area of consolidation. Lung injury seems more severe than with usual NSIP and is sometimes described as acute lung injury, OP with fibrosis, or fibrosing OP. Differential diagnosis may include DLI of NSIP, OP, organizing DAD pattern, or infectious disease.

6.4.6 Limitation of Pattern Recognition

Imaging patterns of drug-induced lung injury are classified by comparisons among CT findings of idiopathic diseases [9, 11]. For example, HRCT findings of DLI that include panlobular or multilobular GGO/consolidation with thickened interlobular septa and bronchovascular bundles may resemble findings of acute eosinophilic pneumonia (AEP). Nevertheless, this comparison-based classification does not assure definitive diagnosis of underlying lung injury related to eosinophilic cell recruitment. On the other hand, DLI with eosinophilia can

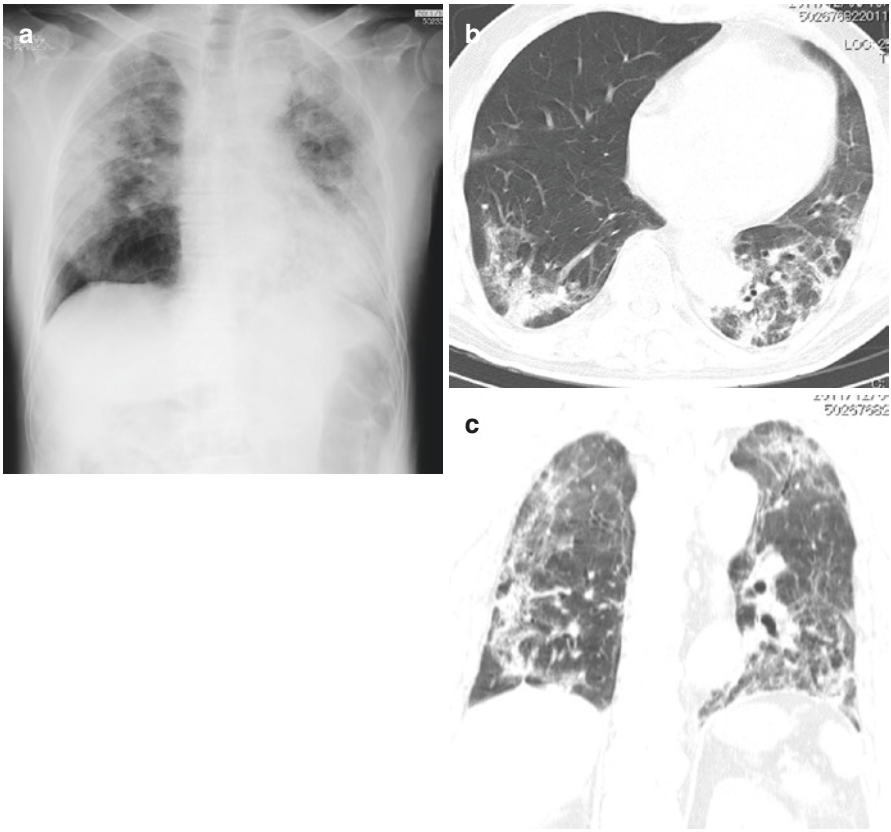

Fig. 6.8 Fibrosing OP-type drug-induced lung injury (herbal medicine). (**a**) Chest X-ray shows ground glass opacity and reticular opacity in bilateral lungs predominantly in upper and middle lung fields. (**b**) HRCT shows ground glass opacity overlapping with peribronchovascular foci of consolidation mimicking organizing pneumonia with fibrosis pattern. (**c**) Coronal reconstruction CT: CT with coronal reconstruction shows abnormal opacity with upper to middle lung field predominance

demonstrate various patterns that may resemble AEP and/or include diffuse GGO or small fine nodular opacities. We must know these limitations when we apply this imaging classification.

6.4.7 Practical Values of Imaging Classification

Imaging patterns somewhat reflect the mechanism of the disease process. Diffuse alveolar damage (DAD) is the presumed pathology underlying a pattern of DLI that resembles acute interstitial pneumonia (AIP), and DAD is the most severe form of DLI and bears an unfavorable life prognosis [12]. A pattern resembling that of

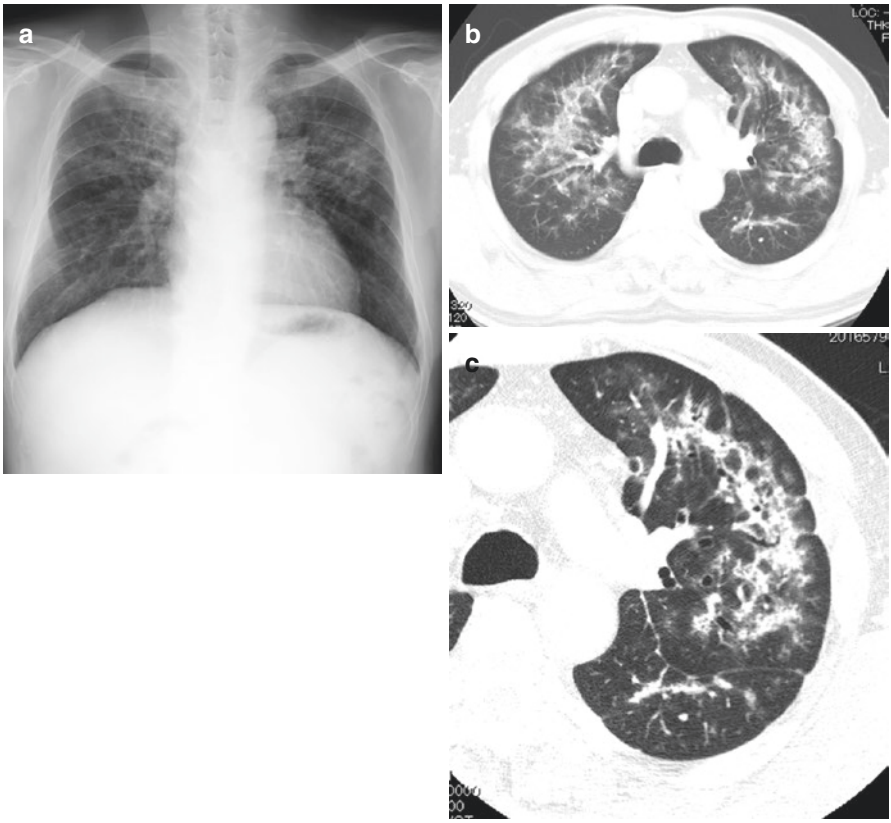

Fig. 6.9 Nonspecific interstitial pneumonia (fibrosing OP)-like pattern TKI for renal cell cancer. (**a**) Chest X-ray shows abnormal opacity predominantly in upper and middle lung fields. (**b**) CT shows ground glass opacity and peribronchovascular consolidation in bilateral lungs. (**c**) HRCT shows ground glass opacity and peribronchovascular consolidation in bilateral lungs

hypersensitivity pneumonia (HP) shows diffuse GGO without structural distortion (HP-like pattern), and the presumed underlying pathology is interstitial pneumonia with infiltration by lymphocytes and plasma cells into the alveolar septa and formation of small granulomata. However, the patterns of other disease processes, such as alveolar hemorrhage, can also resemble that of HP.

Recognition of imaging patterns can aid differential diagnosis. As examples, a major differential diagnosis of the HP-like pattern is *Pneumocystis jirovecii* pneumonia (PCP), and a major differential diagnosis of a pattern resembling cryptogenic organizing pneumonia (OP) includes infectious bacterial pneumonia and a chronic form of eosinophilic pneumonia (CEP).

It is important to recognize radiological findings that suggest DAD, such as the structural distortion of traction bronchiectasis. Still, traction bronchiectasis is not apparent in HRCT findings of the early exudative stage of DAD but becomes evident after the organizing phase, so the absence of such structural distortion does not exclude a diagnosis of DAD (Fig. 6.10). It is necessary to recognize the limitation in determining diffuse alveolar damage in its early stage.

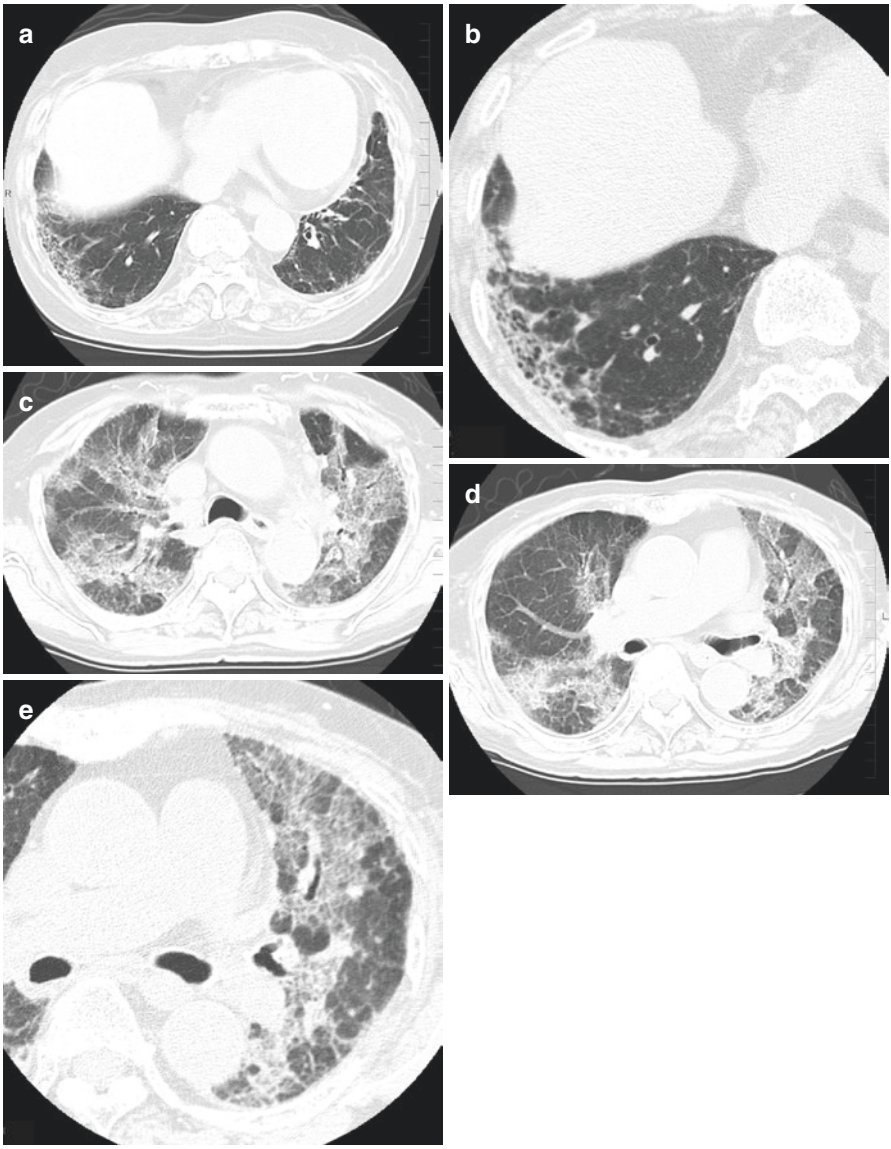

Fig. 6.10 Diffuse alveolar damage (DAD) pattern of drug-induced lung injury (DLI) in a patient with preexisting chronic fibrosing interstitial pneumonia treated with methotrexate and bucillamine. (**a**) Computed tomography before drug administration shows reticular opacity in the subpleural regions of bilateral lower lungs. (**b**) High-resolution computed tomography (HRCT) of the right lung shows reticular opacity and ground glass opacity (GGO) in the lower lung more clearly. (**c**) CT after the onset of DLI shows widespread GGO with structural distortion. Traction bronchiectasis is evident. (**d**) CT after the onset of DLI shows widespread GGO with structural distortion. Traction bronchiectasis is evident. (**e**) HRCT of the left lung shows GGO including intralobular reticular opacity and traction bronchiectasis

6.5 Differential Diagnosis of Drug-Induced Lung Injury

The diagnosis of DLI requires the exclusion of other diseases that show similar clinical findings, including infectious disease and progression of underlying diseases.

Exclusion of these diseases mimicking DLI must be excluded based on clinical and imaging findings. Because imaging findings of DLI are nonspecific, the integration of clinical, laboratory, and radiological findings must be mandatory to definitive diagnosis of DLI.

6.5.1 Infectious Diseases

The most frequent infection observed in daily practice is bacterial pneumonia that mimics DLI with an OP-like pattern. Fungal infection may also be observed. *Pneumocystis jirovecii* pneumonia is one of the most important infectious diseases that must be differentiated from DLI. Most cases of PCP show bilateral diffuse or multiple patchy GGO and mimic hypersensitivity pneumonia-like DLI, and it is often impossible to differentiate HP-like DLI and PCP solely based on HRCT findings. An increased serum level of beta-D-glucan and/or bacteriological identification of *Pneumocystis jiroveci* is useful to establish the diagnosis of PCP (Fig. 6.11). Other organisms common in patients with RA include tuberculosis, nontuberculous mycobacteriosis, and cryptococcus as well as aspergillosis.

6.5.2 Preexisting Lung Diseases

Acute exacerbation of chronic fibrosing interstitial pneumonia (CFIP) and acute/subacute interstitial disease must be differentiated from drug-induced lung injury. Exacerbation of CFIP is most frequently seen in usual interstitial pneumonia (UIP) pattern followed by NSIP pattern. Unclassifiable patterns of CFIP may show acute exacerbation. Exacerbation of CFIP by drugs should be regarded as DLI. Clinical information in addition to HRCT findings are required to determine the cause of acute exacerbation of CFIP.

Organizing pneumonia and OP with fibrosis are other lung injury patterns that mimic DLI, and they may take an acute or subacute course. Organizing pneumonia shows multiple non-segmental foci of consolidation in subpleural regions and/or perivascular regions. OP-like DLI should be considered a differential diagnosis. Lung injury caused by OP with fibrosis that is subacute may show cellular NSIP, organizing DAD, OP depending on the time of biopsy, and more severe lung injury than that of OP. HRCT shows foci of perivascular/subpleural consolidation intermingled with GGO (NSIP-like pattern).

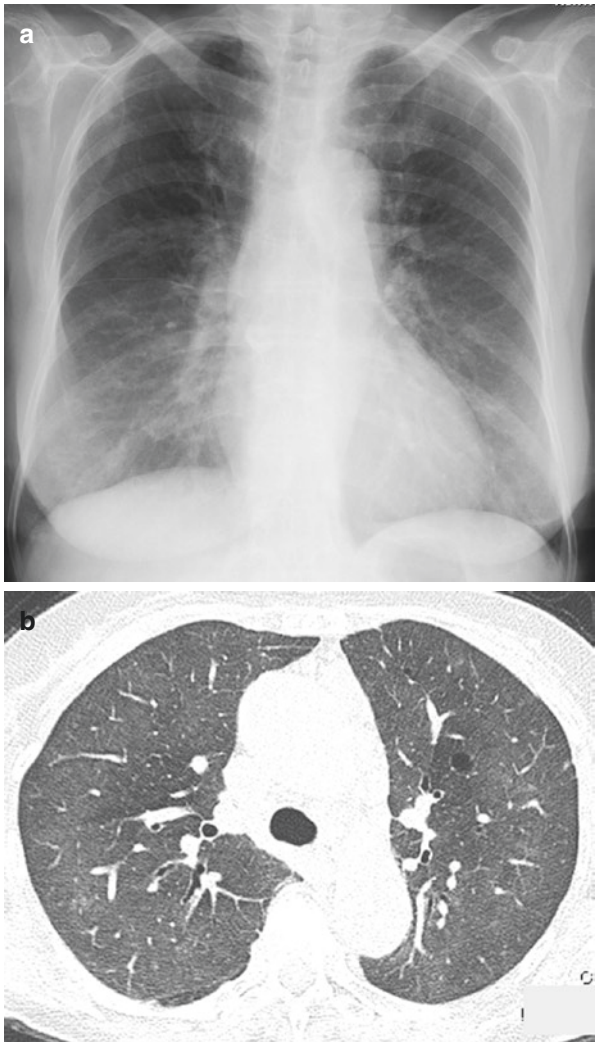

Fig. 6.11 PCP. Anticancer drug and glucocorticoid administration for lymphoma and serum level of beta-D-glucan is elevated. (**a**) Chest X-ray shows ground glass opacity in bilateral lower lung fields, obscuring vascular markings. (**b**) CT: Widespread faint ground glass opacity is noted in bilateral lungs

6.5.3 Progression of Underlying Disease

Progression of underlying diseases (for which suspicious drug was administered) may mimic DLI. For example, lymphangitic spread of lung cancer may mimic AEP-like DLI. Progression of underlying disease must be excluded based on clinical and radiological findings and its course.

6.6 Roles of Imaging in the Diagnosis and Treatment of Drug-Induced Lung Injury

Despite its many limitations, imaging in the diagnosis and treatment of drug-induced lung injury serves to (1) identify chronic fibrosing interstitial pneumonia, a risk factor for the development of DLI, and (2) detect DAD at the onset of DLI, and findings serve as (3) an objective sign of DLI and aid (4) differential diagnosis at the onset of DLI and (5) analysis of the disease process.

6.7 Drug-Induced Lung Injury by Some Specific Drugs

6.7.1 Tyrosine Kinase Inhibitors

Tyrosine kinase inhibitors (TKI) are widely used for varying kinds of malignant tumors (Fig. 6.12). Gefitinib is one of the first-generation TKI and has antineoplastic effects for lung cancer with positive ectodermal growth factor receptor (EGFR)

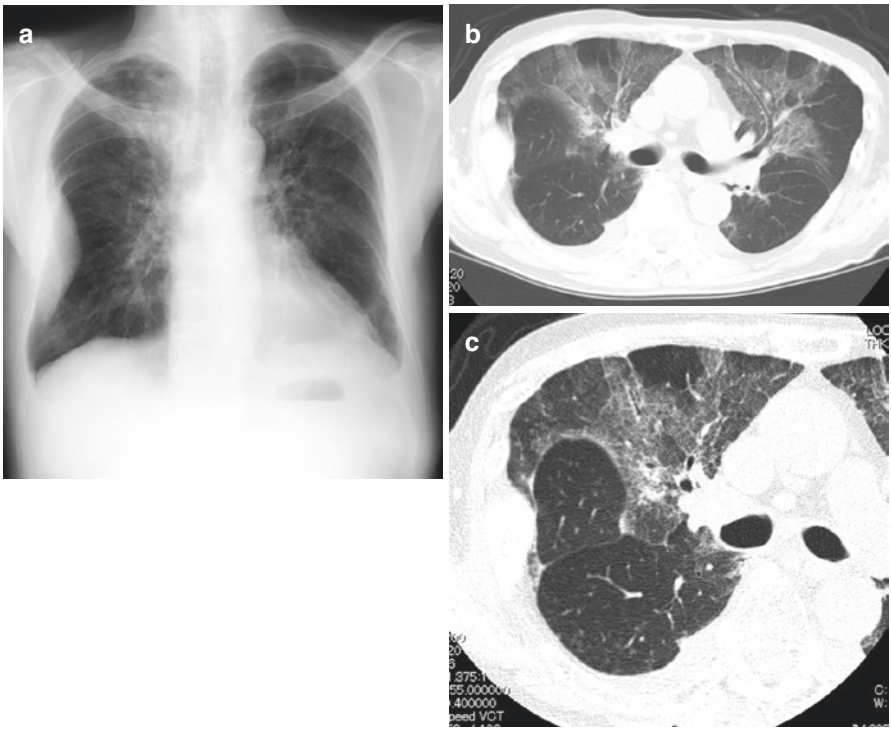

Fig. 6.12 HP-like drug-induced lung injury (TKI for lung cancer). (**a**) Chest X-ray shows faint ground glass opacity predominantly in upper lungs. (**b**) CT shows peribronchovascular ground glass opacity in bilateral lungs. No structural distortion is noted. (**c**) HRCT: Intralobular reticular opacity is noted within ground glass opacity. Some faint centrilobular nodular opacities are also noted

mutation. After that, several kinds of TKI including small molecule and antibody drug (panitumumab, cetuximab, and so on) have been developed not only for lung cancer but also for colorectal cancer, pancreas cancer, renal cell cancer, soft part sarcoma, and so on.

In Japan, gefitinib or erlotinib for treatment of lung cancer evoked DLI approximately in 3–4% of treated patients and 1% mortality rate [33–37]. Frequency of DLI seems to be higher than other chemotherapeutic agents. Frequencies of DLI for malignant tumor in other organs are almost 0.1–1% of treated patients, less frequent than those of lung cancer patients. High incidence rate of DLI in lung cancer may have effect of preexisting lung disease. Antibody EGFRTKI can evoke DLI as small-molecule TKI.

Imaging features of DLI by TLI are not different from those of other kinds of drugs. Mortality rates are approximately same as other drugs in the event of DLI.

6.7.2 Mammalian Target of Rapamycin (mTOR) Inhibitors [38–40] (Fig. 6.13)

Mammalian target of rapamycin (mTOR) inhibitors has been applied for many kinds of cancer. Temsirolimus and everolimus are approved in Japan. mTOR inhibitors show specific clinical and imaging features; incidence of DLI is very high up to 40%, but frequency of mild form without subjective symptoms is high and mortality is low. In these cases, only abnormal opacity at CT is only sign of DLI. Most cases show non-DAD or HP-like pattern.

Considering antineoplastic effect, continuance of drug administration can be approved in mild DLI case without clinical symptoms and effective antineoplastic therapeutic effect under strict observation of clinical course.

6.7.3 Antirheumatic Drugs

At present low-dose MTX is one of the standard drugs of rheumatoid arthritis (RA). MTX-induced lung injury most frequently shows widespread GGO (HP like pattern) ground glass opacity, which cannot be differentiated from pneumocystis pneumonia (PCP) solely based on imaging findings. Other antirheumatic drugs can show DLI, and the most frequent imaging pattern is NSIP (fibrosing OP)-like pattern (Fig. 6.14).

Since recent popularization of TNF inhibitors induces RA patients to immunodeficiency, opportunistic infection becomes one of the most frequent acute/subacute complications of treated RA patients. However, DLI may be induced by TNF inhibitors. Imaging pattern by TNF inhibitors shows OP pattern most frequently, but other imaging patterns including HP-like pattern, DAD pattern, and sarcoidosis-like pattern have been reported.

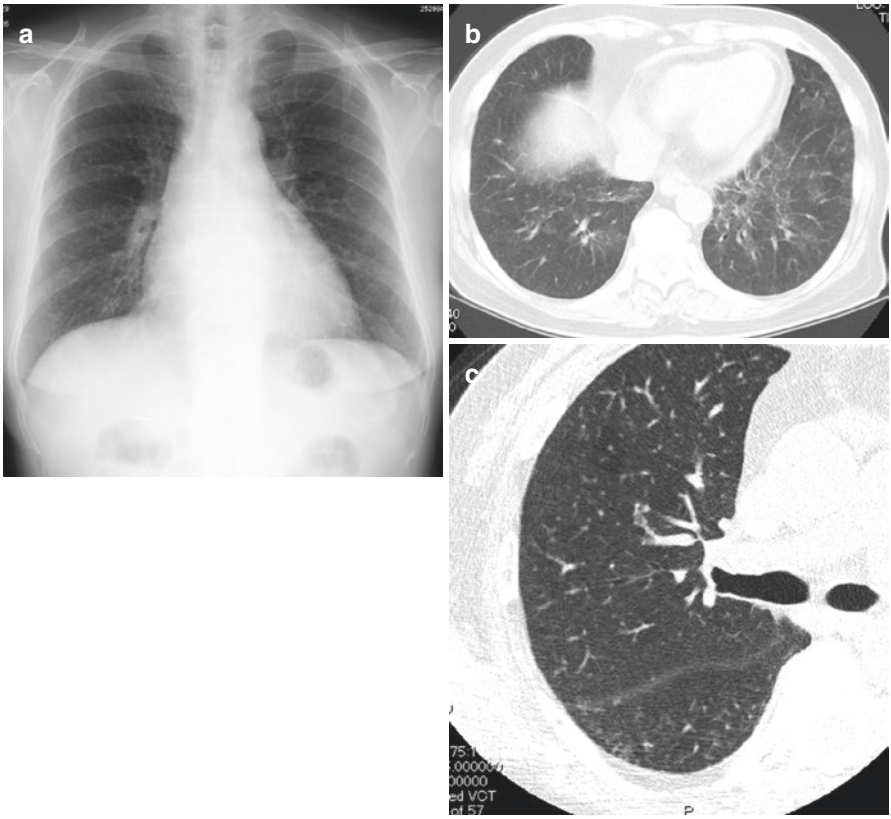

Fig. 6.13 HP-like drug-induced lung injury (mTOR inhibitor for renal cell cancer). (**a**) Chest X-ray shows very faint ground glass opacity in bilateral lungs. (**b**) CT shows faint peribronchovascular ground glass opacity in lower lungs. (**c**) HRCT shows patchy faint ground glass opacity and fine nodular opacity

In acute/subacute complication of treated RA patients, differential diagnosis includes infectious disease including PCP, NTM, DLI, and complication of RA itself; OP and OP with fibrosis; and acute exacerbation of chronic fibrosing interstitial pneumonia. Other differential diagnoses include lymphoma/lymphoproliferative disorders (LPD) and angiitis when they show subacute onset.

6.7.4 Immune Checkpoint Inhibitors (Fig. 6.15)

Nivolumab (anti-PD-1 human IgG4 antibody) has been introduced as clinically available immune checkpoint inhibitor for melanoma, lung cancer, renal cell carcinoma, and so on. Nivolumab induced hyperimmune state for cancer and preexisting infection [41]. Early experience of Nivolmub induced DLI includes (1) OP-like pattern DLI is more frequent (2) OP like shadow around tumor (Fig. 6.15), recall of radiation pneumonitis and exacerbation of infection similar to immune reconstitution syndrome, in addition to DLI similar to other drugs. These unfamiliar patterns to other

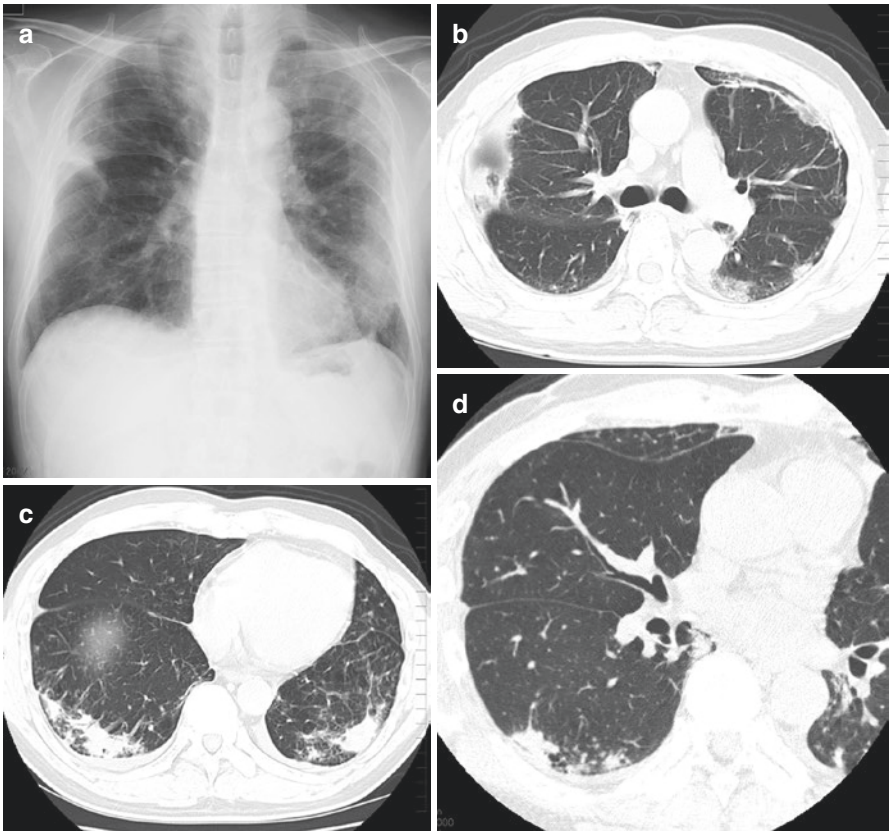

Fig. 6.14 OP-like pattern lung injury induced by methotrexate and etanercept. (**a**) Chest X-ray shows multiple patchy foci of consolidation in subpleural regions. (**b**) Computed tomography (CT) at the level of the carina shows multiple foci of consolidation in subpleural regions. (**c**) CT at the level of the lower lung shows multiple foci of consolidation in subpleural regions. (**d**) High-resolution CT shows these findings more clearly

drugs are supposed to have something to do with excess immune reaction caused by immune checkpoint inhibitors (immunoreactive adverse effect of the lung).

The combination use of other antineoplastic drugs such as TKI may induced severe DLI by immunologic augmentation of adverse effect of drugs, even if sequential use of other drugs, because it is not known how long effect of nivolumab continue. Strict caution must be required for the combination use of other drugs with immune check point inhibitors.

6.8 Conclusions

Imaging findings of drug-induced lung injury are nonspecific. The correct diagnosis of drug-induced lung injury requires the integration of clinical and radiological findings and pathological features if available.

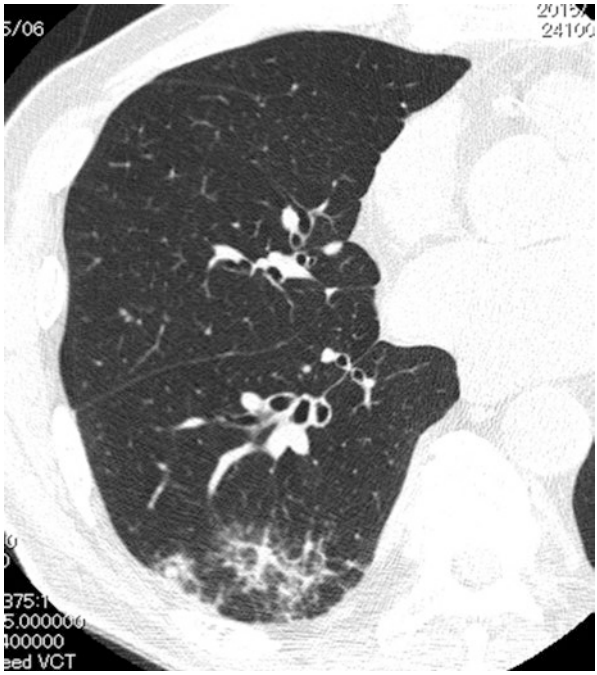

Fig. 6.15 OP-like drug-induced lung injury (nivolumab for malignant melanoma). HRCT shows peribronchovascular consolidation. Consolidation is noted surrounding metastatic nodule

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Chapter 7
Pathology of DLI: What Is the Pathological Significance of DLI?

Yasuhiro Terasaki and Yuh Fukuda

Abstract The diagnosis of drug-induced interstitial lung disease (DI-ILD) requires the careful exclusion of other etiologies, but it is difficult to determine whether pathological findings are due to drug toxicity. However, the number of drugs that induce lung disease as a side effect is expected to increase as new agents are developed. Early and accurate diagnosis of DI-ILD is critical because drug withdrawal often results in symptom improvement even in some eventually fatal cases. Clinical information, such as drug type, dose, and the timing of administration relative to the onset of pulmonary symptoms, and lung imaging data are essential for accurate diagnoses. It is also crucial to understand the pathological features of DI-ILD, even though they are nonspecific, including the evaluation of the time process of the lung lesions, as well as investigations for specific findings of infectious or malignant disease. Some drugs produce characteristic histopathological patterns of involvement that enable almost immediate recognition of a DI-ILD etiology. Thus, lung biopsy is key if DI-ILD is suspected clinically. Given the many new therapeutic agents in clinical use, pathologists and clinicians must monitor patients for emerging forms of drug toxicity through clinico-radiologic-pathological diagnostics.

Keywords Drug-induced interstitial lung disease • Drug toxicity • Pathological features • Clinico-radiologic-pathological diagnosis

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7.1 Introduction

Drugs can induce specific respiratory reactions, or the lungs may be affected as part of a generalized response to treatment. A large variety of drugs, including chemotherapeutic agents, antiarrhythmic agents, and antibiotics, can cause lung injury at therapeutic or toxic levels. This damage can be acute or chronic and can be due to direct toxicity, indirect damage from drug metabolites, or an idiosyncratic reaction to drugs. More than 380 medications are known to cause drug-induced respiratory diseases; however, the true frequency of these reactions is unknown [1].

The recognition of drug-induced lung injury is a challenge in lung pathology because most drug-induced histopathological changes are nonspecific and mimic those observed with other causes of lung injury [2] [3, 4]. Most drugs of comparable classes induce similar patterns of pulmonary involvement, which suggests a common cytopathogenic mechanism. However, some drugs can produce more than one pattern of histopathological involvement in the same patient.

Patients affected by drug-induced pulmonary toxicity frequently have underlying diseases for which a drug has been administered, and some of these diseases also have underlying idiopathic pulmonary manifestations. In addition, some of these patients may also be prescribed multiple drugs that may cause lung injury. Thus, the diagnosis of a drug-induced lung injury requires careful exclusion of other causes. Although the global incidence of interstitial lung disease (ILD) is unknown, 2.5–3% cases are drug induced [5].

The number of drugs that cause lung disease is expected to increase as new agents are developed. In particular, some of the more recently developed targeted molecular therapies, such as epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) [6] and interferon (IFN)-α [7], are associated with a higher mortality rate when diffuse acute injury occurs. Thus, early and accurate diagnosis of drug-induced ILD (DI-ILD) is critical because drug withdrawal often results in symptom improvement even in some fatal conditions.

A clear onset of pulmonary symptoms with drug administration and the abatement of symptoms on cessation of the drug may not be easily discernable; however, clinical information regarding the drug type, dose, and timing of administration relative to the onset of pulmonary symptoms as well as lung imaging data are essential to an accurate diagnosis. In addition to these clinical evaluations, an understanding of the pathological features of drug-induced lung injury, even though nonspecific, and evaluations of the time process of the lesions and specific findings related to infectious conditions are key. Especially, some drugs produce characteristic histopathological patterns of involvement that enable almost immediate recognition of the drug etiology.

Drug-induced lung injury may involve the airways, lung parenchyma, mediastinum, pleura, pulmonary vasculature, or neuromuscular system in a wide variety of patterns (Table 7.1) [2]. Some drugs cause a single pattern of involvement, but occasionally patterns are mixed or slightly different in appearance, as occurs in an idiopathic setting.

Table 7.1 Pathological patterns of drug-induced lung disease [2–4]

1. Alveolar/interstitial lesions
Interstitial pneumonia
(1) Diffuse alveolar damage (DAD)
(2) Organizing pneumonia (OP)
(3) Usual interstitial pneumonia (UIP)
(4) Nonspecific interstitial pneumonia (NSIP)
(5) Lymphocytic interstitial pneumonia (LIP)
(6) Desquamative interstitial pneumonia (DIP)
(7) Eosinophilic pneumonia (EP)
(8) Hypersensitivity pneumonia (HP)
(9) Granulomatous interstitial pneumonia
Others
(1) Pulmonary edema
(2) Alveolar proteinosis
(3) Alveolar hemorrhage
2. Bronchiolar lesions
(1) Bronchial asthma
(2) Bronchiolitis obliterans (BO)
3. Vascular lesions
(1) Vasculitis
(2) Pulmonary hypertension
(3) Pulmonary veno-occlusive disease (PVOD)
4. Pleural lesions
(1) Pleuritis

The primary and most common form of drug-induced lung toxicity is DI-ILD. Drugs can produce virtually all histopathological patterns of interstitial pneumonia, including diffuse alveolar damage (DAD), organizing pneumonia (OP), nonspecific interstitial pneumonia (NSIP), eosinophilic pneumonia (EP), and granulomatous pneumonitis (Table 7.2) [2, 8]. The primary role of the pathologist in such cases is the identification of the correct histopathological pattern(s) of lung injury. The differential diagnosis and identification of possible etiologies can be initiated after the accurate classification of the lung reaction pattern.

This chapter presents the general mechanisms of adverse drug reactions, describes representative drugs in the classes associated with the development of DI-ILD, and focuses on the major histopathological patterns of drug toxicity, in particular the DI-ILD patterns, as well as other representative reactions such as bronchiolitis obliterans (BO). Representative pathological images of each pattern from patients affected by specific drugs accompany the text. Finally, this chapter ends with a summary of the general clinico-radiological-pathological features of DI-ILD.

Table 7.2 Pathological patterns of drug-induced interstitial lung disease [2–4]

Pathological pattern	Prototypic drug(s)
Diffuse alveolar damage (DAD)	Amiodarone, bleomycin, busulfan, BCNU, colchicine, cyclophosphamide, penicillamine, gold salts, melphalan, methotrexate, gefitinib, leflunomide, bortezomib, erlotinib, IL-2
Organizing pneumonia (OP)	Amiodarone, bleomycin, cyclophosphamide, mitomycin, methotrexate, minocycline, gold salts, TS-1, NSAID, anastrozole with radiation
Nonspecific interstitial pneumonia (NSIP)	Amiodarone, bleomycin, BCNU, chlorambucil, gold salts, methotrexate, TS-1, NSAID
Usual interstitial pneumonia	Cyclophosphamide, chlorambucil, methyl-CCNU
Eosinophilic pneumonia (EP)	Bleomycin, ampicillin, tetracycline, carbamazepine, methotrexate, chlorpropamide, procarbazine, NSAID
Granulomatous pneumonitis	Methotrexate, rituximab, interferons

7.2 Mechanisms of Adverse Drug Reactions [9]

The mechanisms of adverse drug reactions are based on the following:

- Reactions that can occur in any individual, such as
  - Overdose: toxicity linked to excess dose or impaired excretion
  - Side effects: undesirable pharmacological effects that occur at recommended doses
  - Interactions with other drugs
- Reactions that occur only in susceptible subjects
  - Intolerance: a low threshold to the normal action of the drug.
  - Idiosyncrasy: an abnormal reaction to a drug based on a genetically determined metabolic or enzymatic deficiencies.
  - Allergy in the form of any of the four main hypersensitivity reactions (Coombs types I–IV). Most drugs (penicillins, sulphonamides) have low molecular weights (haptens) and bind with proteins before being recognized by lymphocytes or antibodies.
    Type I: immediate immunoglobulin (Ig) E-mediated hypersensitivity
    Type II: IgG- or IgM-mediated cytotoxicity
    Type III: IgG- or IgM-mediated immune complex disease
    Type IV: T-cell-mediated cellular hypersensitivity
  - Pseudoallergic reaction: a reaction with the same clinical manifestations as an allergic reaction (e.g., occurring via the direct release of histamine by opioids or complements activation by radioactive contrast media) but lacking immunological specificity [9].

7.3 Drugs Associated with the Development of ILD [10]

A variety of agents are associated with the development of ILD, including:
Cytotoxic/chemotherapeutic agents, such as bleomycin (oxidants, active oxygen radicals, and antioxidant systems), carmustine, busulfan (alkylating agents), and cyclophosphamide (cross-linking DNA strands)
Cardiovascular drugs such as amiodarone
Anti-inflammatory drugs, such as aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), and methotrexate
Antimicrobials and antibiotics such as nitrofurantoin and amphotericin B
Biological agents, such as tumor necrosis factor (TNF)-α blockers, recombinant IFN-α, T-cell antiproliferative agents
Other drugs such as cetuximab, bevacizumab, alemtuzumab, or trastuzumab
Miscellaneous drugs such as bromocriptine

Information on the long list of potentially pneumotoxic drugs is available at Pneumotox Online (http://www.pneumotox.com). A useful scheme for assessing whether a particular clinical manifestation represents an adverse drug reaction considers a patient's previous experience with the drug, alternative etiological agents, the timing of symptom occurrence, drug levels, and the effect of withdrawing the drug and drug re-challenge [11].

7.4 Patterns of DI-ILD

7.4.1 DAD

The DAD pattern is a nonspecific pattern of acute alveolar injury caused by a variety of noxious conditions such as severe infection or acute pancreatitis. It is the chief pathological finding in acute respiratory distress syndrome. DAD is frequently induced by cytotoxic drugs as a dramatic manifestation of pulmonary drug toxicity, and many drugs are known to cause DAD, including chemotherapeutic agents (bleomycin, busulfan, carmustine, and methotrexate) and other agents (amiodarone, colchicine, cyclophosphamide, penicillamine, gold salts, and melphalan).

A recent study reported a case of DAD induced by EGFR TKIs (gefitinib and erlotinib) in addition to cytotoxic chemotherapies such as paclitaxel, docetaxel, and gemcitabine. Preexisting pulmonary fibrosis was reported as a significant risk factor for DAD in addition to older age, poor performance status, male sex, smoking history, and concurrent cardiac disease [12]. Ethnic variations may also be risk factors for EGFR-induced DAD owing to genetic differences in responses to EGFR TKIs.

The relative risk for drug-induced DAD was found to be greater in Japanese lung cancer patients than in non-Japanese patients; ILD occurred in 2–4% of Japanese patients and 0.3% of US patients treated with this agent [6]. Newer anti-inflammatory drugs, such as the anti-TNF-α inhibitor infliximab [13], are also associated with adverse reactions, including an apparent risk for pulmonary infections such as tuberculosis and aspergillosis followed by DAD and pulmonary fibrosis.

Essentially, the pathological changes of DAD caused by noxious conditions can be divided into overlapping phases of exudation (1–7 days), proliferation (7–21 days), and fibrosis (>21 days; Fig. 7.1). The acute exudation phase is characterized by intra-alveolar edema and hemorrhage due to injuries to pneumocytes, endothelial cells, and the basement membrane, which result in the exudation of proteins and fibrin-rich fluid into interstitial and air spaces. This fibrinous material and the necrotic debris of pneumocytes form hyaline membranes that line the alveo-

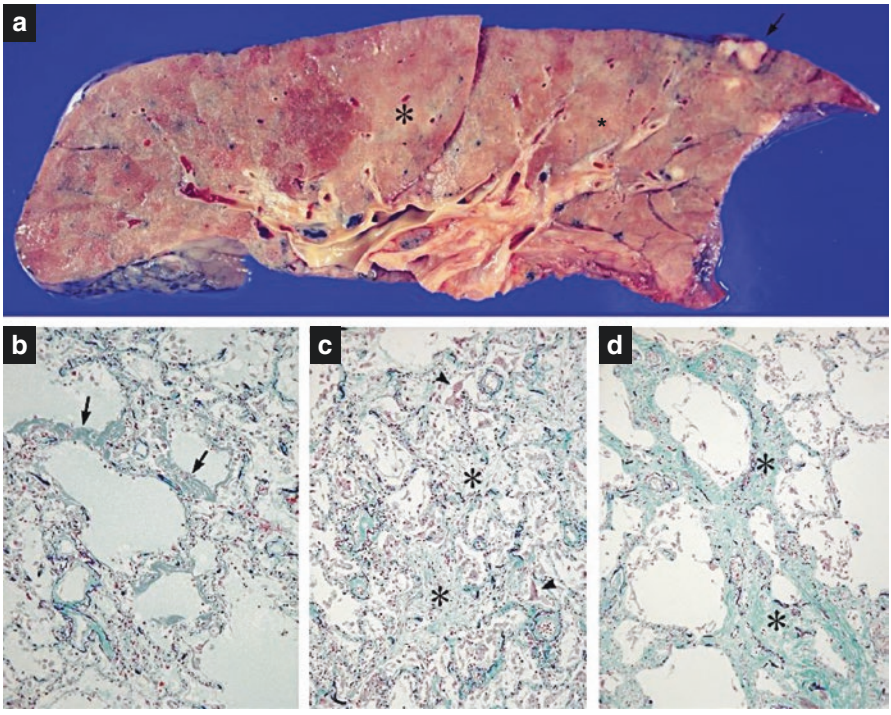

Fig. 7.1 DAD pattern: erlotinib. Photomicrograph showing the diffuse alveolar damage (DAD) pattern of interstitial lung disease (ILD) induced by erlotinib. (**a**) Gross findings include patchy abnormal whitish lesions (*asterisks*) in addition to metastatic nodes. (**b**) In the exudation phase, hyaline membranes appear as *dark-gray* areas (*arrows*) along the alveolar wall, in particular around the alveolar ducts, with Elastica Masson–Goldner (EMG) staining. (**c**) Proliferative phase characterized by the organization of exudate (*asterisks*) associated with the proliferation of pneumocytes (*arrowheads*) with cytological atypia and multinucleated changes. (**d**) In the fibrotic (chronic) phase, a ring of granulation tissue with mature collagen deposition around the alveolar ducts appears *green* with EMG staining (*asterisks*) [3]

lar wall, particularly around the alveolar ducts, and appear pink with hematoxylin and eosin staining. Hyaline membranes usually appear dark gray with Elastica Masson–Goldner (EMG) staining. Thus, it is easy to distinguish these membranes from fibrin alone (Fig. 7.1b). However, fibrin content in the hyaline membranes is occasionally increased in patients with DI-ILD who have more severe alveolar damage. Minimal interstitial mononuclear inflammatory infiltrates and fibrin thrombi in small pulmonary arteries also are observed.

The proliferative phase is characterized by the organization of exudate associated with the proliferation of pneumocytes with cytological atypia (Fig. 7.1c). Then, fibroblasts and myofibroblasts proliferate and migrate into the alveolar exudates through defects in the epithelial basement membrane to deposit collagen mainly surrounding the hyaline membranes. Epithelial cells grow over the hyaline membranes on the alveolar peripheral side but not the luminal duct side (Fig. 7.2, arrows) and form small lumina (Fig. 7.2, star). The involvement of the alveolar ducts results in the lining of these structures by a ring of granulation tissue of mature collagen deposition that appears green with EMG staining (Fig. 7.1d) in patients who are put on a ventilator more than 3–4 weeks in the fibrotic (chronic) phase of the condition.

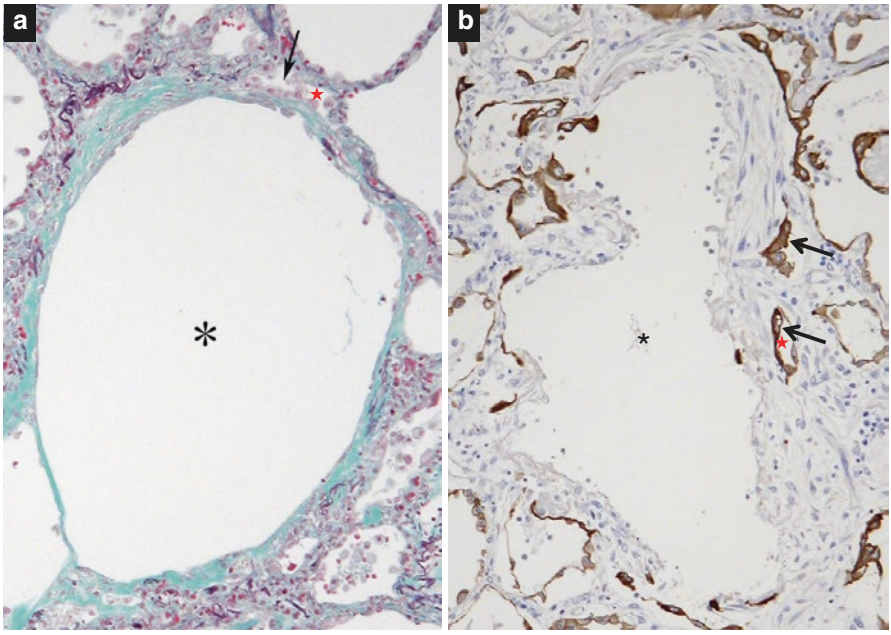

Fig. 7.2 DAD pattern: gefitinib EMG/keratin. Photomicrograph showing the DAD pattern of ILD induced by gefitinib. (**a**) Granulation tissue with collagen deposition around the alveolar ducts appears *green* (*arrow*) with EMG staining. (**b**) Epithelial cells (*arrowheads*) regrow over the hyaline membranes at the alveolar peripheral side, but not luminal duct side, and form small lumina (*star*, Keratin staining)

The histopathological pattern of drug-induced DAD is basically one of nonspecific findings similar to those of DAD with hyaline membranes that result from a variety of noxious conditions as described above. However, some features that suggest a drug-related etiology may be present. For example, clinicopathological differences can be observed between gefitinib-induced DAD and DAD related to severe infection. Patients with the latter condition frequently have multiple organ failure and disseminated intravascular coagulation. Fibroses in the lungs of these patients form mainly in the intra-alveolar spaces during the organization of hyaline membranes owing to systemic and severe circulatory disturbances, and DAD findings of same phase are widely distributed in the whole field of both lungs.

In contrast, patients with DAD caused by gefitinib or other chemotherapy agents show mainly acute respiratory distress syndrome alone and less frequently multiple organ failure. Furthermore, focal findings in these patients often include the presence of mixed phases of DAD in the same lung field. These findings, including findings related to the time process of disease development, are easy to evaluate with EMG staining (Fig. 7.1), and thus compared with infection-related DAD, gefitinib-related DAD is likely to occur more focally in the local lung field.

DAD related to gefitinib or chemotherapeutic agents also shows thickening of the alveolar interstitium with numerous myofibroblasts, which is characteristically more similar to the findings of acute interstitial pneumonia, in addition to fibrous tissue formation in the intra-alveolar spaces as hyaline membranes [14]. In some patients, acute fibrinous and OP findings may be present in addition to DAD findings [14]. These findings can be observed on chest computed tomography images as patchy distributions of ground-glass attenuation or multifocal areas of air space consolidation in some cases of gefitinib-induced lung injury, and the prognosis of these patients is better than that of patients with extensive bilateral ground-glass attenuation or air space consolidation [15].

Methotrexate is a commonly used cytotoxic drug that can cause DAD; however, it also produces other distinctive patterns, such as granulomatous interstitial pneumonia that is seldom seen in association with other common conditions (Fig. 7.3) [16]. Thus, drug-induced DAD may occur more focally with mixed phases in the same lung field, and more than one pattern of histopathological involvement, such as OP, acute interstitial pneumonia, and granulomatous patterns, may appear in the same patient [17] in addition to the typical DAD findings. Preexisting pulmonary fibrosis and genetic background are key findings and significant risk factors that suggest a drug reaction [12]. It is crucial to understand the pathological features of drug-induced lung injury including the evaluation of the time process of lesions as well as their clinical evaluation, especially in cases of DAD.

7.4.2 OP

The OP pattern frequently results from injuries caused by drugs such as bleomycin, mitomycin, minocycline, cyclophosphamide, amiodarone, methotrexate, NSAID–acetaminophen conjugates, ampicillin, gold salts, and TS-1. This pattern consists of

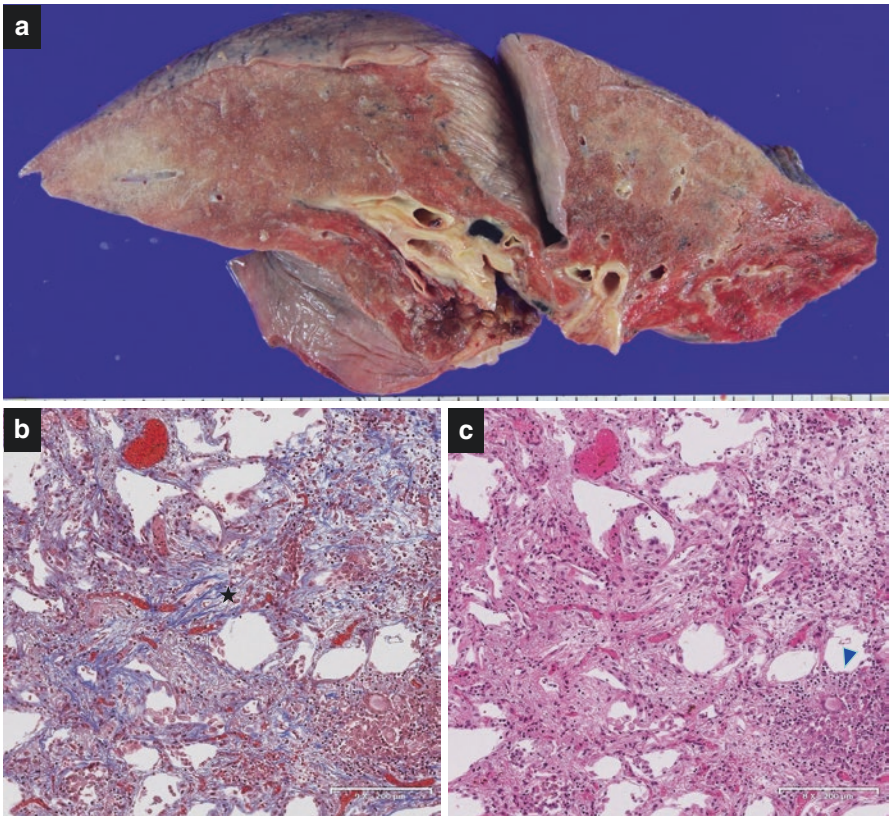

Fig. 7.3 Granulomatous alveolitis pattern: MTX. Photomicrograph showing the granulomatous alveolitis pattern of ILD induced by methotrexate. (**a**) Abnormal whitish lesions are seen in the gross examination. (**b**) Variable widening of alveolar walls by chronic inflammation and fibrosis can be observed with mural incorporation-type intra-alveolar fibrotic lesions (*star*, Masson staining). (**c**) Granulomatous lesions with multinucleated giant cells (*arrowhead*) are associated with the infiltration of chronic inflammatory cells and pneumocyte hyperplasia

patchy areas of consolidation consisting of intra-alveolar bud-type early fibrosis within distal airways, including the alveoli, alveolar ducts, and bronchioles. Many of these fibrotic lesions are covered with regenerated alveolar epithelial cells. EMG staining shows dense collagen globules and fine elastic fibers in association with collagen fibers in some of these lesions (Fig. 7.4). The architecture of the lung is preserved, interstitial chronic inflammation is usually mild, and dense scarring fibrosis is absent. This pattern is observed in a wide range of settings, including infection and collagen vascular disease and as an idiopathic condition. Compared with idiopathic cases, drug-induced cases more frequently show higher grades of lymphocyte/eosinocyte infiltration and the atypical finding of regenerated epithelial cells.

Amiodarone toxicity often results in an OP pattern (Fig. 7.5a), and the combination of findings of phospholipidosis with cytoplasmic fine vacuolation of macrophages and pneumocytes (Fig. 7.5b) is observed as a specific feature of this toxicity.

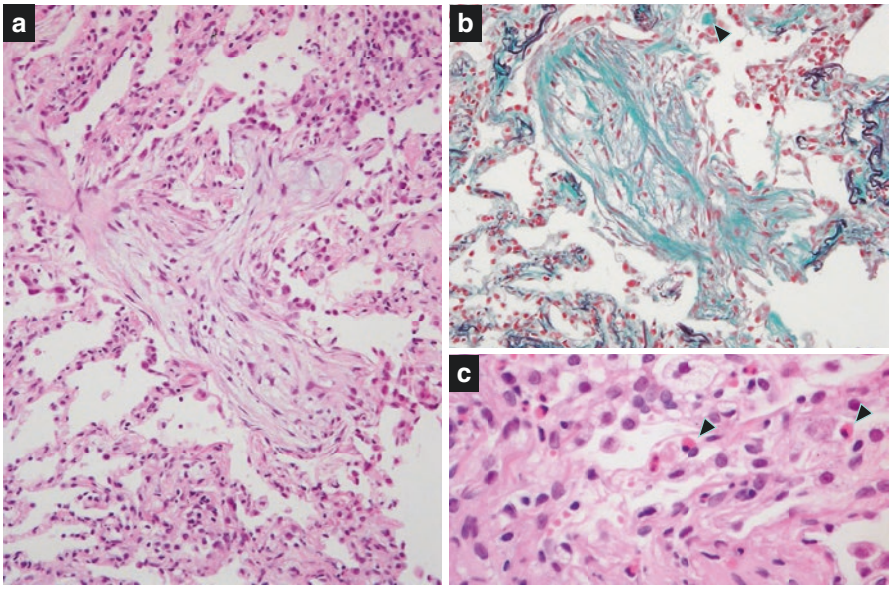

Fig. 7.4 Op pattern: diclofenac sodium. Photomicrograph showing the organizing pneumonia (OP) pattern of ILD induced by diclofenac sodium. (**a**) Bud-type early fibrosis is observed with notable infiltration of lymphocytes. (**b**) Bud-type early fibrosis forms within the distal airways, including the alveoli and alveolar ducts, with collagen globules (*arrowhead*, EMG staining). (**c**) Some eosinocytes (*arrowheads*) appear in the infiltrated inflammatory cells [3, 4]

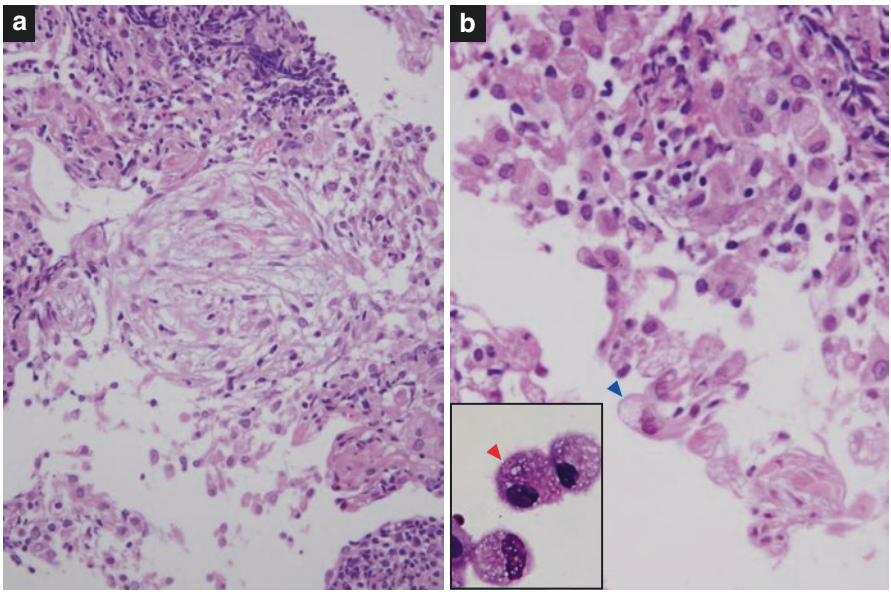

Fig. 7.5 Op pattern: amiodarone. Photomicrograph showing the OP pattern of ILD with vacuolation changes induced by amiodarone. (**a**) Bud-type early fibrosis is observed with notable infiltration of lymphocytes. (**b**) Fine vacuolation is apparent in the cytoplasm of macrophages (inset, *red arrowhead*, Giemsa staining) and pneumocytes (hematoxylin and eosin staining, *blue arrowhead*)

The majority of patients with amiodarone-related pulmonary toxicity recover once the drug is discontinued; however, the hyaline membranes of DAD are occasionally superimposed on interstitial changes in patients with poor prognoses [18].

7.4.3 NSIP

The NSIP pattern is frequently caused by cytotoxic drugs such as chemotherapeutic agents (bleomycin, busulfan, carmustine, cyclophosphamide), amiodarone, acetaminophen, ampicillin, carbamazepine, methotrexate, TS-1, and NSAIDs. This pattern is characterized by variable amounts of chronic inflammation and fibrosis mainly involving the alveolar walls. The distribution is diffuse and uniform and usually lacks evidence of being centriacinar or subpleural/paraseptal. Mural incorporation-type intra-alveolar fibroses are often observed. Bud-type intraluminal fibroses (OP findings) may also be present; however, they are not the dominant component. When fibrosis occurs in the NSIP pattern, it is usually mild and preserves lung structure.

Although this pattern occurs in a wide variety of settings, compared with idiopathic cases, drug-related patterns are characterized by bud-type intraluminal and mural incorporation-type fibroses or even border-type fibrosis (Fig. 7.6) as overlapping

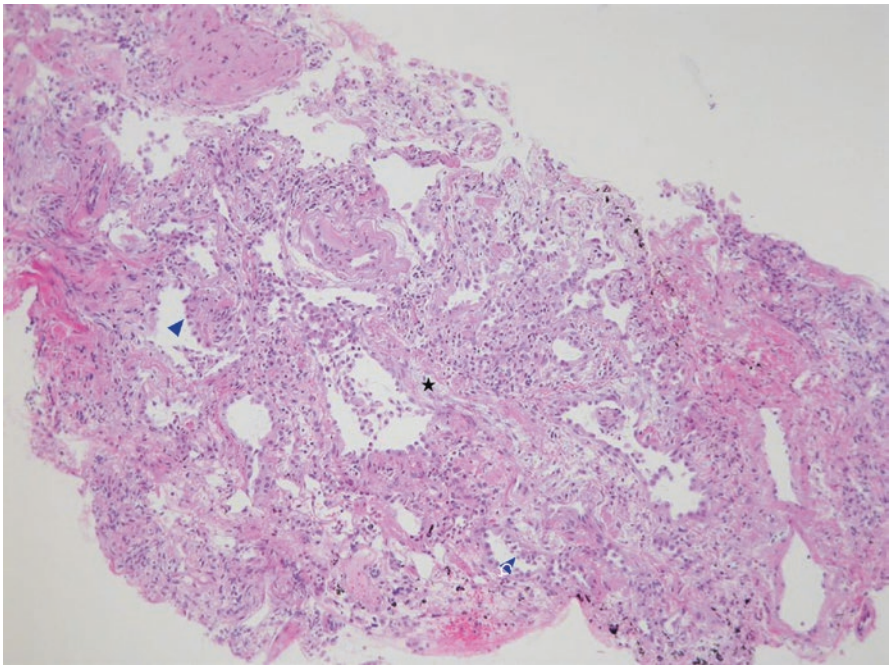

Fig. 7.6 NSIP pattern: *Geranium thunbergii*. Photomicrograph showing the nonspecific interstitial pneumonia (NSIP) pattern of ILD induced by *Geranium thunbergii*. Variable widening of the alveolar walls by chronic inflammation and fibrosis appears with pneumocyte hyperplasia (*arrowheads*) and the infiltration of lymphocytes and plasma cells. Mural incorporation-type intra-alveolar fibrosis is also present (*star*)

features with higher grades of lymphocyte/eosinocyte infiltration and reactive pneumocyte atypia. The NSIP pattern is also a common finding in methotrexate drug reactions, with overlapping features of granulomas that sometimes appear as relatively specific markers for drug reactions (Fig. 7.3) [16].

7.4.4 EP

The EP pattern is a common form of drug injury, and it occurs in association with drugs, such as NSAID–acetaminophen conjugates [19], amiodarone, ampicillin, bleomycin, carbamazepine, methotrexate, tetracycline, aurothiopropanosulfonate, and chlorpropamide. The EP pattern has several distinct clinical presentations, including acute and chronic variants. Peripheral eosinophilia is frequently described but is an inconsistent finding at initial presentation.

The most significant histopathological feature is the presence of interstitial and alveolar eosinocytes, and alveolar septal edema and intra-alveolar fibrin may be present in the acute form. Severe cases of acute EP can also display hyaline membranes with a DAD pattern. It is important to distinguish acute EP from other causes of DAD, because patients typically benefit from systemic corticosteroid treatment and show prompt recovery. Before the initiation of immunosuppressive therapy, infection should be rigorously excluded with culture and special stains because parasitic and fungal infections can also manifest as tissue eosinophilia. In the chronic form of EP, prominent alveolar macrophages or OP may be observed. Eosinophilic abscess with Charcot–Leyden crystals may also be present (Fig. 7.7).

7.4.5 Granulomatous Alveolitis

As an adverse drug reaction, granulomatous alveolitis pattern may take several forms, including non-necrotizing granulomas in a lymphatic distribution with a sarcoid-like pattern, nodular confluent non-necrotizing granulomas, or scattered formed granulomas and lymphocyte infiltration with a cellular and fibrosing interstitial pneumonia. The granulomatous alveolitis pattern is encountered on rare occasions with cytotoxic and other drugs, including methotrexate, bacille Calmette–Guérin immunization, IFNs, ciprofloxacin, antiviral therapy, TNF antagonists, and rituximab (monoclonal antibody against the protein CD20) [20]. In addition to the OP or NSIP pattern, the granulomatous alveolitis pattern with giant cells or small non-necrotizing granulomas is the only relatively specific marker for lung injury due to drugs such as methotrexate (Fig. 7.3) or rituximab (Fig. 7.8) in comparison with other drugs.

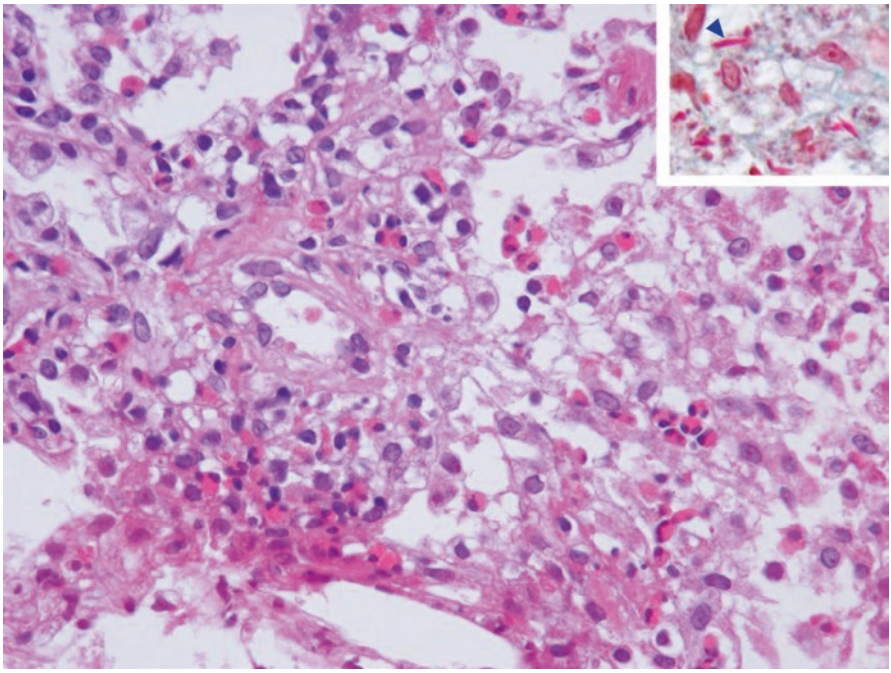

Fig. 7.7 EP pattern: ibuprofen. Photomicrograph showing the eosinophilic pneumonia (EP) pattern of ILD induced by ibuprofen. Alveolar spaces are filled with eosinocytes and plump eosinophilic macrophages, and there is an associated mild interstitial pneumonia with type II pneumocyte hyperplasia. Inset: Charcot–Leyden crystals (*arrowhead*) produced from the breakdown of eosinocytes stained *purplish red* with EMG staining appear as hexagonal bipyramidal structures [3, 4]

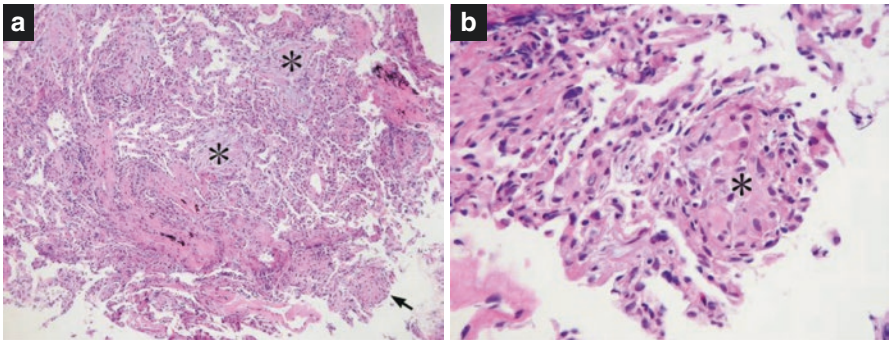

Fig. 7.8 Granulomatous alveolitis pattern. Photomicrograph showing the granulomatous reaction of rituximab pneumonitis. (**a**) Foci of air space organization (OP findings: *asterisks*) are observed with mild to moderate alveolar septal thickening and lymphocyte infiltration. (**b**) Giant cells and small non-necrotizing granulomas (*asterisk*) are relatively specific findings [3]

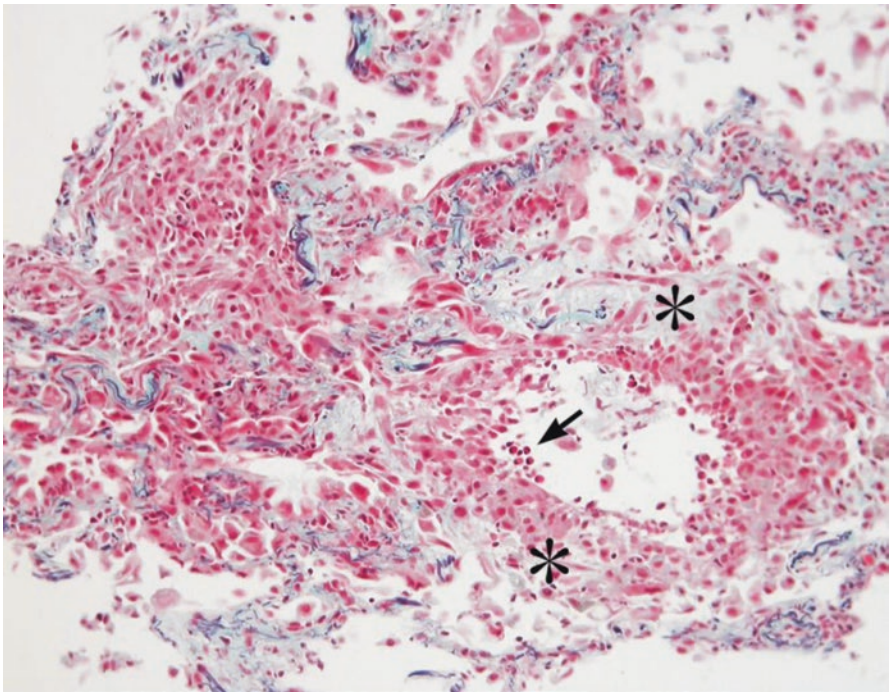

Fig. 7.9 Unclassifiable ILD pattern: loxoprofen sodium. Photomicrograph showing an unclassifiable pattern of ILD induced by loxoprofen sodium. A ring-like structure of granulation tissue is observed around the alveolar ducts with granulomatous macrophage accumulation (*asterisks*). Notable infiltration of lymphocytes and eosinocytes (*arrow*) is present with swollen and desquamative epithelial cells associated with NSIP or OP pattern findings [3, 4]

7.4.6 Unclassifiable ILD

Some cases of DI-ILD are unclassifiable. These cases show mixed findings of the DAD, OP, NSIP, and granulomatous alveolitis patterns in addition to the infiltration of notable lymphocytes and eosinocytes, type II pneumocyte hyperplasia with atypia, and cytoplasmic vacuolation in type II pneumocytes and macrophages. Such mixed findings are a clue to suspect drug reactions among the possible causes of nonidiopathic cases (Fig. 7.9).

7.4.7 Other Patterns

7.4.7.1 Alveolar Proteinosis (AP)

A variety of drugs have been associated with acquired alveolar proteinosis, including immunosuppressant drugs (mycophenolate mofetil, cyclosporine, cyclophosphamide, leflunomide, prednisolone, and sirolimus), antibiotics (imipenem and

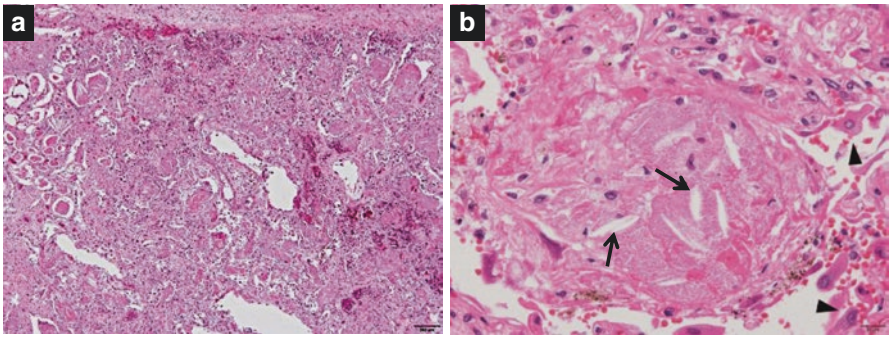

Fig. 7.10 PAP pattern: busulfan. Photomicrograph showing the alveolar proteinosis pattern induced by busulfan. (**a**) Alveoli are filled with eosinophilic amorphous material, and the alveolar walls are unremarkable. (**b**) Eosinophilic amorphous or finely granular material is present and contains acicular clefts (*arrows*) of dissolved cholesterol with desquamative epithelial cells (*arrowheads*)

cilastatin), and antineoplastic drugs (cytarabine, busulfan, and fludarabine). Because the drugs that cause alveolar proteinosis are structurally unrelated, multiple mechanisms are likely involved in the disease process. Histopathologically, the alveoli are filled with a finely granular acellular deposit that is eosinophilic and generally periodic acid–Schiff-positive and diastase-resistant. The surfactant apoprotein can also be identified immunohistochemically. These granular materials are typically accompanied by dense eosinophilic clumps (globules), cholesterol clefts, and foamy macrophages.

This reaction has been described best in the setting of leukemia or myelodysplastic syndromes in association with busulfan (Fig. 7.10) or imatinib [21]. It has also recently been associated with sirolimus (an mTOR inhibitor) [22].

7.4.7.2 BO

In addition to underlying conditions such as rheumatoid disease and chronic transplant rejection, constrictive-type BO reportedly accompanies treatment with drugs such as penicillamine [23] and gold salts. Raw *Sauropus androgynus*, which is consumed as a weight loss aid, causes severe BO (Fig. 7.11) [24]. Histopathologically, the earliest stage is characterized by eccentric subepithelial fibrosis and "onion skin" fibrosis with scattered admixed chronic inflammatory and foamy cells. Concentric fibrosis then progresses over time until the lumen becomes markedly narrowed or entirely obliterated. In other instances, the lumen may initially be occluded by loose fibrous tissue, presumably as a manifestation of active repair after injury to the airway epithelium and basal lamina. Some investigators have distinguished these latter lesions as more typical of BO, asserting that the outer dimensions of the bronchiole remain stable (i.e., not necessarily constricted).

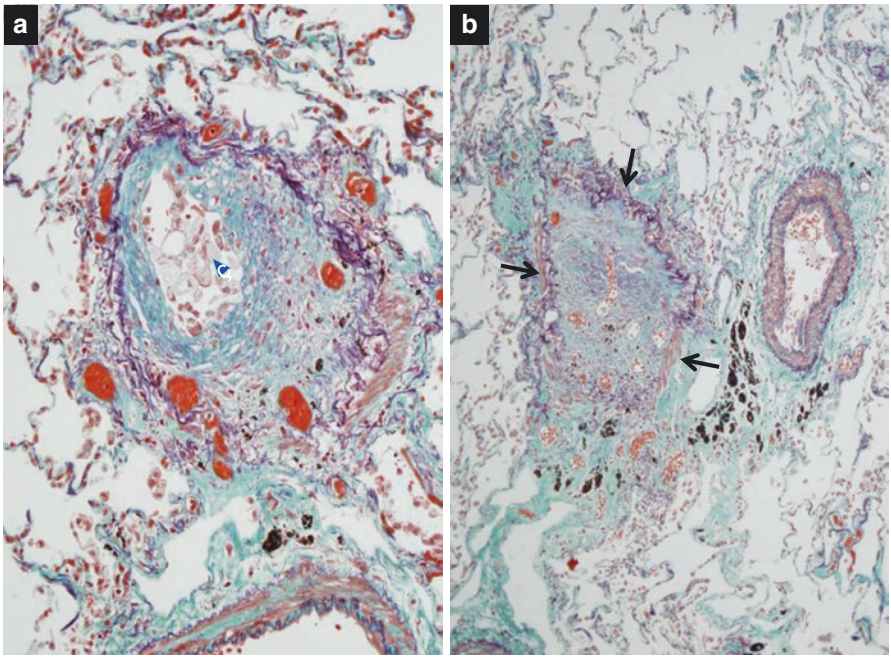

Fig. 7.11 BO pattern: Raw *Sancropus androgyns*. Photomicrograph showing bronchiolitis obliterans induced by raw *Sauropus androgynus*. (**a**) Partial occlusion of a bronchiole by eccentric submucosal fibrous tissue with chronic inflammatory and foamy cells (*arrowhead*). (**b**) An incomplete ring of smooth muscle (*arrows*) provides evidence that this focal pulmonary scar represents an obliterated bronchiole in which the lumen has become markedly narrowed and may be entirely obliterated as concentric fibrosis progresses

7.4.7.3 Diffuse Pulmonary Hemorrhage

Diffuse pulmonary hemorrhage is a potential complication of drug toxicity. Drugs known to cause this condition include abciximab, aspirin, amiodarone, azathioprine, carbamazepine, cyclosporine, docetaxel, fibrinolytics, heparin, hydralazine, oral anticoagulants, penicillamine, platelet receptor inhibitors (e.g., abciximab and clopidogrel), retinoic acid, sirolimus, streptokinase, and urokinase. Diffuse pulmonary hemorrhage may result from anticoagulant interference with the clotting mechanism or from widespread pulmonary capillaritis, the latter of which has been reported in leukemic patients treated with retinoic acid [25, 26]. Pulmonary hemorrhage has also been reported as an idiosyncratic reaction to lymphangiography media [27] and a complication of immunoglobulin infusion [28], whereas the development of anti-basement membrane antibodies resulting in Goodpasture's syndrome or microscopic polyarteritis has been attributed to penicillamine [29].

The histology of acute and chronic pulmonary hemorrhage consists of the intra-alveolar accumulation of red blood cells or hemosiderin-laden macrophages, or both. Because fresh hemorrhaging is a common artifact of a biopsy procedure, it

must be confirmed to be pathological with clinical findings compatible with hemorrhage such as hemoptysis and diffuse alveolar infiltrates on a chest computed tomography image. The presence of hemosiderin-laden macrophages also supports the existence of an ongoing hemorrhagic process. Other histopathological findings compatible with hemorrhage include neutrophilic capillaritis or other acute reactive changes such as prominent pneumocyte hyperplasia with focal disruption of the alveolar walls. Concluding that a pulmonary hemorrhage is caused by drug toxicity requires the exclusion of other causes of pulmonary hemorrhage such as vasculitis and collagen vascular disease (especially systemic lupus erythematosus).

7.5 General Clinicopathological Features of DI-ILD

It is worth bearing in mind that one drug may cause several patterns of disease, and one disease pattern may be produced by a variety of drugs. Furthermore, a drug reaction can develop both long after a drug has been withdrawn and suddenly even though the dose of the drug has not been altered. Drug effects may be augmented by factors such as age, previous radiotherapy, and elevated oxygen levels.

Most drugs of a comparable class induce similar patterns of pulmonary involvement, which suggests a common cytopathogenic mechanism. For example, NSAIDs can cause acute pulmonary hypersensitivity reactions resulting in bilateral interstitial infiltration and EP. However, most of the pathological changes in the lung related to drug toxicity are nonspecific. Drugs can produce more than one pattern of histopathological involvement in the same patient, and these reactions can manifest acutely, subacutely, or chronically. Thus, in comparison to idiopathic cases, drug-mediated injuries are more likely to appear as a mixture of both acute and chronic disease, which can be a clue to the diagnosis.

Moreover, type II pneumocyte hyperplasia with atypia, Mallory bodies, squamous metaplasia, cytoplasmic vacuolation in type II cells and macrophages, and tissue eosinophilia can occur in drug reactions. In particular, some drugs are associated with the production of small-formed granulomas in the lung that mimic infection or hypersensitivity. In chronic drug toxicity, lung fibrosis may occur, sometimes with honeycomb remodeling. In lung injury related to the use of cytotoxic/chemotherapeutic or biological agents, preexisting pulmonary fibrosis has been reported as a significant risk factor in addition to older age, poor performance status, male sex, smoking history, and ethnic variations.

7.6 Conclusion

Although the histopathological changes of drug-induced lung injury are nonspecific, a lung biopsy should be performed if drug-induced lung injury is suspected clinically. A biopsy can also help diagnose infection or malignancy. Examination of

even a small amount of lung biopsy material via transbronchial lung biopsy can help identify a pattern of lung tissue injury as a drug reaction and aid in determining prognosis if precise findings are obtained. Overall, clinico-radiologic-pathological diagnoses should be made for excluding other causes. As new therapeutic agents continue to become available, pathologist and clinicians must be alert for emerging forms of drug toxicity.

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Chapter 8
Differential Diagnoses of DLI: What Are the Differential Diagnoses of DLI?

Akihito Yokoyama

Abstract Lung injury can be diagnosed as drug induced when it develops during the time span of drug intake, when it is a possible side effect of the drug, and after excluding other causes. Even if a new lung injury appears immediately after drug administration, it does not necessarily mean that it is drug induced. Some considerations could be pneumonia caused by an opportunistic infection, exacerbation of underlying disease, or other unrelated diseases. The differential diagnoses of drug-induced lung injury are described in this chapter.

Keywords Microbial pneumonia • Pneumocystis pneumonia • Pulmonary edema • KL-6 • Interstitial pneumonia

8.1 Introduction

Recently, unexpected drug-induced lung injuries (DLIs) are becoming popular due to the variety of drugs being used in daily medical treatment [1, 2]. DLI can be diagnosed if a new lung injury develops during the time span that drugs are used and when other causes can be excluded. However, DLI encompasses various types and characteristics of lung injuries, and the same drug may possibly cause various types of lung injuries. The association between drugs and diseases is complicated, considering that the duration of drug administration and lung injury do not always correlate. In addition, a patient with suspected DLI may not recuperate by stopping the drug. All these factors can lead to difficulty in diagnosis in some cases.

In this review, several diseases that should be considered in the differential diagnoses of DLI will be described.

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8.2 Differential Diagnosis

To ascertain that a lung injury is caused by drugs, the most important process is the differential diagnosis. Integration of information obtained from patient's symptoms, physical findings, history of drug use, diagnostic images, and pathologic findings is necessary. However, excluding exacerbation of the underlying disease and opportunistic infections is sometimes difficult, especially if immunosuppressive drugs, such as biological agents, are being given [3].

Differential diagnosis of DLI entails two processes. One is the abovementioned exclusion of other causes, and the other is to determine the causative agents. Because several drugs are often used concurrently, especially in elderly patients, detailed history of each drug use is essential (Fig. 8.1). When asking about history of drug use, it is important to confirm detailed information on all drugs taken, not only those that were prescribed. In addition, as is mentioned in the other article, challenge test and drug sensitivity test may lack of specificity [2, 4].

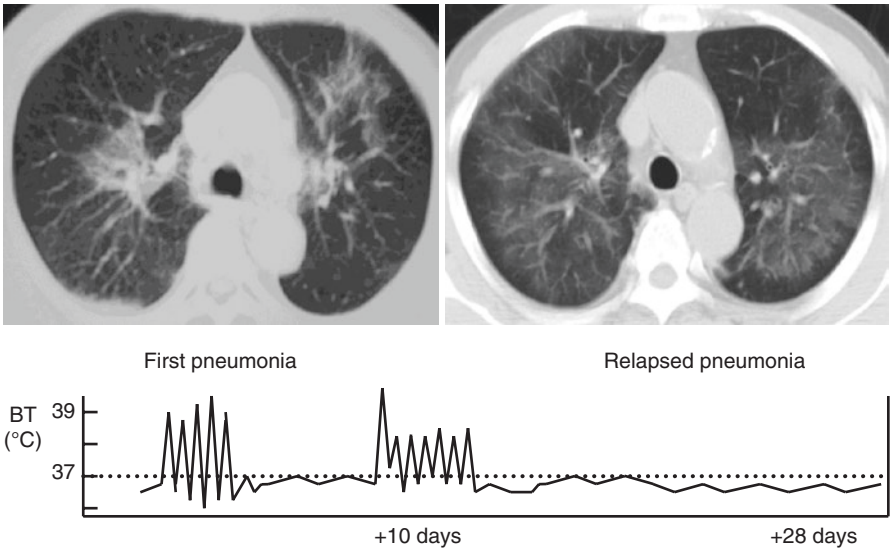

Fig. 8.1 A case of drug-induced eosinophilic pneumonia. An old man consulted a clinic due to cough and fever and was diagnosed as bacterial pneumonia. After taking antibacterial drugs, his cough and fever almost disappeared. However, about 10 days later, his illness relapsed. Based on examination, his illness was diagnosed as drug-induced eosinophilic pneumonia, not infectious pneumonia. In this case, the patient had been taking three kinds of Chinese medicines, which he stopped after being diagnosed as pneumonia. When his detailed drug history was carefully gathered after he recovered from symptoms of second pneumonia, it was proven that only "saiko-karyukotsuboreito" was administered. Therefore, the medicine was considered as the cause of his disease

8.3 Underlying Diseases

Cases with acute exacerbation of underlying interstitial pneumonia (IP), such as idiopathic IP and collagen vascular disease-associated IP, may present as critical acute lung injury with diffuse alveolar damage (DAD) on histology. This condition could manifest after invasive procedures, such as surgery; however, the mechanisms are unknown. Acute exacerbation of IP is usually diagnosed as severe drug-induced pneumonia when acute lung injury develops during administration of a possible offending drug. Such condition is prevalent in Japan and seemed to be rare and almost ignored in Western countries until recently [5]. A retrospective national cohort study conducted on 1763 lung cancer patients who developed IP after thoracic surgery between 2000 and 2009 at all hospitals certified by the Japanese Association for Thoracic Surgery showed that 164 cases (9.3%) were acute exacerbation of IP; in addition, the mean time from surgery to acute exacerbation of IP was 7 days, with a mortality rate of 43.9% [6].

International comparison of the frequency of DLI shows that among gefitinib-treated patients, 5.8% patients in Japan developed drug-induced IP, whereas only 0.3% in Western countries acquired the condition. On the other hand, the percentage of patients who developed methotrexate (MTX)-induced lung injury was the same at 0.3% among countries. Based on this, critical DLIs with DAD are especially prevalent in Japan. This corresponds to the fact that acute exacerbation of interstitial pulmonary fibrosis (IPF) is also prevalent in Japan [7].

Because correlation between IPF and lung cancer is common, many patients treated for lung cancer have IP. In fact, acute exacerbation of IP after chemotherapy was reported to occur in about 20%, with a mortality rate of 6%. The incidence of acute exacerbation was associated with old age, low performance status, and computed tomography (CT) patterns of usual interstitial pneumonia (UIP, 30%, vs. non-UIP, 8%) [8]. In such exacerbated cases, the possibility of carcinomatous lymphangitis should be differentiated.

In patients with IP, many drugs have to be administered with prudence and information on prohibited drugs should be known. Anticancer drugs that are strictly prohibited in patients with IP include irinotecan, amrubicin, gemcitabine, bleomycin, pepleomycin, and a type of peginterferon. Detection of IP accompanying lung cancer is important. Drug-induced pneumonia can be predicted by interstitial shadows on chest CT scan but not on chest X-ray film [9].

8.4 Concomitant Pneumonia

When considering DLI, the possibility of lung infections is important to exclude. The radiographic findings are almost similar among pneumonia caused by pathogenic microbes, eosinophilic pneumonia (EP), chronic organizing pneumonia (COP), and

alveolar hemorrhage caused by drugs. In addition, interstitial shadows can often be caused by aspiration pneumonia, which may resemble with drug-induced pneumonia. Symptoms of DLI, such as cough, fever, and abnormal lung shadows, appear like bacterial pneumonia. Therefore, in the diagnosis of drug-induced lung disorders, one should always exclude pneumonia caused by microbes, including tuberculosis, chlamydophila, mycoplasma, virus, and fungus [3].

Opportunistic infection is especially important in the differential diagnosis when drugs with immunosuppressive effects are used. Conversely, a final diagnosis of drug-induced pneumonia is usually obtained in many cases that do not respond to prolonged antibiotic treatment. Pneumococcal pneumonia as an opportunistic infection may have an atypical presentation. Figure 8.2 shows a case of a middle-aged woman who was administered biological drugs [antitumor necrosis factor (TNF) antibody] for rheumatoid arthritis (RA) and acquired microbial pneumonia. Patients with RA tend to suffer from microbial pneumonia. Notably, administration of biological agents augments this tendency and increases the risk for mortality. When biological agents are being administered, the infecting organism may not be the usual bacteria. However, in this case (Fig. 8.2), a diagnosis of the most common pneumococcal etiology of pneumonia was obtained by sputum Gram's stain.

Patients with RA often suffer from drug-induced pneumonia, frequently due to MTX, which is a basic drug. A typical shadow of MTX-induced pneumonia looks similar to that of hypersensitivity pneumonia [10]. Moreover, administration of MTX, as well as corticosteroids, may often cause pneumocystis pneumonia (PCP).

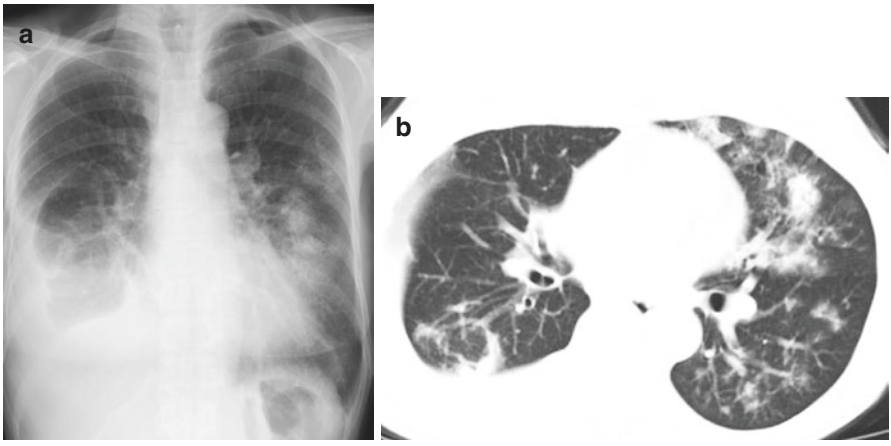

Fig. 8.2 A case of atypical pneumonia caused by *Streptococcus pneumoniae*. A 55-year-old woman was administered infliximab every 3 months for 6 years for rheumatoid arthritis. On one occasion, she suffered from symptoms of common cold, including cough; this happened 3 days after taking the drug. After 7 days, she still had fever above 38°C and started to become short of breath. (**a**) Routine chest radiography on admission shows bilateral pneumonia shadows and pleural effusion on the right. (**b**) Computed tomography scan of the chest shows multiple bronchopneumonia shadows on both lungs

8.5 Others

Hypersensitivity pneumonitis (HP) and EP could be caused by drugs. In such conditions, it is essential to exclude other causes, such as summer-type HP, bird fancier's lung, occupational HP (farmer's lung), and EP attributed to parasites, smoking, and other uncertain causes [11]. As described, the typical characteristics of MTX-induced pneumonitis are similar to those of acute HP. Such knowledge of the typical clinical presentation will help us suspect DLI.

Cases with cardiac failure or pulmonary edema due to drug-induced depression of cardiac function need to be differentiated from DLI. Pulmonary edema is a commonly encountered pathologic condition that is important to differentiate from drug-induced pneumonia (Fig. 8.3). For example, pulmonary edema caused by beta-blockers is not lung injury. Other conditions with similar images on chest CT and that need to be differentiated from DLI include pulmonary alveolar proteinosis, acute EP, and carcinomatous lymphangiosis. Figure 8.3b shows a case of non-cardiogenic pulmonary edema in acute respiratory distress syndrome. It should be noted that this kind of serious lung edema may be due to not only chemotherapy and antirheumatic drugs but also blood transfusions.

In patients with leukemia or lymphoma, the causes of abnormal lung shadows are many and include lung infiltration of abnormal cells, opportunistic infection, and lung injury from blood infusion [12]. In patients with RA, lymphoproliferative disease was reported to have an incidence that was 2–4 times higher than that of

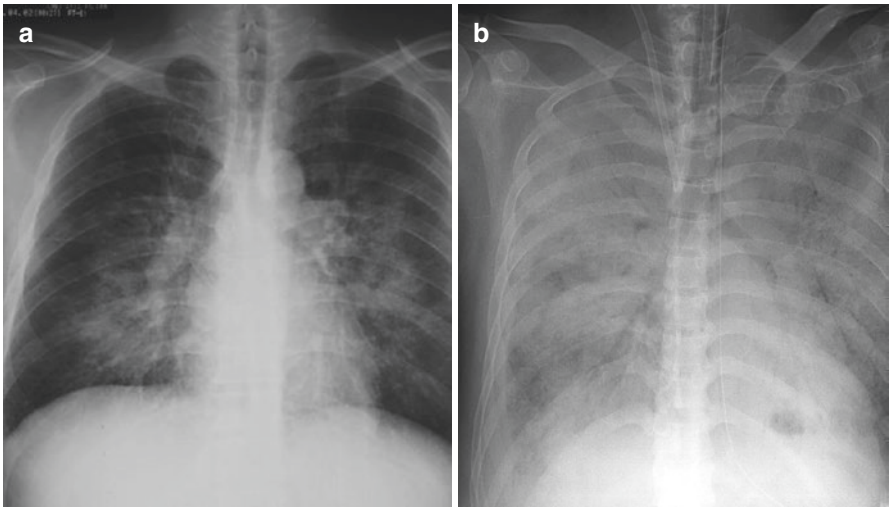

Fig. 8.3 A chest radiograph of pulmonary edema. (**a**) A typical butterfly pattern is seen. If the patient is young, the pattern may be acute eosinophilic pneumonia. The pattern may also be that of carcinomatous lymphangiosis or alveolar proteinosis. (**b**) An image of serious pulmonary edema. In this case, pneumococcal pneumonia developed rapidly into acute respiratory distress syndrome

healthy controls and accounted for 6–7% of all deaths [13]. In cases of lymphoma caused by MTX, activation of Epstein-Barr virus is seen, and a part of them disappears by stopping MTX.

8.6 Laboratory Tests

Before administration of drugs that often cause lung injuries, chest X-ray or CT film and measurement of KL-6, a biomarker for interstitial pneumonias, should be obtained for future comparison. In addition, constant monitoring of these parameters during drug use is necessary for early detection of lung injury. For some drugs, such instructions are described in the package insert. It is also important to watch out for any changes in symptoms, lung sounds, or oxygen saturation, in order to detect new lung injury as soon as possible. While we have to be careful for changes in symptoms, as well as in physical and laboratory findings, it is also important to search for faint radiographic changes among serial images. In particular, image comparison is very important in cases of PCP. If chest X-ray films suggest something suspicious, conducting chest CT scans, if available, would be diagnostic.

In the diagnosis of infectious lung diseases, sputum examination for usual smear and culture is important. The polymerase chain reaction (PCR)-based detection of tubercle bacillus, nontuberculous mycobacterium, and *Pneumocystis jirovecii* in sputum is also useful [14]. Moreover, methods for rapid identification of pathogens are available; these include IgM antibodies for mycoplasma, urine antigen of Legionella, and *Streptococcus pneumoniae* [15]. For cytomegalovirus infection, serum antigen detection, PCR for DNA, and pathologic examination are used. For fungal infection, *Cryptococcus* or *Aspergillus* antigen is available. Serum β-D glucan has a high value in cases of PCP and some fungal infections, such as aspergillosis, because its circulating levels correlate with the microbial load [16]. Procalcitonin may also be used as a marker of bacterial sepsis [17].

Bronchoscopic examinations, including bronchoalveolar lavage (BAL) and transbronchial lung biopsy, are not diagnostic for DLIs. However, these are useful for exclusion of other diseases, such as respiratory infections and malignant diseases. Furthermore, BAL is easy to perform and may provide information on histopathologic findings [18]. In patients who are suspected to have drug-induced pneumonia based on abnormal shadows on chest X-ray films, there is a possibility of missing serious diseases unless other conditions are definitively excluded.

Figure 8.4 shows the case of an old woman who was suspected to have drug-induced pneumonia due to an over-the-counter medicine for common cold. One week later, she stopped all of her medicines and revisited the doctor. However, the fever and abnormal shadows remained. As a matter of fact, she had symptoms of acute leukemia, although she felt to be suffered from a cold. Eventually, her lung

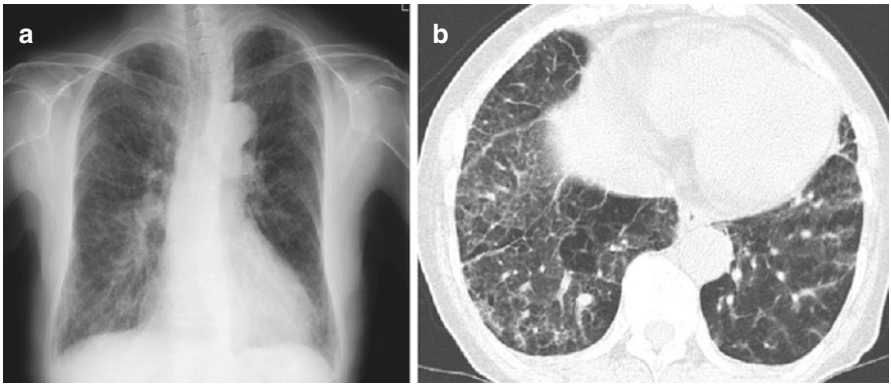

Fig. 8.4 A 74-year-old woman with lung infiltration of leukemic cells. She took non-prescription drugs for fever and fatigue due to common cold. After taking the drugs, she felt even worse and visited a clinic. On chest X-ray (**a**) and chest HRCT (**b**), ground glass opacity was seen in both lungs. Drug-induced pneumonia from the common cold medicine was suspected. Although her doctor suggested that she would promptly recover by stopping the medication, the fever did not disappear. Then she visited our out-patient clinic. On analysis of bronchoalveolar lavage fluid, 40% of the total number of cells comprised atypical lymphocytes. The disease was proven to be acute leukemia by bone marrow examination

shadows were proven to be not due to drug-induced pneumonia but from infiltration of leukemic cells. IP induced by acetaminophen [19] or non-prescription, over-the-counter cold medicines is well known in Japan because of a warning from the Ministry of Health, Labor and Welfare. However, this case serves as a lesson that it is important to eliminate preconceived bias and make a diagnosis according to standard procedures.

8.7 Biomarkers

Serum markers, including KL-6, are used to differentiate infectious diseases from drug-induced pneumonia [20]. However, according to our experience, the sensitivity of KL-6 in the diagnosis of drug-induced pneumonia is not so high at 50–60%. When compared with patterns on high-resolution CT of the chest, an increase in the level serum markers has been linked with DAD, chronic IP, and non-specific IP, whereas there was no change in serum markers in cases of lung edema, HP, EP, and COP [13]. It should be noted that the sensitivity of serum markers in differentiating between EP/COP and microbial pneumonia is very low. In general, surfactant protein (SP)-A has a high sensitivity and low specificity but is often increased in microbial pneumonia. Therefore, KL-6 and/or SP-D, but not SP-A, is recommended for use in the differential diagnosis (Fig. 8.5).

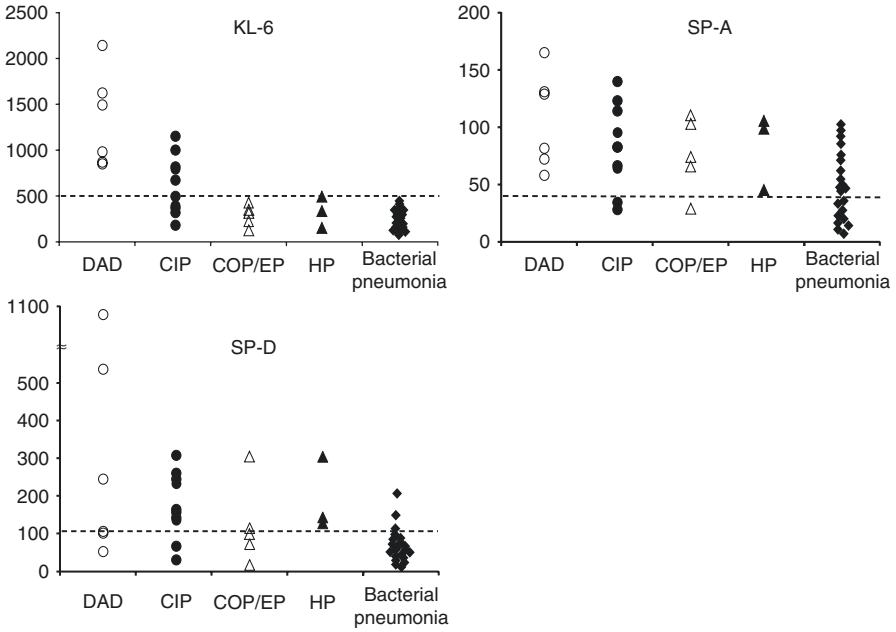

Fig. 8.5 Serum markers in the differential diagnosis. Circulating levels of KL-6, SP-A, and SP-D in 45 patients with drug-induced pneumonia ($n = 24$) and bacterial pneumonia ($n = 21$) are shown. The levels of these markers depend on the patterns observed on high-resolution computed tomography. KL-6 and SP-D have good sensitivity and specificity and are useful to differentiate drug-induced pneumonia from microbial pneumonia. SP-A has a high sensitivity but very low specificity

8.8 Conclusions

Exclusion of other causes is essential for the diagnosis of DLI. Other causes include exacerbation of underlying diseases, opportunistic infection, hypersensitivity pneumonias, idiopathic eosinophilic pneumonias, pulmonary edema, and so on. Imaging, biomarkers such as KL-6, bronchoscopic examinations including BAL, and transbronchial biopsy could be useful for differential diagnosis.

Needless to say, the use of drugs should be accompanied by knowledge of the potential side effects. When unfamiliar medicines are used, the latest information should be obtained from the attached leaflet or package insert. Instructions written on the document should be followed, unless there is a specific reason, as mentioned by the Japanese Supreme Court. Therefore, an accident due to neglect of the drug instructions will held accountable to the physician. The latest information, including documents of the attached leaflets and urgent safety information, is available on the website of the Pharmaceuticals and Medical Device Agency of Japan (http://www.info.pmda.go.jp/) [20].

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Part III
Treatment

Chapter 9
Therapeutic Strategies for DLI: How Should DLI Be Treated?

Sakae Homma

Abstract The lungs are vulnerable to toxins because of their large surface area and act as a metabolic site for some substances. Drugs may induce specific respiratory reactions, or the lungs may be affected as part of a generalized response. Drug-induced lung injury (DLI) can involve the airways, lung parenchyma, mediastinum, pleura, pulmonary vasculature, and/or the neuromuscular system. The most common form of DLI is drug-induced interstitial lung disease. There are no disease types specific to DLI, and DLIs are diagnosed on the basis of clinical findings, chest CT images, and histopathologic findings. The first principle of management of DLI is early detection and cessation of treatment with the suspected drug. Response to corticosteroid therapy depends on the histopathologic pattern of drug-induced interstitial lung disease. Prognosis depends on the specific drug and underlying clinical, physiologic, and pathologic severity of lung disease. To minimize DLI morbidity and mortality, all health-care providers should be familiar with the possible adverse effects of medications they prescribe. Individual variability in drug response is an important concern in clinical practice and drug development. Such variability is multifactorial and includes extrinsic factors such as environmental features and genetic and intrinsic factors that affect the pharmacokinetics and pharmacodynamics of drugs.

Keywords Therapeutic strategy • Drug-induced lung injury (DLI) • Drug-induced interstitial lung disease (DILD) • Treatment

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9.1 Introduction

The number of drugs that cause lung disease will continue to increase with the development of new agents, such as biologics and immune checkpoint inhibitors [1–4]. Drug-induced lung injuries (DLIs) can affect the airways, lung parenchyma, mediastinum, pleura, pulmonary vasculature, and/or neuromuscular system. The most common form of DLI is drug-induced interstitial lung disease (DILD). Orally and parenterally administered drugs are the most frequent causes of DLI; however, nebulized and intrathecal agents have also been implicated. DLI may result from a direct or indirect drug effect; direct effects may be idiosyncratic or caused by a toxic reaction to the drug or one of its metabolites.

Diagnosis of DLI is difficult because the clinical, radiologic, and histologic findings are nonspecific. The connection with drug use and the development of related inflammatory damage or idiosyncratic toxicities is hard to recognize and quantify, especially in patients using multiple drugs [5].

9.2 Disease Types and Characteristics

There are no disease types specific to DLIs, and DLIs are diagnosed on the basis of clinical features, chest computed tomography (CT) images, and histopathologic findings. The pulmonary lesions, disease types, and corresponding histopathologic findings of DLIs are shown in Table 9.1 [6].

9.2.1 DLI Disease Types and Major Causative Drugs

Representative drugs reported to cause DLIs are listed in Table 9.2 [7].

9.2.1.1 DILD

DILD must be differentiated from diffuse lung diseases, including idiopathic interstitial pneumonias (IIPs), interstitial pneumonia associated with connective tissue disease, acute and chronic hypersensitivity pneumonia (HP), eosinophilic pneumonia (EP), acute lung injury (ALI)/acute respiratory distress syndrome, and *Pneumocystis jiroveci* pneumonia (PCP). However, it is particularly difficult to determine whether a new shadow detected in a diagnostic image of the lungs is attributable to primary disease or a drug.

Drugs reported to induce diffuse alveolar disease (DAD), organizing pneumonia (OP), nonspecific interstitial pneumonia (NSIP), and HP include amiodarone, cyclophosphamide (CPA), gefitinib, erlotinib, cetuximab, panitumumab, methotrexate

Table 9.1 Pulmonary lesions, disease types, and histopathological findings of DLIs [6]

Pulmonary lesions	Disease types	Histopathological findings
1. Alveolar and interstitial legions	Acute respiratory distress syndrome/ acute lung injury (ARDS/ALI)	Diffuse alveolar damage (DAD) (clinically severe)
	Acute interstitial pneumonia (AIP)	Diffuse alveolar damage (DAD) (clinically severe)
	Idiopathic pulmonary fibrosis (IPF)	Usual interstitial pneumonia (UIP)
	Nonspecific interstitial pneumonia (NSIP)	Nonspecific interstitial pneumonia (NSIP)
	Desquamative interstitial pneumonia (DIP)	Desquamative interstitial pneumonia (DIP)
	Cryptogenic organizing pneumonia (COP)	Organizing pneumonia (OP)
	Lymphocytic interstitial pneumonia (LIP)	Lymphocytic interstitial pneumonia (LIP)
	Eosinophilic pneumonia (EP)	Eosinophilic pneumonia (EP)
	Hypersensitivity pneumonia (HP)	Hypersensitivity pneumonia (HP)
	Granulomatous interstitial lung diseases	Granulomatous interstitial pneumonia
	Pulmonary edema	Pulmonary edema
	Capillary leak syndrome	Pulmonary edema
	Pulmonary alveolar proteinosis	Alveolar proteinosis
	Diffuse alveolar hemorrhage	Alveolar hemorrhage
2. Airway	Bronchial asthma	Bronchial asthma
	Bronchiolitis obliterans syndrome (BOS)	Constrictive bronchiolitis obliterans (CBO)
3. Blood vessels	Vasculitis	Vasculitis
	Pulmonary hypertension	Pulmonary hypertension
	Pulmonary veno-occlusive disease	Pulmonary veno-occlusive disease
4. Pleura	Pleuritis	Pleuritis

(MTX), bleomycin (BLM), gold drugs, salazosulfapyridine (SASP), penicillamine, hydralazine, beta-blockers, azathioprine, busulfan, procarbazine, and nitrofurantoin, among others.

9.2.1.2 Eosinophilic Pneumonia (EP)

Drug-induced EP is a collective term for diseases with respiratory manifestations—including dyspnea—that develop as a consequence of lung tissue damage caused by eosinophilic infiltration during drug treatment. Drugs that have been reported to induce EP include loxoprofen, acetylsalicylic acid, acetaminophen, MTX, penicillins, levofloxacin, phenytoin, imipramine, hydralazine, amiodarone, *shosaikoto*, and others [8, 9].

Table 9.2 Pulmonary lesions and causative drugs of DLIs [7]

Pattern of DLIs	Causative drugs
Diffuse alveolar damage (DAD)	Amiodarone, cyclophosphamide (CPA), gefitinib, erlotinib, cetuximab, panitumumab, methotrexate (MTX), and others
Organizing pneumonia (OP)	Bleomycin (BLM), MTX, CPA, gold drugs, amiodarone, salazosulfapyridine (SASP), penicillamine, and others
Nonspecific interstitial pneumonia (NSIP)	Amiodarone, MTX, penicillamine, gold drugs, hydralazine, and others
Hypersensitivity pneumonia (HP)	Beta-blockers, azathioprine, busulfan, procarbazine, nitrofurantoin, and others
Eosinophilic pneumonia (EP)	Loxoprofen, acetylsalicylic acid, acetaminophen, MTX, penicillins, levofloxacin, phenytoin, imipramine, hydralazine, amiodarone, shosaikoto, and others
Pulmonary edema (NCPE)	Cytarabine arabinoside (Ara-C), gemcitabine (GEM), MTX, amphotericin B (AMPH-B), acetazolamide, aspirin, morphine, and others
Bronchial asthma	Beta-blockers, NSAIDs, aspirin, and others
Bronchiolitis obliterans	Penicillamine, ampicillin, salazosulfapyridine, sauropus androgynus, and others
Pulmonary thromboembolism	Estrogen preparations, contraceptives, olanzapine, risperidone, and others
Alveolar hemorrhage	Heparin sodium, rivaroxaban, dabigatran etexilate, aspirin, clopidogrel sulfate, propylthiouracil, and others
Pulmonary hypertension	Aminorex, cocaine, methamphetamine, and others
Pleuritis	Amiodarone, procarbazine, methotrexate, infliximab, and others

9.2.1.3 Pulmonary Edema

Drug-induced pulmonary edema is typically non-cardiogenic pulmonary edema (NCPE). However, if the causative drug has a direct effect on the cardiovascular system that leads to decreased left ventricular function, the pathology is similar to cardiogenic pulmonary edema. Drugs reported to induce NCPE include cytarabine arabinoside (Ara-C), gemcitabine (GEM), MTX, amphotericin B (AMPH-B), acetazolamide, aspirin, morphine, and others [10, 11].

9.2.1.4 Airway Lesions

Drug-induced asthma or bronchospasm is broadly divided into three disease types, according to the causative agent, as follows: disease induced by beta-blockers; disease induced by nonsteroidal anti-inflammatory drugs, as in aspirin-induced asthma; and disease induced by inhalation of powdery substances, as in occupational asthma [7]. Bronchiolitis obliterans is induced by penicillamine, ampicillin, salazosulfapyridine, and *Sauropus androgynus*, among other drugs [12–14].

9.2.1.5 Pulmonary Vessel Lesions

Pulmonary Thromboembolism

Because estrogen preparations and oral contraceptives promote blood coagulation, their use is considered a risk factor for pulmonary thromboembolism. Numerous studies have reported that the use of psychotropic drugs to treat psychiatric disorders, including schizophrenia, was associated with pulmonary thromboembolism development [15].

Alveolar Hemorrhage

Drug-induced alveolar hemorrhage occasionally occurs during the use of antithrombotic drugs, such as anticoagulant, antiplatelet, and thrombolytic drugs, or as a complication of vasculitis related to antineutrophil cytoplasmic antibodies, which are typically present in patients treated with antithyroid drugs [16].

Drugs reported to induce alveolar hemorrhage include heparin sodium, rivaroxaban, dabigatran etexilate, aspirin, clopidogrel sulfate, and propylthiouracil, and others.

Pulmonary Hypertension (PH)

Drug-induced PH is reported to account for approximately 10% of all PAH cases and is induced by aminorex, cocaine, and methamphetamine, among other drugs [17].

9.2.1.6 Pleural Lesions

Drug-induced pleural lesions are rare. To date, over 40 drugs have been reported to induce pleural lesions, including amiodarone, procarbazine, methotrexate, infliximab, etanercept, and others [18, 19].

9.3 Current Status of and Response to DLI Treatment

9.3.1 Current Status of Treatment

The first principle of management for DLIs is early detection and cessation of treatment with the suspected drug. The primary goal of treatment is suppression of the inflammatory response and prevention of lung fibrosis.

Table 9.3 Disease severity and treatment strategy for DLIs [6]

Degree of severity	PaO_2 (room air)	Treatment strategy
Mild	≥80 Torr	Discontinuation of the suspected drug
Moderate	60 to <80 Torr	Discontinuation of the suspected drug Corticosteroid therapy
Severe	<60 Torr (PaO_2/FiO_2 < 300)	Discontinuation of the suspected drug. mPSL pulse therapy for 3 days and then continuous corticosteroid therapy

Acute episodes of DLIs usually resolve within 24–48 h after drug discontinuation, but chronic syndromes take longer. Because hypoxemia is common in DLIs, supplemental oxygen therapy is often provided. If a cytotoxic DLI is severe or appears to progress despite drug discontinuation, empirical administration of corticosteroids is advisable.

If continued treatment is necessary, the suspected drug should be replaced by a drug that is less likely to induce DLIs. Antineoplastic drugs therapy, however, should not be resumed until the injury has resolved. Recent evidence indicates that treatment approaches for everolimus- or temsirolimus-induced interstitial pulmonary disease and immune-related adverse events should be based on disease severity (Table 9.3) or grade (Table 9.4).

Patients with a moderate DLI should be treated with corticosteroids at a dose equivalent to 0.5–1.0 mg/kg/day of prednisolone (PSL), depending on the suspected drug and condition of the patient, in addition to discontinuation of the suspected drug. Treatment at the initial dose should be continued for 2–4 weeks and then gradually tapered. Patients with a severe DLI should be treated with methylprednisolone (mPSL) pulse therapy consisting of an mPSL dose equivalent of 500–1000 mg/day for 3 days, followed by treatment with corticosteroids at a dose equivalent to 0.5–1.0 mg/kg/day of PSL for 2–4 weeks, which is then tapered. If lung injury and hypoxemia resolve immediately, corticosteroid therapy can be ceased after 1–2 months (Fig. 9.1).

Recent research on the side effects of the immune checkpoint inhibitor nivolumab showed that DILD was less frequent in patients with melanoma (approximately 2–5%) than in those with renal cancer or non-small cell lung cancer (NSCLC) (approximately 5%). Treatment-related deaths from DILD have been reported, and the frequencies of such deaths were similar in melanoma and NSCLC patients receiving pembrolizumab. Ipilimumab monotherapy results in pneumonitis in up to 5% of patients, although the percentages of patients with dyspnea and cough are higher. Combination administration of ipilimumab and nivolumab is associated with the highest rate of ILD (5–10% for any grade and 2% for grade 3/grade 4) [4, 20–26].

Observation and continued treatment with the suspected drug are acceptable for patients with asymptomatic DILD; however, development of symptoms warrants interruption of immune checkpoint delivery and initiation of corticosteroid treatment (Table 9.4).

Table 9.4 Management of DILD caused by immune checkpoint inhibitors [4]

Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life threatening)
Asymptomatic; clinical or diagnostic observations; no intervention needed: delay drug administration. Consider steroids (e.g., prednisone 1 mg/kg/day PO or methylprednisolone 1 mg/kg/day IV). Follow-up: reassess management after 3 weeks—if completely resolved or non-drug-related continue treatment. If worsens treat as grade 2 or grade 3/grade 4	Symptomatic; medical intervention indicated; limits instrumental ADLs: delay drug administration. Consider hospitalization, daily monitoring of symptoms. Steroids recommended (e.g., prednisone 1–2 mg/kg/day PO or methylprednisolone 1–2 mg/kg/day IV). Consider empiric antibiotics (if suspicious for concurrent infections). Follow-up: reassess management every 1–3 days. If improving, taper steroids and continue treatment if symptoms resolve completely. If it worsens treat as grade 3/grade 4	Severe symptoms; limits self-care ADLs; oxygen indicated: discontinue drug administration. Hospitalization. High-dose steroids with methylprednisolone (e.g., 1 g/day IV). Add prophylactic antibiotics for opportunistic infections. Consider bronchoscopy with biopsy. Reassess management daily. If not improving after 48 h or worsening, administer additional immunosuppressive therapy (e.g., infliximab, mycophenolate, immunoglobulins). If improving, taper steroids. Discontinue treatment permanently	Life-threatening respiratory compromise; urgent intervention indicated (e.g., intubation): as per grade 3. Intensive care support required

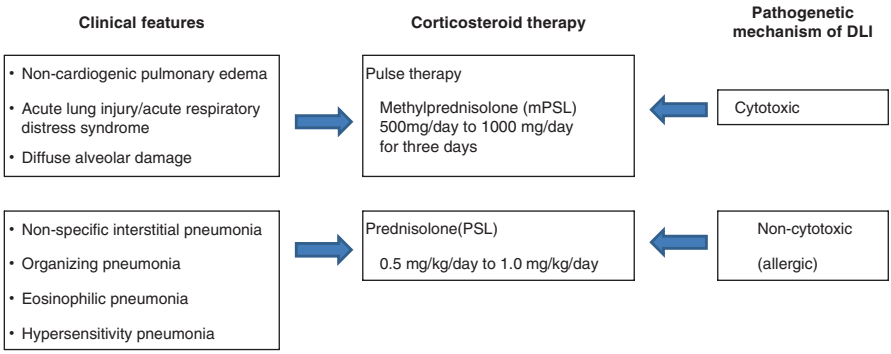

Fig. 9.1 Treatment strategy for DLIs [6]

9.3.2 Responses to Treatment

The response to corticosteroid therapy depends on the histopathologic pattern of DILD. Histopathologic changes for most drug reactions are nonspecific, but some drugs (e.g., amiodarone) have a characteristic histopathologic pattern of involvement that enables almost instant recognition of the causative agent. Methotrexate, for example, causes acute granulomatous DILD, which mimics an opportunistic infection [27].

Drugs can produce nearly all histopathologic patterns of interstitial pneumonia, including HP, OP, DAD, nonspecific interstitial pneumonia (NSIP), EP, pulmonary hemorrhage, and granulomatous pneumonitis. Most drugs in a comparable class induce a similar pattern of pulmonary involvement, which suggests a common cytopathic mechanism. However, some drugs produce more than one pattern of histopathologic involvement in the same patient. These reactions may be acute, subacute, or chronic (Table 9.2).

DLIs caused by allergic reactions and EP, HP, cellular NSIP, and OP associated with DILD generally respond to corticosteroids. However, DAD caused by cytotoxic mechanisms may not respond to corticosteroids. With respect to histopathologic findings, the following types of DLI cases will likely respond to corticosteroids: (1) cases in which histopathologic findings indicate inflammation characterized by lymphocyte infiltration or development of granulomatous lesions with no, or very limited, tissue damage or fibrosis and (2) cases in which histopathologic findings suggest EP or organic changes in alveoli. However, cases of DAD and those involving advanced fibrosis are unlikely to respond to corticosteroids.

Patients with OP, EP, or HP and normal serum KL-6 levels respond to corticosteroids; thus, those with DLIs and normal KL-6 levels are also likely to respond to corticosteroids, as long as the injury corresponds to any of the OP or HP clinical disease types for DLIs [28].

Treatment planning must carefully consider the severity of DLI and the morbidity associated with failure to treat the underlying disease. Alternative agents, if available, should be used. Because many patients with DILD are treated with immunosuppressive medications, which modestly increase the risk of infection, patients with DILD should receive the pneumococcal vaccine and yearly influenza virus vaccine. Furthermore, the incidence of tuberculosis is highly associated with antitumor necrosis factor monoclonal antibody therapy. The increased risk associated with early antitumor necrosis factor treatment and lack of an optimal chemopreventive treatment favor reactivation of latent tuberculosis.

9.4 Prognosis

Prognosis is favorable when acute DLIs are diagnosed early, and complete recovery can be expected in such cases. However, undiagnosed DLIs are associated with substantial morbidity and mortality. Prognosis depends on the specific drug and underlying clinical, physiologic, and pathologic severity of lung disease. Typical

complications of DLIs are pulmonary fibrosis and respiratory failure requiring mechanical ventilation. Unfortunately, if the initial injury or abnormal repair of injury is not stopped, progressive tissue damage can lead to worsening physiologic impairment and even death.

The prognosis for DILD varies in relation to the frequency of the DAD pattern. Thus, it is important to determine whether the presenting DILD has a DAD pattern. Histopathologic examination is required for diagnosis. However, patients often present in serious condition, when it is difficult to perform a lung biopsy. In such cases, high-resolution CT is helpful in determining the DILD pattern. In general, the suspected drug should be immediately discontinued and re-administration avoided.

9.5 Conclusions

DLIs can involve the airways, lung parenchyma, mediastinum, pleura, pulmonary vasculature, and/or the neuromuscular system. The first principle of management of DLIs is early detection and cessation of treatment with the suspected drug. Response to corticosteroid therapy depends on the histopathologic pattern of DILD. Prognosis depends on the specific drug and underlying clinical, physiologic, and pathologic severity of lung disease. In addition, the clinical and radiographic features of DILD are often difficult to distinguish from those of other causes of DILD (e.g., infections, lung involvement of an underlying disease, pulmonary edema, connective tissue disease), and no signs, symptoms, or laboratory or radiologic findings are considered pathognomonic. Therefore, it is essential for physicians to be familiar with iatrogenic diseases that may affect their patients. In addition, clinical and genetic risk stratification may improve prevention of DILD in the future.

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Part IV
Drugs Causing DLI

Chapter 10
DLI Induced by Nonmolecular Target Antineoplastic Drugs: What Are the Characteristics of DLI in Nonmolecular Target Antineoplastic Drugs?

Yasuo Saijo

Abstract All cytotoxic antineoplastic drugs can potentially cause drug-induced lung injury (DLI), although the frequency and type of DLI vary and the time of DLI onset depends on the drug. Risk factors for DLI include longer treatment time, poor performance status, heavy smoking history, and underlying lung comorbidities. The risk of DLI caused by cytotoxic antineoplastic drugs increases when they are combined with other antineoplastic drugs and irradiation. Therefore, all patients treated with cytotoxic antineoplastic drugs are at risk of DLI. During treatment with cytotoxic antineoplastic drugs, patient oxygen saturation should be monitored by oximetry. When respiratory symptoms occur, it is important to suspect DLI and to perform computed tomography immediately to diagnose DLI.

Keywords Antineoplastic drugs • Cancer • Interstitial pneumonia

10.1 Introduction

Drug-induced lung injury (DLI) caused by antineoplastic drugs was firstly recognized with bleomycin [1]. Subsequently, nearly all cytotoxic antineoplastic drugs have been reported to cause DLI. Recently developed antineoplastic drugs, including molecular targeting drugs, induce DLI more frequently than conventional antineoplastic drugs [2], probably because that they are more cytotoxic and are widely used to treat cancer patients with poor performance status and that the awareness of DLI is increased. Notably, the incidence of DLI is generally high in Japanese patients (Table 10.1) [3].

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Table 10.1 Incidence of DLI with each drug in Japan (%)

Paclitaxel	0.54
Docetaxel	0.1
Amrubicin hydrochloride	2.2
Gemcitabine hydrochloride	1.50
Pemetrexed	3.6
Vinorelbine	2.45
Irinotecan	1.30
Cyclophosphamide	Not described
Bleomycin	10.20
Cisplatin	0.38
Oxaliplatin	Not described
S-1	0.3

The information was obtained from the drug information sheets of the pharmaceutical companies

10.2 Mechanisms of DLI

Multiple mechanisms may be responsible for DLI caused by cytotoxic antineoplastic drugs. One of the mechanisms is direct cytotoxicity to alveolar epithelial cells or the alveolar capillary endothelium, with the subsequent release of cytokines and recruitment of inflammatory cells. Other mechanisms involve immune responses and reactive oxygen species (ROS) [4]. The systemic elevation of cytokines directly or indirectly results in capillary leakage and pulmonary edema. Methotrexate (MTX) induces the release of free oxygen radicals, such as nitric oxide, and various cytokines [5]. DLI can also be caused by the generation of ROS triggered by mitomycin C (MMC) and bleomycin. Susceptibility to bleomycin toxicity in the lungs may arise because bleomycin is preferentially distributed in lung tissue, and the lung is relatively deficient in the hydrolase enzyme that detoxifies bleomycin [6]. In addition to these mechanisms of DLI, several factors may influence the development of DLI, including age, total volume of the cytotoxic drugs, combined drugs, radiation therapy, underlying respiratory comorbidities, smoking history, oxygen therapy, and ethnicity.

On chest x-rays and computed tomography (CT), DLI can cause ground glass opacity, fibrosis, infiltrating shadows, and pleural effusions. The clinical features of DLI caused by cytotoxic antineoplastic drugs include bronchospasm, interstitial pneumonia, cryptogenic organizing pneumonia, eosinophilic pneumonia, lung edema, pleural effusion, and pulmonary fibrosis.

The time to onset varies with each cytotoxic anticancer drug and the mechanism. While gemcitabine and taxanes can cause DLI within a few days, DLI caused by busulfan develops in a mean of 3.5 years and can develop 10 years after using busulfan [7].

10.3 DLI Caused by Individual Cytotoxic Antineoplastic Drugs

10.3.1 Alkylating Agents

10.3.1.1 Cyclophosphamide

Although cyclophosphamide (CPA) itself is not toxic to pulmonary endothelial cells, hepatic metabolites of CPA are toxic [8]. The clinical manifestations of CPA-induced DLI include subacute pneumonia, cryptogenic organizing pneumonia, acute respiratory distress syndrome (ARDS), pulmonary fibrosis, and airway spasm. There are two distinct clinical patterns of CPA-induced DLI: acute and chronic [9]. Acute DLI occurs after 1–6 months from the start of treatment and can be improved by discontinuing the CPA and starting corticosteroid therapy. Chronic DLI occurs from several months to several years after CPA treatment and involves progressive pulmonary fibrosis with pleural thickening and poor response to corticosteroid therapy after prolonged treatment. There is no clear correlation between total dose of CPA and DLI risk. CT shows scattered or diffuse ground-glass opacities in the early phase, with rapid progression to fibrosis with honeycombing. CPA can lead to opportunistic infectious pneumonia caused by immunosuppression.

10.3.1.2 Busulfan

Busulfan was one of the first cytotoxic drugs associated with DLI. However, the mechanism of busulfan-induced DLI is still unknown. About 6% of patients treated with busulfan develop DLI an average of 3.5 years after starting on busulfan [7]. The response to corticosteroid therapy varies individually. There is a clear correlation between DLI and the total dose of busulfan. Concomitant irradiation may increase the risk of DLI. Although a clinical pattern of pulmonary fibrosis is seen, chest x-ray reveals a pulmonary proteinosis-like pattern in some cases [10]. Currently, busulfan is used only to prepare patients for autologous and allogenic bone marrow transplantation.

10.3.1.3 Nitrosoureas

The nitrosourea drugs include nimustin, carmustine, lomustine, and ranimustine. There have been several case reports of DLI caused by nitrosoureas since 1970. DLI includes acute interstitial pneumonia early on and progressive pulmonary fibrosis that is predominant in the upper lobe later. Carmustine-induced lung injury occurs in 20–30% of treated patients overall, and the incidence increases to 50% if the

cumulative dose exceeds 1.5 g/m^2 [11]. The odds ratio of DLI in patients treated with more than 450 mg/m^2 is 2.5 times that in patients treated with less than 450 mg/m^2 [12]. Pulmonary toxicity increases when nitrosoureas are combined with CPA or irradiation. The pneumothorax occurring in patients with pulmonary fibrosis caused by nitrosourea is characteristic.

10.3.2 Antimetabolites

10.3.2.1 Methotrexate

DLI occurs in 5–10% of patients treated with methotrexate (MTX) and usually develops within 1 month of starting therapy and rarely from several months to several years later. DLI can also occur in patients with rheumatoid arthritis. Allergic mechanisms are thought to cause DLI because the respiratory symptoms are often accompanied by fever and peripheral eosinophilia. The prognosis is generally favorable on discontinuing the MTX therapy, without corticosteroid therapy. The CT features of MTX-induced pulmonary injury vary and may include diffuse parenchymal opacification, reticular opacities, and centrilobular nodules [13]. Bilateral hilar lymph nodes and pleural effusions are seen in 10% of patients. *Pneumocystis carinii* pneumonia can occur after MTX use because of immunosuppression and should be considered in the differential diagnosis.

10.3.2.2 Cytarabine

High-dose cytarabine (Ara-C) can cause fatal non-cardiogenic pulmonary edema and ARDS [14]. DLI develops in 13–28% of patients during Ara-C treatment, and half of these cases develop within 1 month after completing the Ara-C treatment. The mechanism is not clear and the mortality rate is high. Treatments include mechanical ventilation, control of body fluids, and the prevention of infection.

10.3.2.3 Gemcitabine

The clinical features of gemcitabine (GEM)-induced lung injury include dyspnea, fever, pulmonary infiltrates, and cough. Taxanes (docetaxel and paclitaxel) are frequently co-administered in cases of DLI caused by gemcitabine. About 10% of patients receiving GEM develop DLI, with the highest rates (22–42%) observed in Hodgkin disease patients treated with a regimen that included GEM and bleomycin [15]. CT typically reveals diffuse ground-glass attenuation with smooth interlobular septal thickening and reticular opacities, which may progress to ARDS and death (Fig. 10.1). The majority of cases respond to steroid therapy, but some patients require careful monitoring of body fluids. Concurrent radiotherapy with GEM after

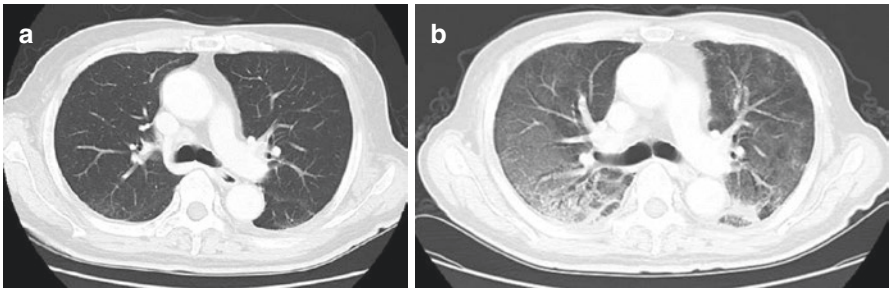

Fig. 10.1 Gemcitabine-induced lung injury in pancreas cancer. A patient with advanced pancreas cancer was treated with gemcitabine. Ground glass opacity in CT was shown after gemcitabine treatment. (**a**) Before, (**b**) after

induction with GEM and carboplatin causes excessive pulmonary toxicity (31.6%) [16]. Therefore, the use of GEM with thoracic radiotherapy should be avoided.

10.3.2.4 Pemetrexed

The reported frequency of pulmonary injury caused by pemetrexed (MTA) is 1.9% in Japan, compared with 0.3% in the rest of the world. The reported incidence of DLI associated with the combination of MTA and cisplatin for malignant mesothelioma was 1.6% in a large Japanese case registry study [17]. The frequency of DLI in patients with preexisting asbestosis was higher (5.3%) than that in patients without it (1.2%).

10.3.2.5 Fludarabine

DLI reportedly develops in 8% of patients after several days on fludarabine in early-onset cases. CT reveals interstitial shadows or infiltrating shadows in the alveolar spaces. Other patients develop DLI as eosinophilic pneumonia or multiple nodular shadows. Almost all cases improve on discontinuing the fludarabine and starting steroid therapy.

10.3.2.6 5-Fluorouracil, Capecitabine, and S-1

The exact incidence of DLI with 5-fluorouracil (5-FU) monotherapy is unknown, but it is rare. 5-FU is often used in combination with other antineoplastic drugs, including oxaliplatin and irinotecan for colorectal cancer. The FOLFOX and FOLFIRI cancer regimens include 5-FU and oxaliplatin or irinotecan and induce DLI in 1.5% of cases: it is fatal in about one-third of these [18]. The frequency of DLI caused by S-1 and capecitabine, prodrugs of 5-FU, alone is quite low.

10.3.3 Antineoplastic Antibiotics

10.3.3.1 Mitomycin C

Mitomycin C (MMC) has been replaced by newly developed antineoplastic drugs and is now used only for anal cancer. The incidence of DLI is 8% and it occurs when the total accumulated dose exceeds 20 mg/m^2. DLI caused by MMC includes acute bronchospasm, diffuse alveolar damage, and interstitial pneumonia. MMC also causes thrombotic microangiopathy (TMA), and approximately 50% of cases of MMC-TMA are associated with acute respiratory failure due to acute lung injury [19]. TMA usually develops 6–12 months after MMC treatment, and 95% of patients with TMA with acute respiratory failure ultimately die of the disease.

10.3.3.2 Bleomycin

Bleomycin (BLM) is a typical anticancer drug that causes pulmonary injury. Bleomycin-induced toxicity occurs predominantly in the lungs and skin because these tissues lack the BLM-inactivating enzyme, bleomycin hydrolase [20]. BLM induces lung toxicity via the induction of oxygen radicals, with the recruitment of leukocytes and fibroblasts augmenting the early inflammatory and later fibrotic reactions. The rate of development of DLI with BLM is about 20%, of which 1% is fatal. The risk of developing DLI increases significantly with a total cumulative dose greater than 400 units. Of patients treated with more than 550 units, 10% develop DLI. Age over 70 years, lung comorbidity, and chronic kidney disease all increase the risk of DLI. Concurrent or prior thoracic radiation or combination with cyclophosphamide or gemcitabine increases the pulmonary toxicity [15]. Importantly, oxygen use within 6 months after BLM treatment worsens the pulmonary toxicity.

The most common manifestation of BLM-induced DLI is diffuse alveolar damage, but it may also present as cryptogenic organizing pneumonia, with unilateral or bilateral patchy airspace consolidation in a subpleural and peribronchial distribution. There are no proven effective treatments for BLM-induced DLI, although corticosteroids are widely used. The pulmonary fibrosis caused by BLM is progressive, resistant to steroid therapy, and sometimes fatal. BLM is still used for germ cell tumors, skin cancer, and Hodgkin lymphoma, so clinicians should be aware of its pulmonary toxicity.

10.3.4 Microtubule Inhibitors

10.3.4.1 Vinca Alkaloids (Vincristine, Vinorelbine, and Vinblastine)

Lung toxicity has rarely been reported with vinblastine and vinorelbine. When used as a single agent for lung cancer, vinorelbine is associated with interstitial pneumonitis in 2.45% of patients in Japan. The combination of vinblastine and MMC causes bronchospasm, interstitial pneumonia, and non-cardiogenic pulmonary edema. The combination of vinorelbine and gemcitabine increases the risk of DLI.

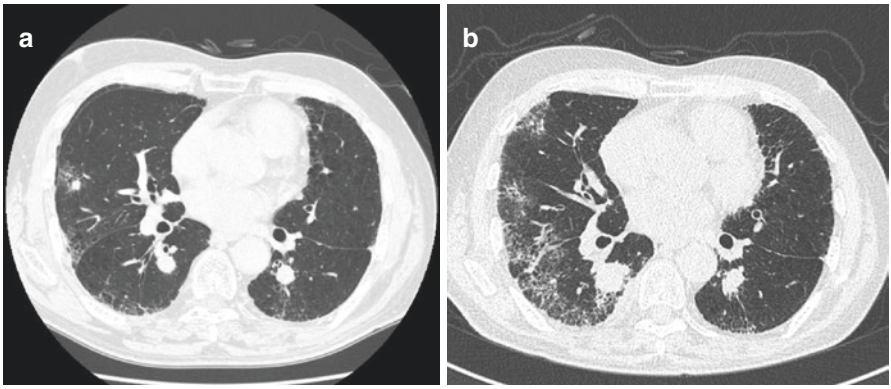

Fig. 10.2 Docetaxel-induced lung injury in non-small cell lung cancer. A patient of lung cancer underlying pulmonary fibrosis suffered acute exacerbation of fibrosis after two courses of docetaxel. (**a**) Before, (**b**) after

10.3.4.2 Taxanes (Paclitaxel and Docetaxel)

Some patients develop shortness of breath, cough, wheezing, and chest tightness, with interstitial shadows on chest x-rays, as an allergic reaction shortly after starting paclitaxel. These symptoms disappear quickly with no therapy or with corticosteroid therapy. The most common pulmonary toxicity of taxanes is interstitial pneumonia, which can develop within several days to weeks of receiving either drug or later in the course of therapy (Fig. 10.2). The interstitial pneumonia induced by taxanes is thought to be an immune-mediated delayed hypersensitivity reaction [21]. Combination with gemcitabine or radiotherapy increases the risk of DLI. High-dose docetaxel (100 mg/m^2) resulted in a significantly higher percentage (2.2%) of grade 3/4 DLI cases compared with 0.6% with a low dose (60 mg/m^2). Another trial reported a higher rate of interstitial pneumonia in patients receiving docetaxel for lung cancer weekly (27%) compared with every 3 weeks (6%) [22]. No differences in DLI by dose or administration schedule have been reported for paclitaxel. Weekly paclitaxel causes grade 3/4 dyspnea in 7% of patients compared with 4% with a triweekly schedule.

10.3.5 Topoisomerase Inhibitors

10.3.5.1 Irinotecan

Irinotecan (IRT) monotherapy caused DLI in 1.7% of cases in a clinical trial in Japan [23]. The incidence of DLI increases when IRT is combined with gemcitabine or thoracic irradiation or when there is preexisting pulmonary fibrosis. IRT-induced DLI includes interstitial pneumonia and pulmonary fibrosis (Fig. 10.3). In patients receiving concurrent chemoradiotherapy for lung cancer including weekly IRT, pneumonitis

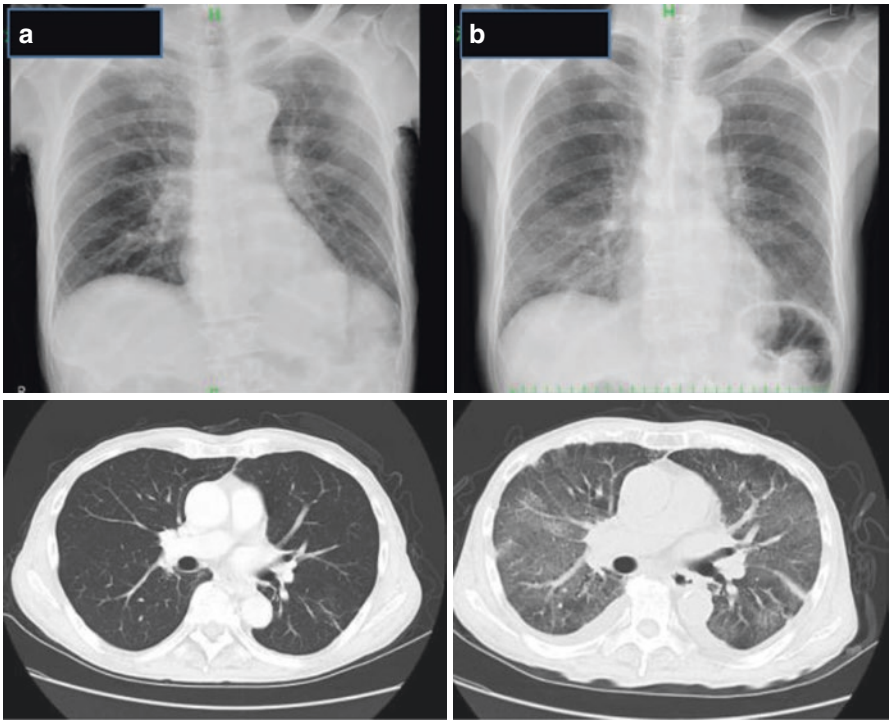

Fig. 10.3 Irinotecan-induced lung injury in gastric cancer. A patient with gastric cancer was treated with irinotecan and cisplatin. Ground glass opacity was observed after treatment. (**a**) Before, (**b**) after

was more frequent than in those without IRT (56.3% vs. 13.6%) [24]. Therefore, IRT should not be used with thoracic irradiation or in patients with preexisting pulmonary fibrosis. Glucocorticoids have been used to treat the pneumonitis with good results. However, deaths have been reported despite empiric glucocorticoid therapy.

10.3.5.2 Etoposide

Pulmonary toxicity is rare with etoposide, and most cases develop DLI appearing as non-cardiogenic lung edema and subacute interstitial pneumonia after prolonged oral administration rather than intravenous therapy.

10.3.5.3 Doxorubicin and Amrubicin

Doxorubicin (DXR) has been used widely in a variety of cancers, but DLI cases are quite rare. DXR can cause lung edema and chest pain. Severe pulmonary toxicity has been reported when combined with other antineoplastic drugs. In contrast, the reported frequency of pulmonary injury with amrubicin (AMR) was 2.2% in a

clinical trial for lung cancer. While DLI occurs in 33% of patients with underlying pulmonary fibrosis, it occurs in only 3% of those without pulmonary fibrosis [25]. AMR should not be used in patients with underlying interstitial lung disease.

10.3.6 Platinum (Cisplatin, Carboplatin, Oxaliplatin)

The frequency of DLI with cisplatin (CDDP) and carboplatin (CBDCA) is quite low. Oxaliplatin (L-OHP) is frequently used in the FOLFOX, XELOX, and SOX regimens for colorectal and gastric cancer. The pulmonary toxicity with L-OHP is variable and is reported primarily in cases treated in combination with other antineoplastic drugs [26]. The pulmonary toxicity includes cryptogenic organizing pneumonia, pulmonary fibrosis, diffuse alveolar damage, and bronchospasm. With repeated administration, the risk of anaphylaxis with bronchial spasm and dyspnea increases.

10.3.7 Others

10.3.7.1 All-Trans Retinoic Acid

All-trans retinoic acid (ATRA) induces so-called retinoic acid syndrome, which is characterized by dyspnea, fever, weight gain, hypotension, and pulmonary infiltrates [27]. This is treated effectively by giving dexamethasone and withholding the ATRA.

10.3.7.2 Interferon

Patterns of pulmonary injury with interferon (IFN) vary. DLI includes an acute exacerbation of asthma, sarcoidosis-like granulation, interstitial pneumonia, and cryptogenic organizing pneumonia. DLI develops from several weeks to several months after initiating IFN treatment. Symptoms improve on withdrawing the IFN or administering corticosteroid.

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Chapter 11
DLI Induced by Molecular Target Antineoplastic Drug: What Are the Characteristics of DLI in Molecular Target Antineoplastic Drugs?

Nobuyuki Koyama

Abstract The standard therapeutic strategy for patients with advanced cancer is treatment with antineoplastic drugs. With the progress in the development of antineoplastic drugs, the prognosis of these patients has improved, despite the difficulty of achieving a complete cure. Molecular target antineoplastic drugs have often provided a paradigm shift in cancer therapy and currently hold a prominent position in cancer therapeutic strategies. While these drugs have clinical benefits, the toxicity profile of these drugs is different from that of conventional cytotoxic chemotherapy. Molecular target antineoplastic drugs consisting of various types of molecules may demonstrate diverse characteristics, although drug-induced lung injury (DLI) is commonly observed in treatment with most of these antineoplastic drugs. In this chapter, reports of DLI associated with molecular target neoplastic drugs were reviewed in order to understand its characteristics and thereby lead to prevention of its occurrence and exacerbation. Diverse patterns of DLI have been commonly observed in patients treated with molecular target antineoplastic drugs, whereas similar DLI patterns have been obtained from various drug types. The incidence and frequency of fatality from DLI also display a wide range. These events were more frequently observed in Japanese patients than in other ethnic groups, suggesting the association of ethnicity with the development and severity of DLI. Clinicians should note the diversity of DLI and the role of ethnicity in DLI in treatment with molecular target antineoplastic drugs.

Keywords Molecular target therapy • Small molecule • Monoclonal antibody • Diversity • Ethnicity

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11.1 Introduction

Molecular target therapy focuses on the molecular mechanisms underlying diseases, targets specific key molecules within such mechanisms, and disrupts their functions, such as a signal transduction or a cellular proliferative pathway, leading to antitumor or anti-inflammatory effects. In the context of this therapeutic strategy, a molecular target drug is designed to specifically prevent the activity of its target that plays a crucial role in the pathogenesis of a variety of diseases including tumors and autoimmune diseases. This kind of drug consists of a wide variety of molecular compounds that range from small molecules such as tyrosine or serine/threonine kinase inhibitors to large protein molecules, such as monoclonal antibodies. Notably, many molecular target antineoplastic drugs that showed significant efficacy in patients with diverse tumors are currently available in a clinical setting.

While clinical benefits of molecular target antineoplastic drugs have clinical benefits, these drugs develop various adverse events that are sometimes serious or fatal. Of these events, drug-induced lung injury (DLI) is one of the most life-threatening adverse events. DLI is additionally induced by many types of drugs other than molecular target antineoplastic drugs, and the same drug can develop various injury patterns. However, there are fewer data regarding the DLI that is due to the relatively novel molecular target antineoplastic drug. Based on previous reports of gefitinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), the ethnicity and the underlying disease of the patient may be associated with susceptibility to such DLI [1]. Therefore, the DLI that is associated with molecular target antineoplastic drugs needs to be comprehensively investigated.

To understand the characteristics of molecular target antineoplastic drugs, the molecular target drugs with the antineoplastic action that are currently available in a clinical setting were considered for this chapter, and the reports of DLI associated with their treatment were reviewed.

11.2 Tyrosine Kinase Inhibitors

Small molecules that play a major role as molecular target antineoplastic drugs are mainly chemical compounds that target and inhibit various signaling molecules and pathways involved in tumorigenesis. Among these molecules, tyrosine kinase inhibitors (TKIs) prevent signals of cellular proliferation and survival through competitive blocking of the adenosine triphosphate (ATP) binding to the kinase. TKI-induced lung injury shows diverse clinicopathological characteristics that are represented by various imaging and pathological findings and clinical courses. Even the same drugs can show a variety of imaging findings and have diverse clinical courses. This section focuses on the characteristics of lung injuries induced by these TKIs.

11.2.1 ErbB Receptor Tyrosine Kinase Inhibitors

Members of the ErbB receptor family, which consists of ErbB receptors 1 (epidermal growth factor receptor (EGFR)), 2 (human epidermal growth factor receptor 2 (HER2)), 3 (HER3), and 4 (HER4), are composed of three types of domains: an extracellular domain, a transmembrane domain, and an intracellular domain. Multiple ligands including EGF, HER3, HER4, amphiregulin, and tumor necrosis factor-α (TNF-α) bind to the extracellular domains of EGFR, HER3, and HER4 and promote homodimerization or heterodimerization between EGFR, HER2, HER3, and HER4. The dimerization of these receptors induces phosphorylation of a tyrosine residue in the intracellular domain through ATP, leading to the activation of signaling pathways. Inhibitors of ErbB receptor tyrosine kinases are currently available for treatment of non-small cell lung cancer (NSCLC), breast cancer, and pancreatic cancer in clinical practice. These TKIs competitively bind to the ATP-binding site of the respective receptor and inhibit its signaling, thereby exerting antitumor effects. However, these drugs sometimes induce serious lung injuries that progress to a fatal outcome. The characteristics of lung injuries induced by ErbB receptor inhibitors are reviewed in this section.

11.2.1.1 Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitors

There are four EGFR-TKIs in use in clinical practice; gefitinib and erlotinib are the first-generation, afatinib is the second-generation, and osimertinib is the third-generation inhibitor. EGFR-TKIs are known to have a dramatic beneficial effect on NSCLC with *EGFR* mutations. On the other hand, these drugs are also associated with some severe adverse events including skin rash, diarrhea, and interstitial lung disease (ILD). Notably, ILD is the most characteristic toxicity in treatment with EGFR-TKIs and is the most critical because of its lethality. Common computed tomography (CT) findings of ILD induced by EGFR-TKIs were airspace consolidation or extensive bilateral ground-glass opacity (GGO) with histologically diffuse alveolar damage (DAD), leading to high mortality [2]. These findings are further classified into four radiological patterns: a nonspecific area with GGO, multifocal areas of airspace consolidation, patchy distribution of GGO accompanied by interlobular septal thickening, and extensive bilateral GGO or airspace consolidations with traction bronchiectasis.

Gefitinib, which was the first approved EGFR-TKI, reversibly binds to the ATP-binding pocket of the EGFR and showed antitumor effects. Gefitinib confers significant benefits on the progression-free survival (PFS) of NSCLC patients with activating *EGFR* mutations. An FDA summary reported the estimated incidence of gefitinib-induced ILD and median time to onset of ILD were 2% and 24 days in Japanese patients and 0.3% and 42 days in US patients, respectively [3]. Ethnic differences in the incidence and fatality of gefitinib-induced ILD between patients in

Japan and other countries have been previously reported; ILD incidences were 3.5–4.0%, and ILD-related deaths in patients with ILD were 31.6–44.3% in previous retrospective and cohort studies of Japanese patients [1, 4]. These studies also reported some risk factors for developing ILD including male gender, a history of smoking, preexisting idiopathic pulmonary fibrosis (IPF), poor performance status, old age, and prior thoracic radiation or chemotherapy.

Erlotinib is also a reversible first-generation EGFR-TKI. This drug shows a modest effect against NSCLC with wild-type EGFR and a very strong effect against NSCLC with activating *EGFR* mutations. Furthermore, erlotinib has also been approved for treatment of pancreatic cancer in combination with gemcitabine. An FDA summary reported an overall incidence of ILD of 0.8% when using erlotinib, and previous phase III trials also showed a lower incidence rate of ILD. An ILD incidence of 1% was reported in the TRIBUTE trial, and a rate of 2.4% was reported in the NCIC CTG study of pancreatic cancer, although the toxicity profile of erlotinib is relatively similar to that of gefitinib [5–7]. However, a higher ILD incidence rate of 4.3% and a lethality rate of 1.5% were reported in a post-marketing surveillance in Japan, and rates of 5.3% and 2.2%, respectively, were reported in a Japanese clinical study. A systematic review and meta-analysis of clinical trials with first-generation EGFR-TKIs showed marginally decreased incidence and relative risk of ILD events with erlotinib compared with gefitinib [8]. The time to onset of ILD with erlotinib was reported to range from 4–6 days to 47 days [5, 9]. Imaging and histological characteristics as well as the risk factor of ILD are likely to be similar to those with gefitinib.

Afatinib, a second-generation irreversible EGFR-TKI, is a pan-HER TKI that covalently binds to the EGFR, HER2, and HER4 but not to HER3 that lacks the tyrosine kinase domain. An integrated analysis of global phase III trials (LUX-Lung 3 and 6) that reported beneficial outcomes of afatinib in NSCLC patients with activating *EGFR* mutations, respectively, showed that afatinib significantly prolonged overall survival in NSCLC patients with *EGFR* exon 19 deletion mutations. According to the pooled analysis of prospective trials for NSCLC patients with activating *EGFR* mutations who were treated with gefitinib, erlotinib, or afatinib, the toxicity profile of afatinib was similar to that of first-generation EGFR-TKIs, whereas diarrhea and skin toxicity of grade 3 or worse were more frequently observed in patients treated with afatinib than in those treated with first-generation EGFR-TKIs [10]. That study also showed no significant differences in the frequency of ILD of grade 3 or worse among EGFR-TKIs; an ILD incidence of 0.5% was reported for afatinib. In the LUX-Lung 3 trial, the incidence of ILD with afatinib was 1.3% (3.7% in Japanese patients), and time to onset ranged from 11 to 126 days. Overall rates of the incidence and the mortality of ILD in 46 clinical trials were 28/3865 (0.7%) and 5/3865 (0.1%), respectively. Imaging and histological findings are similar to those of ILD induced by first-generation EGFR-TKIs.

Osimertinib, a third-generation irreversible EGFR-TKI, targets NSCLC with *EGFR* T790 M point mutations that evoke acquired resistance to first-generation EGFR-TKIs. Covalent binding of osimertinib to the *EGFR* mutation site exerts antitumor effects that overcome the T790 M-mediated resistance; a response rate of 61% and a median progression-free survival of 9.6 months were reported [11]. The toxicity profile of osimertinib included electrocardiographic QT prolongation and cytopenia in addition to skin toxicity and diarrhea, all of which are similar to toxicity profiles of other EGFR-TKIs. The incidence and mortality of ILD with osimertinib were 11/411 (2.7%) and 4/411 (1.0%) of the overall population and 5/80 (6.3%) and 2/80 (2.5%) of the Japanese population, respectively, in the integrated analysis of two clinical trials (AURA and AURA2). The median time to onset of ILD ranged widely from 17 to 230 days (median time, 83 days). Imaging and histological findings are currently under analysis. In the recent TATTON phase Ib trial, combination therapy with osimertinib and durvalumab, an anti-programmed cell death (PD)-L1 antibody, developed ILD in 38.2% of treated patients without fatal events; the median time to onset was 69 days. Based on this result, the trial was aborted. Furthermore, in clinical practice and other trials, a series of ILD events were reported in treatment with nivolumab, an anti-PD-1 antibody that has recently attracted considerable attention and is further described below.

Thus, among a variety of existing TKIs, EGFR-TKIs are commonly known to develop serious lung injury. EGFR-TKIs should therefore be administered with great caution in terms of the development of ILD because ILD is regularly induced by these EGFR-TKIs and is often fatal.

11.2.1.2 Human Epidermal Growth Factor Receptor 2 (HER2) Tyrosine Kinase Inhibitors

Lapatinib is a small molecule tyrosine kinase inhibitor that targets both the EGFR and HER2. This drug is currently used as a HER2-TKI for refractory metastatic breast cancer based on previous studies, one of which showed a significant benefit of time to progression in combination with capecitabine [12]. According to previous studies, the toxicity profile of lapatinib includes skin toxicity, diarrhea, nausea, vomiting, cardiac toxicity, hepatotoxicity, and embolic events [12, 13]. The incidence of pulmonary events in the Lapatinib Expanded Access Program (LEAP) was 0.2% (7/4283), which included pneumonitis in three patients, interstitial lung disease in two patients, and lung infiltration in two patients; this incidence was similar to the 0.3% (36/12795) incidence in the overall lapatinib program. The median time to onset was 51 days (range, 6–157 days) and no fatality due to lapatinib was identified. These previous reports indicate a low frequency of lapatinib-induced ILD.

11.2.2 BCR-ABL Inhibitors

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder of hematopoietic stem cells. CML is characterized by the presence of the Philadelphia (Ph) chromosome, which consists of a reciprocal translocation [t(9;22)(q34;q11)] and fusion between the breakpoint cluster region (BCR) on chromosome 22 and the Abelson (ABL) tyrosine kinase gene on chromosome 9. The BCR-ABL oncogene encodes a 210 kDa fusion protein that exerts its oncogenicity as a constitutively active tyrosine kinase. This oncogene has been identified in CML, acute lymphoblastic leukemia (ALL), and acute myelocytic leukemia (AML). BCR-ABL tyrosine kinase inhibitors (TKIs) competitively block the ATP-binding domain of the kinase, thereby inactivating the BCR-ABL tyrosine kinase activity and leading to inhibition of cellular proliferation and tumor formation. The most commonly reported pulmonary toxicity induced by the several BCR-ABL-TKIs that are clinically available is pleural effusion, whereas reports of ILD have been less common.

Imatinib, the first approved BCR-ABL-TKI for Ph+ CML, targets not only BCR-ABL but also the proto-oncogene protein tyrosine kinase kit (c-KIT), the platelet-derived growth factor receptor (PDGFR), and the ABL-related gene (ARG). Thus, this TKI also exerts beneficial effects on gastrointestinal stromal tumor (GIST). Based on the inhibitory effects of imatinib against the PDGFR, which is considered to be associated with pulmonary fibrogenesis, a randomized trial of imatinib treatment for idiopathic pulmonary fibrosis (IPF) was undertaken. However, imatinib provided no benefits of survival or lung function, although uncommon serious adverse events and infrequent acute exacerbation of IPF were observed. Imatinib-induced pulmonary toxicity, which is characterized by pleural effusion and pulmonary edema, was rarely developed (2.3%) [14]. The development of imatinib-induced ILD has been mostly reported in sporadic case reports, especially in Japan, in which all ILDs were reversible with corticosteroids and drug cessation [15, 16]. In a previous report of approximately 5500 Japanese patients who were treated with imatinib, ILD developed in 27 patients during imatinib treatment [17]. In that report, the median time to ILD onset was 49 days (range, 10–282 days), and the median daily dose of imatinib was 400 mg (range, 200–600 mg). Imaging characteristics of the induced ILD were classified into six patterns: a hypersensitivity reaction (HR) pattern (30%), an interstitial pneumonia (IP) pattern (26%), a cryptogenic organizing pneumonia (COP) pattern (15%), a nodular pattern (11%), a peribronchovascular bundle (PBVB) pattern (15%), and an unclassifiable pattern (3%). No diffuse alveolar damage (DAD) pattern was observed.

Dasatinib is a second-generation tyrosine kinase inhibitor that targets BCR-ABL, PDGFR-β, c-KIT, and v-src sarcoma viral oncogene homolog (SRC) family kinases including SRC, lymphocyte-specific protein tyrosine kinase (LCK), v-yes Yamaguchi viral-related oncogene homolog (LYN), and Yamaguchi sarcoma viral oncogene homolog 1 (YES). This TKI is applicable to patients who are refractory

or intolerant to imatinib. A previous phase II trial showed that pleural effusion cases were more common in the dasatinib-treated group than in the imatinib-treated group (17% vs. 0%, respectively) [18]. In another phase I/II trial, the incidence of pleural effusion with dasatinib was 35% (all grades) and 17% (grade ≥3). A small study of 40 patients treated with dasatinib showed 9 patients with pulmonary complications, 2 patients with pleural effusions, 3 patients with lung parenchymal changes with either ground-glass or alveolar opacities and septal thickening, and 4 patients with both manifestations. All complications were resolved after dasatinib cessation [19]. The median time to onset of pulmonary complications was 229 days (range, 20–510 days). Pulmonary arterial hypertension (PAH) has also been reported as a characteristic pulmonary toxicity of dasatinib; an incidence of 0.6% and a median time to onset of 19.2 months (range, 0–93.2 months) were reported in a pooled population of 2712 patients.

Bosutinib is a competitive second-generation tyrosine kinase inhibitor of SRC and ABL with minimal activity against the PDGFR or c-KIT. In a previous phase I/II study, pleural effusion was a common pulmonary toxicity (10% of all grades, 3% of grade ≥3) with a median time to onset of 541 days (range, 3–1993 days), whereas pneumonia and pneumonitis rarely developed [20]. However, 0.9% of pneumonia/pneumonitis cases were fatal. Treatment modification and discontinuation were required for 0.7% of pleural effusion cases, 0.5% of pneumonitis cases, and 0.4% of pneumonia cases.

Nilotinib is also a second-generation tyrosine kinase inhibitor of BCR-ABL, c-KIT, and PDGFRα/β. Different from the second-generation ABL-TKIs, nilotinib has minimal effects on SRC family kinases, whereas this TKI is 10–50-fold more potent than imatinib as an ABL inhibitor. Pleural effusion as a result of nilotinib treatment was reported as 2% (all grades) and less than 1% (grade ≥3) [21]. Similar to imatinib, in vitro studies reported that nilotinib exerts beneficial effects on lung injury. A case of nilotinib-induced ILD was reported, although such an event is rare [22].

Thus, pleural effusion is a common manifestation of lung injury induced by BCR-ABL inhibitors, although the incidence of lung parenchymal changes is infrequent.

11.2.3 Other Tyrosine Kinase Inhibitors

As shown in Table 11.1, small molecule tyrosine kinase inhibitors other than the tyrosine kinase inhibitors described above include a diversity of molecular target drugs, which have been associated with the development of various types of lung injuries. Although the incidence rate of most injuries is less than 5%, clinicians who use these drugs should be alert to the possibility of lung injury, especially of ILD and pulmonary or alveolar hemorrhage because some cases had fatal outcomes.

Table 11.1 Lung injury induced by other small molecules

Drug	Injury type	Frequency (%)	Image type (ILD)	Time to onset
Bruton's tyrosine kinase (BTK) inhibitor				
			OP	
Ibrutinib	ILD	Rare	HP	1–4 months
			DAD/ALI	
Idelalisib	ILD	24/760 (3)	OP ■ DAD/ALI	
		19/760 (2.5) (grade 3–4)		
		3/760 (0.4) (grade 5)		
Janus kinase inhibitor				
Ruxolitinib	Tuberculosis	1%		
Raf kinase inhibitor				
Sorafenib	ILD	6/1045 (0.6)	NSIP	1 week–6 months
		2.9% (ALI)	DAD/ALI	
			OP	
Vemurafenib	ILD	Rare (two cases)	NSIP	
			Recall radiation pneumonitis (rare)	
Dabrafenib	No reports of ILD			
Multikinase inhibitor				
Vandetanib	ILD Pulmonary edema	Global (848)		Median 2 months (0.2–7.4 months)
		4 (0.5) 1 (0.1) (grade 5)		
		Pulmonary edema (231): 1 (0.4)		
		Japanese (139) 16 (11.5), 3 (2.2) (grade 5)		
			OP	Median 6.8 months (1.35–21.5 months)
Sunitinib	ILD	6/226 (2.7)	NSIP	
			DAD/ALI	
Axitinib	Pulmonary embolism	Pulmonary embolism: 3/356 (0.8), 1 (0.3) (grade 3)		
		1 (0.3) (grade 4)		
	Lung injury	Lung injury: 1 (0.3) (grade 3)		
	ILD	ILD: 1/240 (0.4)		
Pazopanib	Pleural effusion	Pleural effusion: 1/240 (0.4)		
	Pulmonary hemorrhage	Pulmonary hemorrhage: 1/240 (0.4)		

Table 11.1 (continued)

Drug	Injury type	Frequency (%)	Image type (ILD)	Time to onset
Lenvatinib	Pulmonary hemorrhage Pulmonary embolism ARDS Pulmonary infiltrate Pleural effusion ILD	Pulmonary hemorrhage: 4/261 (1.5) Pulmonary embolism: 7/261 (2.7) (grade ≥3) 1/261 (0.4) (grade 5) ARDS: 1/261 (0.4) (grade 4) Pulmonary infiltrate: 1/261 (0.4) Pleural effusion: 3/261 (1.1) ILD (Japan): three cases (one case, grade 5)	DAD/ALI	
Nintedanib	ILD	9/652 (1.4) in combination with docetaxel		
		2/345 (0.6) in combination with pemetrexed		
Regorafenib	ILD Pulmonary hemorrhage Pulmonary thrombus Pleural effusion Lung injury Pneumonitis Pleuritis Alveolar hemorrhage	Pulmonary hemorrhage: 2/500 (0.4) 1/500 (0.2) (grade ≥3) ILD: 22 cases (grade ≥3) Pleural effusion: four cases Lung injury: two cases (grade 3) Pneumonitis: two cases (one case, grade ≥3) Pleuritis: one case Pulmonary thrombus: one case Alveolar hemorrhage: one case		
Cabozantinib	No reports of ILD			

ILD interstitial lung disease, *OP* organizing pneumonia, *HP* hypersensitivity pneumonitis, *DAD* diffuse alveolar damage, *ALI* acute lung injury, *NSIP* nonspecific interstitial pneumonia, *ARDS* acute respiratory distress syndrome, *BO* bronchiolitis obliterans

11.3 Monoclonal Antibodies

A monoclonal antibody is an immunoglobulin derived from a single clone that binds to a target molecule and disrupts its function. Some antibodies have antibody-dependent cellular toxicity (ADCC) activity that enhances cytotoxicity against targets through the recruitment of effector cells such as natural killer cells and macrophages. This kind of protein is applicable to antitumor therapy, and in fact, diverse monoclonal antibodies have been developed as a therapeutic strategy for many tumor types. However, a monoclonal antibody is a large molecule that may promote an immune response, leading to a serious adverse event. In this section, lung injury induced by monoclonal antibodies targeting tumors is discussed.

11.3.1 Immune Checkpoint Inhibitors

Immune checkpoint receptors expressed on a T-cell surface positively or negatively regulate T-cell function through binding to their ligands. Among these receptors, CD152 (cytotoxic T lymphocyte-associated protein 4 (CTLA-4)) and CD279 (programmed cell death protein 1 (PD-1)), both of which negatively modulate immune systems are currently good targets for antitumor therapy. Inhibitors of these receptors currently available in a clinical setting include an anti-CTLA-4 antibody and an anti-PD-1 antibody, which are used for the therapy of multiple tumor types. Immune checkpoint inhibitors show efficacy against these tumors, and a string of novel immune checkpoint inhibitors are now being developed. However, these inhibitors have characteristic immune-related adverse events (irAEs) that are absent in the use of other antineoplastic drugs including type 1 diabetes, thyroid dysfunction, serious colitis, myasthenia, and cytokine release syndrome. Drug-induced ILDs associated with the occurrence of fatalities require particular attention. The review in this section focuses on lung injuries induced by the immune checkpoint inhibitors, an anti-CTLA-4 antibody and an anti-PD-1 antibody.

11.3.1.1 Anti-CD152 (Cytotoxic T lymphocyte-Associated Protein 4 (CTLA-4)) Antibody

CTLA-4, which is an immune checkpoint receptor, binds to CD80 or CD86 on the surface of antigen-presenting cells (APCs), transmits an inhibitory signal to T cells, and inactivates T-cell proliferation and function. Ipilimumab is an anti-CTLA-4 antibody that has been approved for malignant melanoma. Ipilimumab blocks the inhibitory signal that is transmitted to T cells through CTLA-4, thereby augmenting T-cell immune responses against tumor cells. This novel drug that has an innovative antitumor mechanism provides significant clinical benefits in multiple tumors, although it also has irAEs that have not previously been reported with other drugs

[23]. Regarding lung injury, incidence of 0.3% (grade 3, 1/380) of pneumonitis and 0.3% (1/380) of fatal ARDS were developed by ipilimumab in a global phase III trial. A meta-analysis reported incidence of 2.1% (5/234) of pneumonitis and 0.4% (1/234) of ARDS. In a retrospective study, the median time to onset of pneumonitis (5%, 8/162) was 2.3 months (range, 1.1–8.3 months). In post-marketing surveillance in Japan, 2.5% (7/285) of patients with 40s–70s developed ILD, and its median time to onset was 71 days (range, 22–90 days). OP, NSIP, and sarcoid-like lymphadenopathy have been reported as image findings of ipilimumab-induced lung injury [24]. An OP pattern was predominantly observed. However, care should be taken when treating with ipilimumab because fatal ARDS has also been reported, although only a limited number of such cases have been reported.

11.3.1.2 Anti-CD279 (Programmed Cell Death Protein 1 (PD-1)) Antibody

PD-1 is also an immune checkpoint receptor on the surface of T cells. Unlike CTLA-4, PD-1 binds to PD-L1 and PD-L2, both of which belong to the B7 family, and this binding inhibits T-cell activation and reduces autoimmune responses. These ligands are distributed on macrophages and APCs, and PD-L1 in particular is also expressed on a variety of tumor cells. PD-L1 expression underlies tumor evasion from T-cell responses. Nivolumab is an anti-PD-1 antibody that has shown significant survival benefits in malignant melanoma, and it has also been approved for NSCLC and renal cell carcinoma (RCC). Similar to ipilimumab, nivolumab induces irAEs including lung injury, leading to the fatalities. A global phase III trial of nivolumab for melanoma reported incidences of 2.1% (10/474) of pneumonitis and 0.2% (1/474) of ILD, and the median time to onset was 61 days (range, 25–108 days) [25]. A global phase III trial of nivolumab for NSCLC showed incidences of 0.5% (2/418) of ILD (grade 34, 1/418), 0.2% (1/418) of pulmonary infiltrates, and 3.1% (31/418) of pneumonitis (grade 34, 3/418), and the median time to onset was 30–201 days (range, 16–596 days) [26]. On the other hand, the incidence of ILD in a Japanese phase II trial for NSCLC was 4.5% (5/111; grade 34, 2/111), and that of pneumonitis was 0.9% (1/111). In the global phase III trial of nivolumab for RCC, incidences of 3.9% (16/406) of pneumonitis (grade 34, 6/406) and 0.5% (2/406) of ILD were reported, and the median time to onset was 125 days (range, 13–680 days) (grade 34, 111 days ranging from 13 to 427 days) [27]. In post-marketing surveillance of 9369 patients with either melanoma or NSCLC in Japan, lung injury included 0.1%> (grade ≥3, one patient) of ARDS, 0.1%> (grade ≥3, one patient) of hemothorax, 0.1%> (grade ≥3, one patient) of IPF, 3.4% (315 patients) of ILD (grade ≥3, 250 patients), 0.1% (11 patients) of lung injury (grade ≥3, six patients), 0.1%> (four patients) of pulmonary edema (grade ≥3, three patients), 0.3% (26 patients) of pleural effusion, 0.2% (23 patients) of pneumonitis (grade ≥3, 19 patients), 0.1% (11 patients) of pneumothorax, 0.1%> (grade ≥3, one patient) of alveolar hemorrhage, 0.1% (11 patients) of pulmonary embolism, 0.1%> (grade ≥3, two patients) of pulmonary hemorrhage, 0.1%> (grade ≥3, one patient) of DAD,

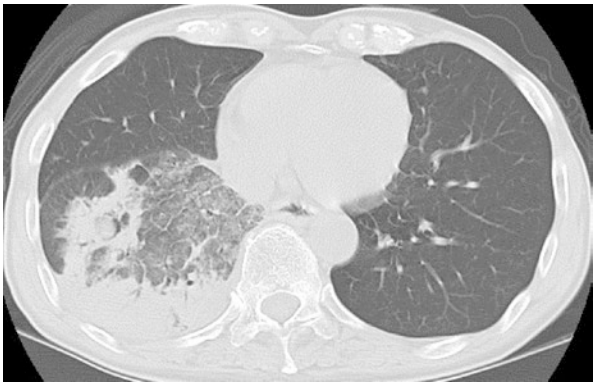

Fig. 11.1 The radiological image pattern of organizing pneumonia (OP) in nivolumab-induced lung injury. The OP pattern was predominantly found in the right lower lung lobe. Levels of lymphocytes were increased in bronchoalveolar lavage fluid (BALF), and transbronchial lung biopsy (TBLB) histologically confirmed OP. The ILD promptly responded to corticosteroid therapy

and 0.3% (25 patients) of OP (grade ≥3, 20 patients). In this analysis, ILD-associated adverse events were observed in 384/9369 patients (4.1%), of whom 304 patients (3.2%) had grade ≥3 events. Radiological image findings in these analyses showed patterns of DAD/acute interstitial pneumonia, OP, bronchiolitis obliterans, NSIP, and HP. Among these findings, the OP pattern is characteristic of nivolumab-induced ILD (Fig. 11.1). In particular, parenchymal lesions that often lead to life-threatening events are predominant in nivolumab-induced lung injury. The findings described in this section suggest that nivolumab should be administered with particular care when it is used for Japanese patients with NSCLC. As described in the section regarding EGFR-TKIs, a series of serious ILDs were reported in NSCLC patients who underwent treatment with these TKIs after nivolumab treatment, and the causal association of nivolumab is currently under investigation. Furthermore, as shown in the meta-analysis of clinical trials for nivolumab and pembrolizumab, a novel anti-PD-1 antibody, pneumonitis developed more frequently in combination therapy with ipilimumab and nivolumab than in monotherapy [28].

11.3.2 Antihuman Epidermal Growth Factor Receptor (HER) Monoclonal Antibody

Human epidermal growth factor receptor (HER), which belongs to the receptor tyrosine kinase receptor (RTK) superfamily, consists of epidermal growth factor receptor (EGFR), HER2, HER3, and HER4. Upon binding of EGFR, HER3, and HER4 to ligands, each protein including HER2 homodimerizes or heterodimerizes with each other, thereby activating multiple signaling pathways. This signaling cascade associated with tumorigenesis has been a good target for antitumor therapeutic strategies.

Among such strategies, anti-EGFR monoclonal antibody and anti-HER2 monoclonal antibody are currently applied to multiple tumor types in a clinical setting. These proteins not only induce adverse events that are common in antibody treatment such as an infusion reaction but also induce lung injury that is observed with drugs other than antibodies. This section describes lung injury induced by these antibodies.

11.3.2.1 Anti-epidermal Growth Factor Receptor (EGFR) Monoclonal Antibody

EGFR binds to seven ligands including EGF and transforming growth factor-α and activates downstream signaling pathways. Monoclonal antibodies against EGFR that are currently available in a clinical setting include cetuximab and panitumumab.

Cetuximab is a mouse/human chimeric monoclonal antibody. It is an IgG1 antibody with antibody-dependent cellular toxicity (ADCC) activity, and it competitively binds to the EGFR with fivefold higher affinity compared to EGF, thereby preventing dimerization of the EGFR and its activation [29]. This drug has been approved for the treatment of metastatic colorectal cancer (mCRC) and head and neck cancer (HNC). However, because of its increased immunogenicity due to the fact that it is a chimeric antibody, cetuximab develops anaphylaxis such as an infusion reaction more frequently than other non-chimeric antibodies. Regarding cetuximab-induced lung injury, three global phase II trials showed the incidence of ILD was 1.5% (2/138) and 0.3% (3/1147) in combination with irinotecan and was 0.6% (1/170) in combination with FOLFOX4. In a global phase III trial of cetuximab, ILD developed in 0.2% (1/600) of patients, and its median time to onset was 78 days (range, 43–217 days) [30]. The incidence of ILD was 2.6% (1/39) in the Japanese phase II trial. Furthermore, in post-marketing surveillance in Japan, ILD developed in 24/2006 patients (1.2%), and 15 patients (0.7%) had grade ≥3 events including ten fatal cases (0.5%). In a Japanese prospective multicentric registry, the median time to onset of ILD was 101 days (range, 17–431 days). Radiological image patterns included NSIP, OP, and DAD/AIP.

Panitumumab is a fully human monoclonal antibody of IgG2 subclasses without ADCC activity that is considered to induce less frequent anaphylaxis than cetuximab. This drug has been approved for mCRC with the wild-type K-RAS gene. Post-marketing surveillance of 3085 patients treated with panitumumab in Japan reported that ILD developed in 39 patients (1.3%) (16/1254 patients in monotherapy and 23/1831 patients in combination therapy), for whom it was fatal in 20 patients (0.6% of the total). Multiple clinical trials have shown that the incidence of ILD was 0.3% (2/585) for panitumumab in combination with FOLFOX4 and 0.3% (2/587) in combination with FOLFIRI and that the median time to onset was 9 weeks–13 months. Radiological image findings presented the patterns of ILD, DAD, HP, and OP.

Compared to EGFR-TKIs, anti-EGFR monoclonal antibody showed less frequent toxicity of lung injury. However, the high fatality in ILD-developed patients should promote awareness regarding lung injury induced by anti-EGFR monoclonal antibody.

11.3.2.2 Anti-HER2 Antibody

HER2 is also a member of the HER family, although no endogenous ligands to this receptor are unknown. Therefore, HER2 is considered to be a preferred heterodimerization partner with other HERs. HER2 is associated with cellular differentiation and proliferation, and amplification or mutation of its gene is known to promote tumorigenesis as an oncogene in various tumors such as breast cancer, ovarian cancer, and gastric cancer. Therefore, antibody treatment targeting HER2 has been developed for these cancers, and trastuzumab including trastuzumab emtansine and pertuzumab are currently available in the clinical setting.

Trastuzumab is an anti-HER2 humanized monoclonal antibody that was approved initially for breast cancer and subsequently for gastric cancer with HER2 gene amplification. Trastuzumab provides significant survival benefits for patients treated with monotherapy or combination therapy in a metastatic and adjuvant setting, although serious adverse events including anaphylaxis, cardiotoxicity, and lung injury have been reported. The incidence of lung injury was 0.5% (4/864) of ILD in the B-31 phase III trial and 0.6% (grade ≥3, 5/808) of pneumonitis or pulmonary infiltrate in the N9831 phase III trial, and one case in each trial was fatal (1/864 patients and 1/808 patients) [31]. The time to onset ranged from 1 week to 6 months, and some injuries may be rapidly progressive. Radiological image findings showed patterns of OP, DAD/AIP, and NSIP. Although there have been fewer reports of lung injury than of anaphylaxis and cardiotoxicity, trastuzumab should be administered with lung injury in mind because its administration is fatal for some patients, especially those with poor performance status and pulmonary complications.

Pertuzumab is also an anti-HER2 humanized monoclonal antibody that binds to HER2 and prevents its heterodimerization with other HERs, and it is used in combination with trastuzumab and docetaxel. This antibody is also considered to exert antitumor effects through ADCC activity. In addition to similar toxicities to trastuzumab such as anaphylaxis, cardiotoxicity, and lung injury, pertuzumab frequently displays toxicity of neutropenia/febrile neutropenia. Regarding lung injury, the CLEOPATRA phase III trial of pertuzumab for 407 patients with breast cancer reported incidence of 1.0% (four patients) of pneumonitis (2/26 Japanese patients), 0.5% (two patients) of ILD (1/26 Japanese patients), 0.2% (one patient) of pulmonary infiltrate, 0.2% (one Japanese patient) of pulmonary fibrosis, 0.2% (one patient) of pulmonary toxicity, 0.2% (one patient) of pulmonary hypertension, and 0.2% (one patient) of pulmonary embolism [32]. Similar to trastuzumab, development of drug-induced lung injury was infrequent, although a high incidence of lung injury was identified in the Japanese population. This finding suggests that more caution should be exercised in Japanese patients treated with pertuzumab than in other patients.

Lung injury induced by anti-HER2 monoclonal antibodies occurs infrequently, although clinicians should note the reports of fatal cases and the higher incidence in Japanese patients.

11.3.3 Other Monoclonal Antibodies

Other monoclonal antibodies used against tumors are shown in Table 11.2. Drug-induced lung injury was observed for most, but not all, of these antibodies. Regarding anti-cluster of differentiation (CD) antibodies, rituximab, an anti-CD20 antibody, presents diverse patterns of lung injury, some of which were fatal, although the incidence of lung injury is unknown. Furthermore, lung injuries induced by brentuximab and gemtuzumab developed more frequently in Japanese patients than in others, which reflects the same tendency as that observed with tyrosine kinase inhibitors. Monoclonal antibodies against vascular endothelial growth factor (VEGF) and VEGF receptor (VEGFR) mainly induced vascular events including hemorrhage and thromboembolism.

Table 11.2 Lung injury induced by other monoclonal antibodies

Drug	Injury type	Frequency (%)	Image type (ILD)	Time to onset
Anti-cluster of differentiation (CD) antibody				
Anti-CD20 antibody				
Rituximab	OP NSIP UIP DAD Intra-alveolar hemorrhage ARDS HP Pulmonary fibrosis Pulmonary hemorrhage BOOP ILD AFOP	Systematic literature review: 45 affected cases (8 cases were fatal) Hypoxemic OP: 37/45 (82.2) ARDS: 5/42 (11.1) Macronodular OP: 3/45 (6.7) Systematic review: 121 affected cases from 20 trials, 30 case reports, and 1 case series ILD: 69/121 (57.0) HP: 1 (0.8) Pulmonary fibrosis: 4 (3.3) ARDS: 3 (2.5) Pulmonary hemorrhage: 1 (0.8) BOOP: 17 (14.0) AFOP: 15 (12.4) OP: 1 (0.8) DAD: 1 (0.8) Others: 9 (7.4)	OP NSIP UIP DAD/ALI BOOP AFOP	Mean 12 weeks
Ofatumumab	ILD	1/33 (3.0) (grade 3)		
Ibritumomab	ILD	Rare (two cases were reported)		

(continued)

Table 11.2 (continued)

Drug	Injury type	Frequency (%)	Image type (ILD)	Time to onset
Anti-CD22 antibody				
Inotuzumab		No reports of ILD		
Anti-CD30 antibody				
Brentuximab	ILD Pneumonia	Global phase II 1/160 (0.6) Japanese phase I/II 13/20 (15.0) Observational retrospective study Pneumonia: 1/22 (4.5) (fatal case)	HP NSIP	
Anti-CD33 antibody				
Gemtuzumab	ILD Lung injury Pulmonary hemorrhage Pulmonary edema ARDS Pleural effusion Pulmonary hypertension Alveolar hemorrhage	Global phase II Lung injury: 7/277 (2.5) Pulmonary hemorrhage: 1/277 (0.4) Pulmonary edema: 6/277 (2.2) ARDS: 1/277 (0.4) Pleural effusion: 10/277 (3.6) Pulmonary hypertension: 1/277 (0.4) Japanese population ILD: 1/40 (2.5) Pulmonary hemorrhage: 1/40 (2.5) Alveolar hemorrhage: 1/40 (2.5) Pleural effusion: 1/40 (2.5)	Gemtuzumab	
Anti-CD 52 antibody				
Alemtuzumab	Pulmonary edema Pneumonitis Pleural effusion	Pulmonary edema: 1/123 (0.8) (grade ≥3) Pneumonitis: 1/123 (0.8) (grade ≥3) Pleural effusion: 1/123 (0.8) (grade ≥3)		
Anti-CD194 (C-C chemokine receptor type 4 [CCR4]) antibody				
Mogamulizumab	Pneumonitis ILD Pleural effusion	Pneumonitis: 1/80 (1.3)–1/37 (2.7) in monotherapy, 1/29 (3.4) in combination therapy (VCAP/AMP/VECP) ILD: 3/29 (10.3) in combination therapy (VCAP/AMP/VECP) Pleural effusion: 2/80 (2.5)–2/27 (7.4) in monotherapy, 1/29 (3.4) (grade ≥3) in combination therapy (VCAP/AMP/VECP)		

Table 11.2 (continued)

Drug	Injury type	Frequency (%)	Image type (ILD)	Time to onset
Anti-receptor activator of nuclear factor kB ligand (RANKL) antibody				
Denosumab	No reports of ILD			
Anti-vascular endothelial growth factor (VEGF) and VEGF receptor (VEGFR) antibody				
Bevacizumab	ILD ARDS Pulmonary edema Pleural effusion Pulmonary artery thrombus Pulmonary embolism Pulmonary thrombus Lung injury Pulmonary hemorrhage Pneumonitis Hemothorax	In combination with chemotherapy ILD: CRC 12/2814 (0.4), breast cancer 1/120 (0.8) ARDS: CRC 4/2814 (0.5), cervical cancer 1/218 (0.5) Pulmonary edema: CRC 1/2814 (0.1>) Pleural effusion: ovarian cancer 4/1215 (0.3), CRC 2/2814 (0.7), cervical cancer 1/218 (0.5) Pulmonary artery thrombus: CRC 4/2814 (0.1), breast cancer 1/120 (0.8) Pulmonary embolism: ovarian cancer 1/1215 (0.1>), CRC 3/2814 (0.1), malignant glioma 14/464 (3.0) Pulmonary thrombus: CRC 2/2814 (0.1>) Lung injury: CRC 1/2814 (0.1>), malignant glioma 1/464 (0.2), ovarian cancer 7/1215 (0.6), cervical cancer 5/218 (2.3) Pulmonary hemorrhage: CRC 1/2814 (0.1>), ovarian cancer 3/1215 (0.1>), cervical cancer 1/218 (0.5) Pneumonitis: ovarian cancer 1/1215 (0.1>), cervical cancer 1/218 (0.5) Hemothorax: breast cancer 1/120 (0.8)	NSIP DAD/ALI	

(continued)

Table 11.2 (continued)

Drug	Injury type	Frequency (%)	Image type (ILD)	Time to onset
Ramucirumab	ILD ARDS Pneumonitis Pulmonary fibrosis Pulmonary infiltrate Pulmonary hemorrhage Pulmonary embolism Pulmonary thrombus	ILD: NSCLC 3/94 (3.2) ARDS: CRC 1/327 (0.3), NSCLC 2/627 (0.3) (grade 5) Pneumonitis: CRC 2/529 (0.4), gastric cancer 4/327 (1.2), NSCLC 7/627 (1.1) (grade 5, one case), 4/94 (4.3) (Japanese) Pulmonary fibrosis: NSCLC 1/627 (0.2) Pulmonary infiltrate: CRC 1/529 (0.2) (Japanese, 1/74), gastric cancer 1/236 (0.4) (grade ≥3), NSCLC 2/627 (0.3) Pulmonary hemorrhage: NSCLC 3/94 (3.2, Japanese) and 13/627 (2.1) (non-squamous type, 7/465; squamous type, 6/157) Pulmonary embolism: 4/236 (1.7) (gastric cancer), 11/627 (1.8) (NSCLC) (grade 5, 2/627), 18/529 (3.4) (CRC) Pulmonary thrombus: gastric cancer 1/327 (0.3)	DAD/ALI NSIP	

ILD interstitial lung disease, *OP* organizing pneumonia, *NSIP* nonspecific interstitial pneumonia, *ARDS* acute respiratory distress syndrome, *UIP* usual interstitial pneumonia, *DAD* diffuse alveolar damage, *HP* hypersensitivity pneumonitis, *ALI* acute lung injury, *BOOP* bronchiolitis obliterans organizing pneumonia, *AFOP* acute fibrinous and organizing pneumonia, *VCAP* vincristine+cyclo phosphamide+doxorubicin+prednisolone, *AMP* doxorubicin +ranimustine+prednisolone, *VECP* vincristine+etoposide+carboplatin+prednisolone, *CRC* colorectal cancer, *NSCLC* non-small cell lung cancer

11.4 Miscellaneous Molecular Target Antineoplastic Drug

The previous sections described lung injuries requiring from the use of small molecule kinase inhibitors and monoclonal antibodies. This section focuses on lung injuries induced by molecular target antineoplastic drugs other than above.

11.4.1 Mammalian Target of Rapamycin (mTOR) Inhibitor

The mammalian target of rapamycin (mTOR) is a serine/threonine kinase, and the PI3K/AKT/mTOR pathway, which is associated with cellular proliferation, survival,

and angiogenesis through hypoxia-inducible factor 1 (HIF-1), is known to be active in many tumor types through different mechanisms. mTOR is a component of mTOR complex 1 (mTORC1) and 2 (mTORC2), both of which phosphorylate and activate various proteins. mTOR inhibitors not only show significant antitumor effects but also function as potent immunosuppressive drugs that inhibit T- and B-cell proliferations and that are applied for posttransplant patients. Among mTOR inhibitors, everolimus and temsirolimus are used as an antineoplastic drug in a clinical setting, and various adverse events induced by these drugs have been reported. In particular, the lung injury that is induced by mTOR inhibitors and that is one of its common adverse events displays characteristic clinical features. One feature is its high incidence; most analyses reported that the incidence of ILD ranged from more than 10% to more than 50%. Therefore, fatal cases are more frequently observed with these inhibitors than with other molecular target drugs. A second feature is that unlike the ILD induced by other drugs, mild mTOR inhibitor-induced ILD of grade 1 without symptoms may allow patients to continue treatment with the drug; such asymptomatic cases may account for half of the mTOR inhibitor-induced ILD events.

Everolimus, a derivative of rapamycin, acts on mTORC1, prevents intracellular signal transduction, and inhibits cellular proliferation, growth, and survival. The adverse events of this drug are the occurrence of a second primary cancer as well as serious infection because of its immunosuppressant activity. Additionally, the incidence of lung injury is generally high. The RECORD-1 global phase III trial of everolimus for metastatic RCCs reported incidences of 11.7% (32/274) of ILD (grade 34, 9/274), 8.4% (23/674) of pneumonitis (grade 34, 6/274), 2.2% (6/274) of interstitial pneumonia (grade 34, 2/274), 0.4% (1/274) of alveolitis, 0.4% (1/274) of alveolar hemorrhage (grade 34, 1/274), and 0.4% (1/274) of pulmonary toxicity. Among these adverse events, the incidence of ILD in Japanese patients was 13.3% (2/15) of ILD and of pneumonitis without grade 45 was 13.3% (2/15), and the median time to onset was 108 days (range, 24–257 days) [33]. No new radiographic findings were correlated with improved efficacy. In a large retrospective study of Japanese patients, ILD developed in 22% (40/180) (grade ≥3, 10/180) [34]. In the RADIANT phase III trial of everolimus for pancreatic neuroendocrine tumors, the incidence of pneumonitis was 17% (35/204; grade 34, 5/204), and in the BOLERO-2 trial for breast cancer, it was 12% (3% of grade 3) [35, 36]. Furthermore, a cohort study for renal transplant recipients reported that ILD developed in 12.7% (13/102) of patients and that the median time to onset was 162 days (range, 38–407 days) [37]. Radiological image patterns included OP, NSIP, LIP, alveolar hemorrhage, and DAD/ALI. Given the results of previous reports, some of everolimus-induced ILD may show a favorable response to corticosteroid therapy or regress with only cessation of everolimus. Especially, the HP pattern may be characteristic of with the image pattern of favorable outcome (Fig. 11.2).

Temsirolimus, a prodrug of rapamycin, is also an mTOR inhibitor that was approved as an immunosuppressant and subsequently as an antitumor drug against RCC. This drug binds to the FK506 binding protein (BP)-12 (FKBP-12), inhibits mTOR, and prevents progression from the G1 to the S phase of the cell cycle, resulting in inhibition of cellular proliferation and growth. Temsirolimus showed

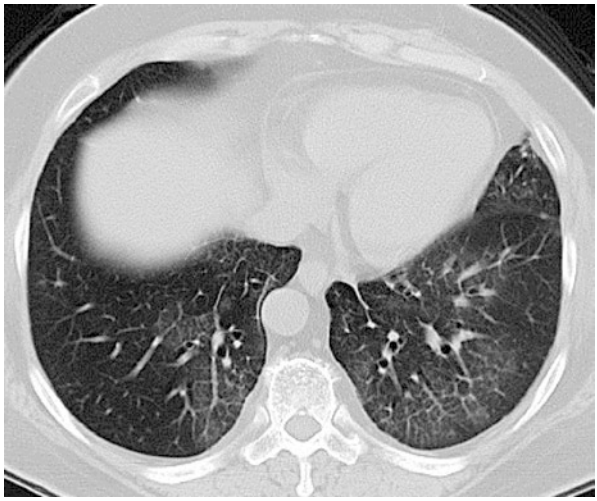

Fig. 11.2 The radiological image pattern of hypersensitivity pneumonitis (HP) in everolimus-induced lung injury. Cessation of everolimus treatment alone resulted in the improvement of the ILD without corticosteroid therapy

significant efficacy in RCC, but it has a similar toxicity profile to everolimus including lung injury, anaphylaxis, infection, hyperglycemia, and neutropenia/febrile neutropenia. In a phase II trial of temsirolimus in Asia, the incidence of ILD was 17.1% (14/82), and 3.7% (3/82) had an event of grade ≥3. The median time to onset was 90.8 days (range, 37–221 days). In the Japanese population of this trial, the incidence of ILD was 35.0% (7/20) (grade ≥3, 2/20), and the median time to onset was 85.7 days (range, 37–205 days). In radiological evaluation of this study, ILD findings were found in 57.1% (44/77) of the total population and in 50% (10/20) of the Japanese population. On the other hand, a global phase III trial of temsirolimus reported that the incidence of ILD was 1.9% (4/208) (grade ≥3, 2/208) and the median time to onset was 92.27 days (range, 48–287 days) [38]. In the radiological evaluation of this study, ILD findings were found in 29.2% (52/178). Radiological image patterns that predominantly presented ground-glass opacity (GGO) and consolidation included HP, OP, and DAD/ALI. Temsirolimus-induced ILD is considered to be non-dose dependent.

mTOR inhibitor-induced lung injury occurs more frequently compared with other molecular target drugs; however, this inhibitor induces mild adverse events that enable continuation of treatment in some cases, although it is fatal for other cases. Hence, different responses to the adverse event of this inhibitor were compared to the responses to other drugs, and decisions must be made regarding whether to stop or continue treatment.

11.4.2 Proteasome Inhibitor

The ubiquitin-proteasome system (UPS) is crucial for the metabolism and biological function of proteins. In this system, the proteasome, 26S proteasome, is an

ATP-dependent proteolytic complex that consists of a cylindrical 20S proteasome and two regulatory 19S complexes. The proteasome activates the nuclear factor κB pathway through proteolysis of IκB and regulates the cell cycle through proteolysis of cyclin and cyclin-dependent kinase, and these mechanisms are associated with tumorigenesis.

In this context, proteasome inhibitors were developed as an antitumor drug, and bortezomib, carfilzomib, and ixazomib are available for multiple myeloma in a clinical setting. These drugs have shown significant efficacy in multiple myeloma but have some serious adverse events including lung injury, hematological toxicity, hepatotoxicity, and tumor lysis syndrome. In particular, cases of serious lung injury have been reported.

Bortezomib selectively and reversibly binds to the 26S proteasome with high affinity, thereby inhibiting the function of the proteasome. Although this drug provided significant antitumor activity against multiple myeloma, severe pulmonary complications have been reported [39]. A global phase III trial of bortezomib reported incidences of 0.4% (1/240) of ARDS, 0.4% (1/240) of pneumonitis, and 0.4% (grade 3, 1/240) of pulmonary embolism. In two Japanese phase I/II trials, the incidence of lung injury was 2.9% (fatal case, 1/34) (JPN-101 trial) and 7.1% (7/99) (JPN-102 trial) of ILD and 11.8% (4/34) (JPN-101 trial) and 5.1% (5/99) (JPN-102) of pleural effusion. Post-marketing surveillance of 1010 patients in Japan reported incidences of 2.8% (28 patients) of ILD (grade ≥3, 18 patients), 0.6% (6 patients) of lung injury (grade ≥3, 2 patients), 0.2% (2 patients) of pulmonary edema (grade ≥3, 1 patient), 0.1% (grade ≥3, 1 patient) of alveolar hemorrhage, 0.1% (grade ≥3, 1 patient) of pulmonary infarction, and 1.3% (12 patients) of pleural effusion. The median time to onset mainly ranged from 1 day to 1 month. Radiological image findings showed patterns of HP, NSIP, and DAD/ALI.

Carfilzomib is a novel proteasome inhibitor that irreversibly binds to the 20S proteasome. Although this drug showed a favorable progression-free survival (PFS) for patients with multiple myeloma, it also had some serious adverse events including lung injury, pulmonary hypertension, cardiotoxicity, tumor lysis syndrome, hematological toxicity, and intravenous thromboembolism. In the ASPIRE global trial of carfilzomib in combination with lenalidomide and dexamethasone, the incidence of each of ILD, BO, eosinophilic pneumonia, and pneumonitis (all cases were grade ≥3) was 0.3% (1/392), and the median time to onset was 234.5 days (range, 99–509 days) [40]. That trial also reported incidences of 2.8% (grade ≥3, 11/392) of pulmonary embolism and 0.3% (1/392) of pleural effusion. In clinical trials and global post-marketing surveillance, pulmonary hypertension was observed in 1303 patients, of whom 3 patients were definitively diagnosed. Radiological image findings included the patterns of OP, BO, and DAD/ALI.

Ixazomib is a peptide boronic acid proteasome inhibitor that provided significant benefits of PFS for patients with multiple myeloma in combination with lenalidomide and dexamethasone. Hematological toxicity, gastrointestinal toxicity, and skin rash increased in the group treated with ixazomib as combination therapy compared

with the placebo group. The incidence of ILD in a global phase III study of ixazomib was 1.0% (grade 12, 4/361) [41].

Bortezomib-induced lung injury has been the most extensively reported of proteasome inhibitor-induced injury because this drug is widely used at present. Furthermore, the incidence of this event was higher in Japanese patients than in others, which suggests that its administration to Japanese patients require special care.

11.4.3 Other Miscellaneous Molecular Target Antineoplastic Drugs

As shown in Table 11.3, there are no reports of lung injury for some other molecular target drugs, and there are sparse clinical data for others. The incidence of lung injury induced by trametinib, a mitogen-activated kinase kinase (MEK) inhibitor, was deemed to be similar to that induced by other molecular target drugs. Thus, lung injury induced by immune-modulating drugs presents diverse patterns, but once it has developed, it often leads to a serious and life-threatening injury.

Table 11.3 Lung injury induced by other miscellaneous inhibitors

Drug	Injury type	Frequency (%)	Image type (ILD)	Time to onset
Mitogen-activated kinase kinase (MEK) inhibitor				
Trametinib	ILD Alveolar hemorrhage	Japanese trial ILD: 3/5 (60), 2/5 (40) (grade ≥3) Alveolar hemorrhage: 1/5 (20) (grade 5) Global trial 9–13% in combination with gemcitabine 5/211 (2.4) (phase III)	DAD	Median 160 days (60–172 days)
Cyclin-dependent kinase (CDK) inhibitor				
Palbociclib	No reports of ILD			
Abemaciclib	No reports of ILD			
Fusion protein				
Aflibercept	No reports of ILD			
Histone deacetylase (HDAC) inhibitor				
Panobinostat	Pulmonary hemorrhage	1/381 (0.3)		
Vorinostat	Pulmonary embolism	4/86 (4.7) (grade ≥3)		

Table 11.3 (continued)

Drug	Injury type	Frequency (%)	Image type (ILD)	Time to onset
Immune-modulating drug				
	ILD ARDS OP Lung injury Pulmonary infiltrate BO Pleural effusion Pneumonitis Alveolar hemorrhage Pulmonary artery thrombus Pulmonary embolism Pulmonary hemorrhage Pulmonary infarction Pulmonary artery hypertension	ILD: 64 cases (grade ≥3) ARDS: three cases (grade ≥3) OP: two cases (grade ≥3) Lung injury: three cases (two cases, grade ≥3) Pulmonary infiltrate: one case (grade ≥3) BO: one case (grade ≥3) Pneumonitis: one case (grade ≥3) Alveolar hemorrhage: one case (grade ≥3) Pulmonary artery thrombus: three cases (grade ≥3) Pulmonary embolism: 22 cases (grade ≥3) Pulmonary hemorrhage: two cases (grade ≥3) Pulmonary infarction: one case (grade ≥3) Pulmonary artery hypertension: one case (grade ≥3) Post-marketing surveillance (2671 cases)		
Lenalidomide	ILD Pneumonitis Pulmonary embolism ARDS Pulmonary edema Pleural effusion Mediastinal hemorrhage Alveolar hemorrhage Pulmonary infarction Pulmonary hemorrhage	ILD: 10/2671 (0.4) (grades 1/2), 23/2671 (0.9) (grade ≥3), 5/2671 (0.2) (grade 5) Pneumonitis: 1/2671 (0.04) (grade ≥3) Pulmonary embolism: 7 (0.3), 5 (0.2) (grade ≥3) ARDS: 3 (0.1) (grade ≥3) Pulmonary edema: 2 (0.1) (grade ≥3) Pleural effusion: 3 (0.1) 2 (0.1) (grade ≥3) Mediastinal hemorrhage: 1 (0.1>) (grade ≥3) Alveolar hemorrhage: 1 (0.1>) (grade ≥3) Pulmonary hemorrhage: 1 (0.1>) (grade ≥3)	HP: 11/33 (45.8) OP: 3/33 (12.5) DAD/ALI: 3/33 (12.5) HP/OP: 1/33 (4.2) BOOP: 1/33 (4.2) Unclassifiable type: 5/33 (20.8)	
Thalidomide	ILD Pulmonary embolism	ILD: 1/38 (2.6) (grade ≥3) Pulmonary embolism: rare	NSIP HP	

ILD interstitial lung disease, *ARDS* acute respiratory distress syndrome, *OP* organizing pneumonia, *BO* bronchiolitis obliterans, *HP* hypersensitivity pneumonitis, *DAD* diffuse alveolar damage, *ALI* acute lung injury, *BOOP* bronchiolitis obliterans organizing pneumonia

11.5 Conclusion

Molecular target antineoplastic drugs range from a small molecule to an antibody. With such diversity, a variety of adverse events have been reported. Among these events, drug-induced lung injury can be classified into various subtypes based on the patterns of images, pathological types, and clinical courses including time to onset, prognosis, and symptoms. In particular, multiple prognoses of different severity have been identified ranging from mTOR inhibitor-induced lung injury, some of which allows for continued treatment, to EGFR-TKI-induced lung injury of which approximately half is fatal. Such diversity of drug-induced injury may reflect the characteristics of molecular target antineoplastic drugs. On the other hand, a high incidence of drug-induced lung injury in Japanese patients appeared to be a common characteristic of these drugs. Of the broad range of drug characteristics, this trend is outstanding, although a similar trend may also be observed in treatment with antineoplastic drugs other than molecular target drugs and even in treatment with drugs other than antineoplastic drugs.

In conclusion, lung injury induced by molecular target antineoplastic drugs is characteristic of the diversity of these drugs and shows a high incidence in Japanese patients. Clinicians should use molecular target antineoplastic drugs paying particular attention to these points.

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Chapter 12
DLI Caused by Disease-Modifying Antirheumatic Drugs: What Are the Characteristics of DLI by Disease-Modifying Antirheumatic Drugs?

Hideto Kameda

Abstract Among patients with rheumatoid arthritis (RA), drug-induced lung injury (DLI) develops in 0.1–0.5% of patients within 6 months after starting synthetic or biological disease-modifying antirheumatic drugs (DMARDs). Fatal outcomes are observed in 5–33% of them. The pathogenesis of DLI by DMARDs, especially biological DMARDs, is complicated by RA, direct effects of DMARDs on the lungs, allergic reaction to DMARDs, and immunosuppression by DMARDs. Therefore, clinical, radiological, and histopathological findings vary among patients. The management of DLI caused by DMARDs includes the tentative discontinuation of the DMARDs, considering a thorough differential diagnosis, and the initiation of antibiotics, such as trimethoprim/sulfamethoxazole, and moderate- to high-dose glucocorticoids.

Keywords Antitumor necrosis factor (anti-TNF) • Disease-modifying antirheumatic drugs (DMARDs) • Methotrexate • Pneumocystis pneumonia • Rheumatoid arthritis

12.1 Introduction

Rheumatoid arthritis (RA) is an autoimmune systemic inflammatory disease characterized by synovitis of diarthrodial joints. Interstitial lung disease (ILD) is one of the major extra-articular manifestations of RA, observed in at least 10–30% of patients [1]. In addition, growing evidence highlights treatment of RA with synthetic or biological disease-modifying antirheumatic drugs (DMARDs) that may

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induce interstitial pneumonia or worsen ILD associated with RA (RA-ILD) [2] (http://www.pneumotox.com). RA-ILD and DLI in RA patients share many clinical, radiographic, and pathological features. For example, the pathological pattern of RA-ILD and DLI in RA includes usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP), and diffuse alveolar damage (DAD). Two or more histological types are often observed in the same patients, simultaneously or sequentially. Therefore, it is crucial to make a proper diagnosis for patient with RA who has developed acute or subacute ILD: RA-ILD or DLI. In addition, pneumocystis pneumonia (PCP) is observed in 0.2–0.4 % of patients receiving biological DMARDs almost exclusively in Japan [3], and the differential diagnosis between DLI and PCP is challenging [4].

12.2 DLI by Synthetic DMARDs

Almost all synthetic DMARDs are known to potentially cause DLI in patients with RA (http://www.pneumotox.com) (Table 12.1).

12.2.1 Gold

Although the frequency is less than 0.1%, DLI by injectable gold is well known as "gold lung." According to the analysis of 140 cases from literature, the median duration from the time of gold injection to the development of DLI is 3 months [5]. Patients who develop DLI experience dyspnea (92.1%), cough (67.2%), fever (46.6%), rash (37.7%), and eosinophilia (37.5%), suggesting an allergic reaction to the gold. Chest radiography and chest high-resolution computed tomography (HRCT) images show

Table 12.1 Scores for each disease-modifying antirheumatic drug according to The Drug-Induced Respiratory Disease Website (http://www.pneumotox.com)

	Total	Acute	Subacute	Eosinophilic	Organizing pneumonia	Pulmonary fibrosis	Diffuse alveolar damage
Gold	3	2	3	2	1	2	
Sulfasalazine	3	1	1	2	1	1	
Bucillamine	1	1	1	1	1		
Methotrexate	5	5	2		1	1	2
Leflunomide	3	1	2	1	1		1
Tacrolimus	1	1	1				
Infliximab	5	1	1	1	1	2	1
Etanercept	4	1	1		1	2	
Adalimumab	3	1	1			1	
Tocilizumab	1				1		

Each score ranges from 1 to 5, if applicable

various findings, including interstitial, alveolar, and bronchovascular bundle opacities. Lung function tests show a restrictive disorder, and a bronchoalveolar lavage fluid reveals a lymphocytosis with a CD4/CD8 ratio <1 in 80% of patients. Histological findings may include lymphocytic and eosinophilic infiltration, OP, or DAD.

12.2.2 Salazosulfapyridine (SASP)

DLI by SASP is a rare disease found in 0.03% of patients with RA in Japan. A total of 47 cases have been reported until March 2010. Among them, 43% of the patients were male. DLI by SASP was observed soon after the commencement of SASP therapy; 65% developed DLI within 1 month and 79% within 3 months, typically in conjunction with fever, rash, and eosinophilia. Although 12% of patients were mortality cases, 83% of patients recovered in an average of 31 days after the discontinuation of SASP and treatment of systemic glucocorticoids for severe cases.

12.2.3 Bucillamine

DLI by bucillamine (BUC) is observed in 0.06% of patients with RA in Japan. A total of 253 cases had been reported by March 2010. Among them, 39% of patients were male, and DLI by BUC developed within 3 months (54%) or 6 months (75%) of the commencement of bucillamine therapy. Chest HRCT reveals panlobular opacity and peribronchovascular consolidation (Fig. 12.1). Histological findings

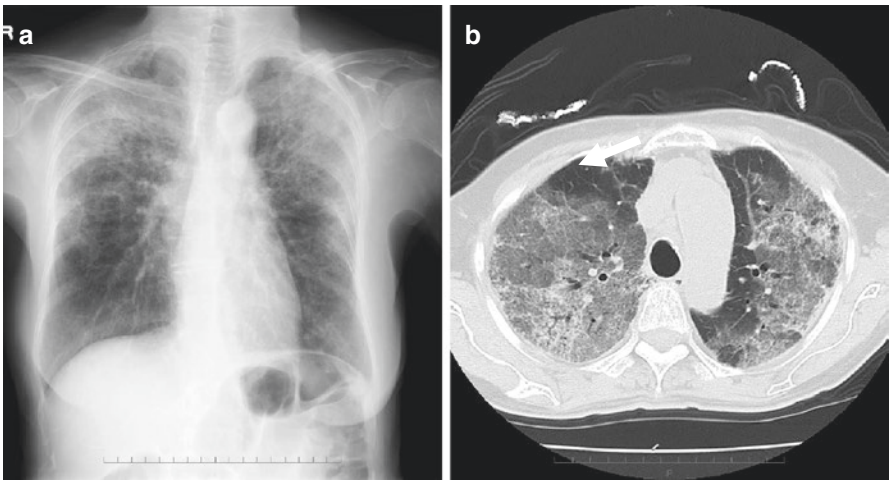

Fig. 12.1 Drug-induced lung injury caused by bucillamine. The chest radiograph (**a**) and computed tomography image (**b**) show bilateral ground-glass opacities predominantly in the upper and middle lung fields. *DLI* drug-induced lung injury, *BUC* bucillamine

include organizing exudates in the alveolar ducts and alveoli and cellular infiltration into alveoli and septa [6]. Although 14% of patients were mortality cases, 79% of patients recovered in an average of 90 days with the discontinuation of bucillamine and treatment with systemic glucocorticoids for severe cases.

12.2.4 Methotrexate (MTX)

MTX, a folic acid inhibitor, is the anchor drug for RA and is currently being received by >70% of patients with RA. DLI by MTX is not dose-dependent and develops within 6 months after the initiation of MTX in ~75% of cases. In the 1990s, 1–5% of RA patients receiving MTX developed DLI in Japan. Men had a higher risk and smoking and preexisting lung diseases were identified as risk factors associated with DLI by MTX [7, 8]. Currently, the screening radiographic tests for preexisting lung diseases are regarded as mandatory, and MTX is usually avoided for patients with clinically significant lung diseases, which has led to the decrease in DLI (0.4% [9]) caused by MTX. Although MTX-induced DLI may be a hypersensitivity reaction, some patients did not reproduce DLI by rechallenge of MTX. Clinical manifestations include a nonproductive cough, exertional dyspnea, and sometimes fever. Chest HRCT images reveal diffuse ground-glass opacities with consolidation, which may have a panlobular pattern. Discontinuation of MTX may be sufficient for mild cases. Severe cases with associated dyspnea, hypoxemia, or diffuse opacity on chest images, with the diagnostic exclusion of possible pulmonary infections, require emergent admission, and intensive care, which includes oxygen supplementation and at least 0.5 mg/kg/day of a prednisolone equivalent, should be considered.

12.2.5 Leflunomide (LEF)

LEF inhibits a key enzyme of pyrimidine synthesis, leading to the suppression of cellular, predominantly lymphocytic, proliferation in the G1 phase of the cell cycle. LEF is characterized by a relatively long serum half-life of 14 days. Despite the rare incidences of DLI (0.02%) in Western countries, mortality cases of DLI were observed after the launch of LEF in Japan in September 2003. Chest HRCT images show diffuse or widespread patchy ground-glass opacities and/or consolidations, frequently accompanied by septal thickening and intralobular reticular opacities [10]. The Study Committee for LEF-induced Lung Injury at the Japan College of Rheumatology reports that preexisting interstitial pneumonia, extremely high serum C-reactive protein, low serum albumin, severe hypoxemia, and mechanical ventilation indicate a poor prognosis [11]. The histopathological finding of the patients who died of DLI was DAD. By January 2012, 98 of 7243 patients (1.4%) developed LEF-induced DLI, with fatal outcomes in 30 patients.

12.2.6 Tacrolimus

Tacrolimus and cyclosporine A are potent calcineurin inhibitors that suppress the activation of nuclear factor of activated T cell (NF-ATc), transcription of interlukin-2 (IL-2), and T-lymphocyte activation. Tacrolimus was approved for RA in 2005 in Japan. Postmarketing surveillance found interstitial pneumonia as an adverse event in 0.5% of patients [12]. The combination of the postmarketing surveillance program and spontaneous reports to a pharmaceutical company identified 27 cases of exacerbation or new development of interstitial pneumonia as of May 2007. A retrospective analyses of clinical, radiological, and laboratory data from ten of those cases revealed that 90% of patients had pulmonary comorbidities, and hypersensitivity pneumonia-like pattern, ground-glass opacity, and OP patterns were observed on the chest HRCT images [13]. Two of the six patients with presumptive tacrolimus-induced DLI were mortality cases.

12.2.7 Iguratimod

Iguratimod was developed and first approved in Japan in June 2012. The mechanism of action of iguratimod includes the suppression of immunoglobulin production from B cells and the inhibition of tumor necrosis factor (TNF) production from monocytes and rheumatoid synovial cells via nuclear factor kappa-light-chain-enhancer of activated B cell (NF-κB) inhibition. Overall safety profiles were fair [14], and DLI caused by iguratimod was observed in 3 of 1030 patients (0.29%) between 134 and 606 days after the commencement of iguratimod without fatal outcome.

12.2.8 Tofacitinib

Tofacitinib is a selective inhibitor of the Janus kinase (JAK) family (JAK1 and JAK3). After its approval for RA in July 2013 in Japan, postmarketing surveillance of all patients receiving tofacitinib for 3 years has been continued with special concerns for infections and malignancies. As of November 2015, 8 of 1125 (0.7%) patients developed interstitial lung disease or acute respiratory distress syndrome.

12.3 Biological DMARDs

12.3.1 Epidemiology and Differential Diagnosis

As of September 2016, seven original biological DMARDs and one biosimilar DMARD (infliximab biosimilar) have been approved for treatment of RA in Japan (Fig. 12.2). Japan College of Rheumatology directed the postmarketing surveillance

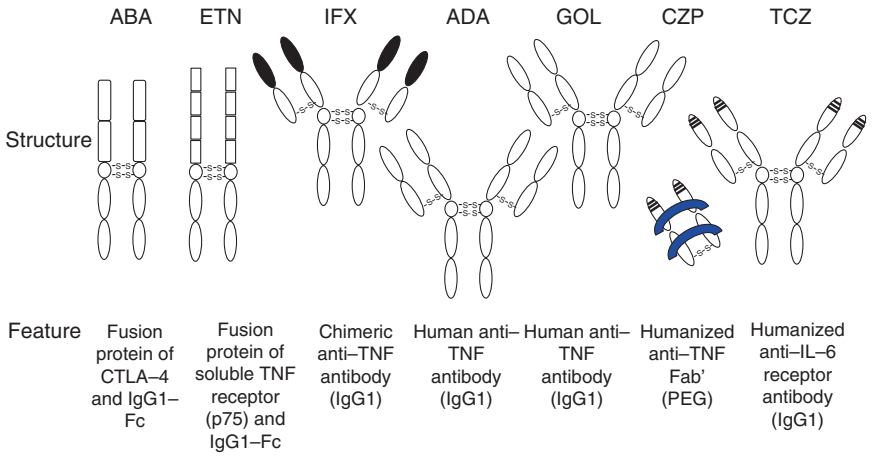

Fig. 12.2 Structures and features of seven (except for biosimilar disease-modifying antirheumatic drugs (DMARDs)) biological DMARDs available in Japan. *ABA* abatacept, *DMARDs* disease-modifying antirheumatic drugs, *ETN* etanercept, *IFX* infliximab, *ADA* adalimumab, *GOL* golimumab, *CZP* certolizumab pegol, *TCZ* tocilizumab

Table 12.2 Major pulmonary adverse events in patients with rheumatoid arthritis receiving biological disease-modifying antirheumatic drugs in Japan according to the postmarketing surveillance program [15–19]

Adverse events	Infliximab	Etanercept	Tocilizumab	Adalimumab	Abatacept
Bacterial pneumonia	2.2	1.3	1.5	1.2	0.7
Tuberculosis	0.3	0.1	0.1	0.1	0.03
Pneumocystis pneumonia	0.4	0.2	0.2	0.3	0.1
Interstitial pneumonia	0.5	0.6	0.5	0.6	0.3

of thousands of patients who were the initial recipients of infliximab, etanercept, tocilizumab, adalimumab, and abatacept and published their results (Table 12.2) [15–19]. The incidence of interstitial pneumonia is comparable (0.3–0.6%) among those biological DMARDs and proportionally (2–3 times) more and less frequent than pneumocystis pneumonia and bacterial pneumonia, respectively, suggesting that microorganisms play a role in the development of DLI. In addition, DLI caused by biological DMARDs is observed less frequently in patients with psoriasis and inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, than in patients with RA receiving anti-TNF biological DMARDs [20]. These results implicate RA as a possible contributor to the development of DLI, in addition to the effect of the biological DMARDs.

ILD incidence rates ranged from 4.0 to 12.2 per 1000 person-years among biological DMARDs using the sensitive definition by the data obtained from the MarketScan Commercial Claims and Encounters and the Medicare Supplemental

and Coordination of Benefit in the United States [21]. There were no significant differences by biologics class. In order to determine the influence of anti-TNF therapy on mortality in patients with preexisting RA-ILD, a national prospective observational study used data from the British Society for Rheumatology Biologics Register and identified 367 patients with preexisting RA-ILD (299 treated with anti-TNF biological DMARDs and 68 treated with conventional synthetic DMARDs) [22]. 70 of 299 (23%) and 14 of 68 (21%) patients died after a median follow-up of 3.8 and 2.1 years in anti-TNF and conventional synthetic DMARDs cohorts, respectively. These data show that the mortality in patients with RA-ILD is not increased by treatment with anti-TNF biological DMARDs compared with that of conventional synthetic DMARDs.

The differential diagnosis of DLI is crucial and complicated, especially in patients with RA receiving biological DMARDs. We conducted a retrospective, multicenter study of acute lung injury (ALI) in patients with RA receiving biological DMARDs [23]. Patients who developed ALI while receiving biological DMARDs (infliximab, etanercept, adalimumab, and tocilizumab) were enrolled in the study. In this study, definite *Pneumocystis* pneumonia (PCP) was defined as patients who showed either *P. jirovecii* organisms in their respiratory samples by microscopic examination or had positive test results for both *P. jirovecii* by DNA-PCR with respiratory samples and an elevated serum 1,3-β-D-glucan level above the cutoff value. Probable PCP was defined as either a positive *P. jirovecii* PCR or an elevated serum β-D-glucan level. Surprisingly, the final diagnoses by the committee members for 26 patients examined were definite PCP for 13 patients, probable PCP for 11, and methotrexate-associated pneumonitis in 2 patients. Importantly, definite and probable PCPs were clinically indistinguishable. This study strongly suggests that the possibility of PCP should be intensively investigated for patients with RA developing ALI while receiving biological DMARDs. Furthermore, an interim analysis of 27 cases of interstitial pneumonia among 4635 patients with RA by Etanercept Postmarketing Surveillance Subcommittee of the Japan College of Rheumatology concluded that only 6 of the 17 patients with available chest images should have been diagnosed as DLI. Therefore, the Japan College of Rheumatology published the diagnostic algorithm of pneumonia during anti-TNF therapy [24], and it has been updated (Fig. 12.3).

12.3.1.1 Infliximab

Infliximab is a chimeric anti-TNF monoclonal antibody. Infliximab postmarketing surveillance in Japan revealed that interstitial pneumonia developed in 0.5% and 0.26% of patients with RA [15] and psoriasis [25], respectively. Interestingly, 15.6% of patients enrolled in the RISING study, a clinical trial of infliximab dose escalation, showed a Krebs von den Lungen-6 (KL-6, a serum biomarker of ILD) elevation, which was defined as ≥500 U/mL and >1.5-fold increase over the baseline value [26]. A KL-6 elevation was also observed in patients enrolled in other

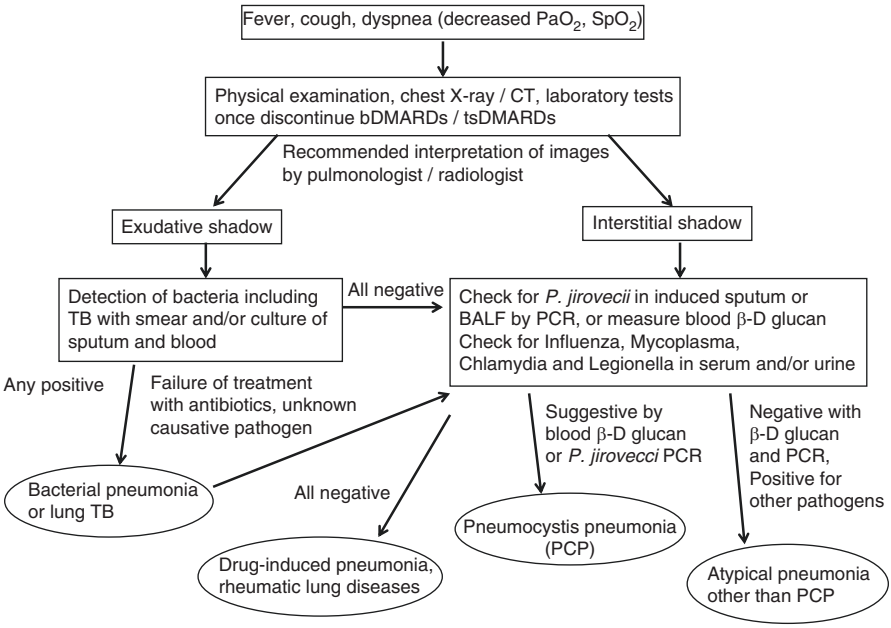

Fig. 12.3 Diagnostic algorithm of patients presenting with fever, cough, and/or dyspnea during treatment with biological disease-modifying antirheumatic drugs (DMARDs) or targeted synthetic DMARDs by the Japan College of Rheumatology (updated in June 2014). *DMARDs* disease-modifying antirheumatic drugs

clinical trials of anti-TNF biological DMARDs such as certolizumab pegol and golimumab, although adverse events did not accompany the elevation of KL-6 in 95.7% of those patients. Moreover, it should be noted that Kramer et al. reported three patients with RA who developed MTX-induced pneumonitis after initiation of infliximab therapy [27].

12.3.1.2 Etanercept

Etanercept is a fusion protein of TNF receptor (p75) and the fragment crystallizable (Fc) region of immunoglobulin G (IgG-Fc). Etanercept postmarketing surveillance in Japan revealed that interstitial pneumonia developed in 0.6% of patients with RA [16]. Literature reports that in the 12 patients with DLI caused by etanercept, 6 patients had preexisting ILD and 2 patients were mortality cases [28]. We have had patients with RA preceded by ILD, who developed acute exacerbation of RA-ILD soon after the start of SASP and etanercept (Fig. 12.4).

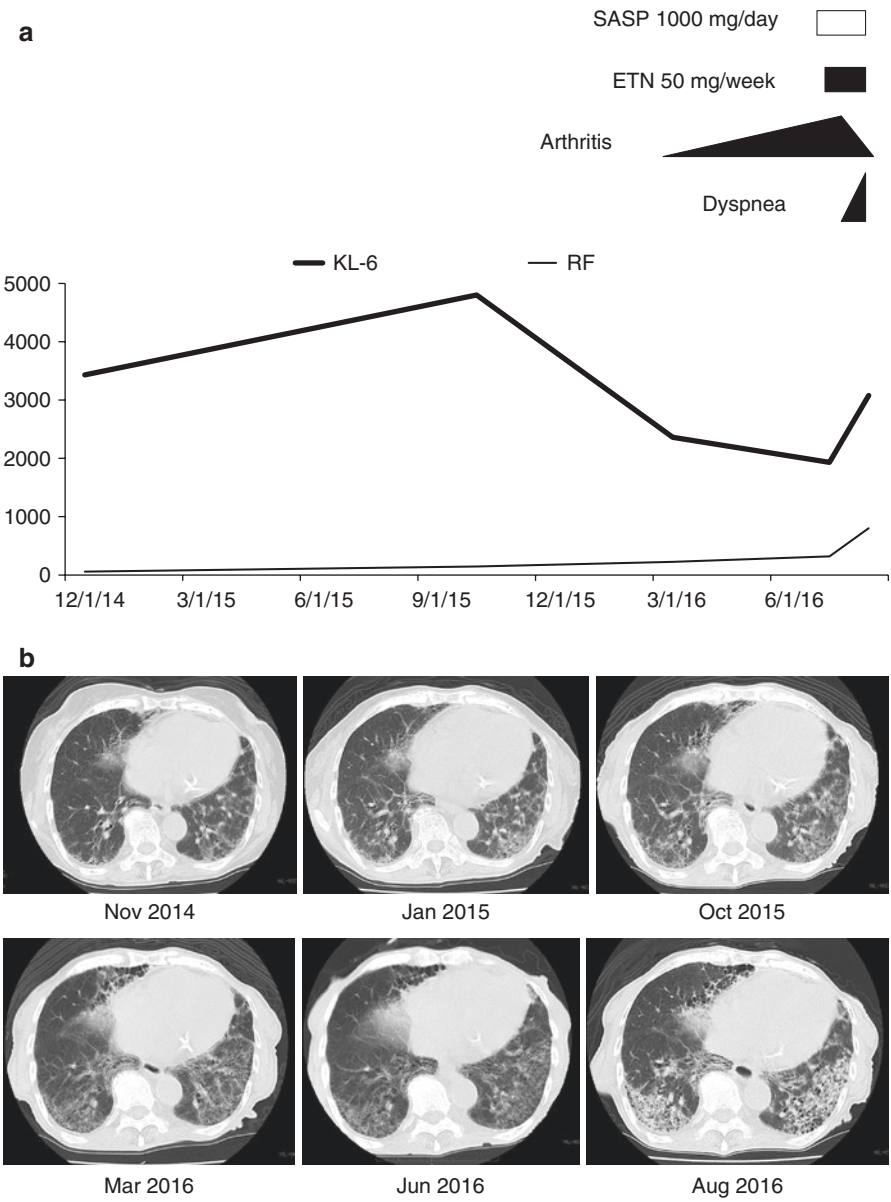

Fig. 12.4 Acute exacerbation of rheumatoid arthritis (RA) with interstitial lung disease (ILD) soon after the start of salazosulfapyridine and etanercept. An 82-year-old woman with nonspecific interstitial pneumonia-like ILD was referred to our hospital in December 2014. She did not have any arthralgia/arthritis and anti-cyclic citrullinated peptide (CCP) antibody was negative, although rheumatoid factor (RF) was positive. She developed arthritis in April 2016, and the diagnosis as RA was made based on polyarthritis for more than 6 weeks, positive results of serum C-reactive protein test and anti-CCP antibody test (77.7 U/mL), and increasing titer of RF (**a**). After the onset of RA, serum Krebs von den Lungen-6 (KL-6) level decreased with no progression of chest high-resolution computed tomography (HRCT) images (**b**). However, 4 weeks after the commencement of RA treatment with SASP and etanercept, acute exacerbation of ILD was observed, which responded to prednisolone at 30 mg/day

12.3.1.3 Adalimumab

Adalimumab is a human anti-TNF monoclonal antibody. Adalimumab postmarketing surveillance in Japan revealed that interstitial pneumonia developed in 0.6% of patients with RA [18]. An interesting case report indicated the improvement of preexisting ILD and the development of additional interstitial pneumonia after starting adalimumab [29].

12.3.1.4 Tocilizumab

Tocilizumab is a humanized anti-interleukin-6 receptor monoclonal antibody. Tocilizumab postmarketing surveillance in Japan revealed that interstitial pneumonia developed in 0.5% of patients with RA [17]. The interim analysis of the initial 3881 patients identified older age and preexisting ILD as risk factors for DLI. A tocilizumab cohort study in Japan reported that 6 of the 78 patients with RA-ILD developed acute exacerbation during tocilizumab treatment. Those patients had significantly higher disease activity than those without acute exacerbation [30].

12.3.1.5 Abatacept

Abatacept is a fusion protein composed of IgG-Fc fused to the extracellular domain of cytotoxic T-lymphocyte-associated protein-4 (CTLA-4). Abatacept binds to CD80 and CD86 and prevents the co-stimulatory signaling necessary for T cell activation. Abatacept postmarketing surveillance in Japan revealed that interstitial pneumonia developed in 0.3% of patients with RA. 4 out of 12 patients were mortality cases [19].

12.3.2 Treatment and Outcome

When patients with RA receiving biological DMARDs develop DLI (definite or probable/possible), discontinuation of biological DMARDs has been recommended. However, immune reconstitution inflammatory syndrome may follow in some patients. Therefore, close monitoring of the immune/inflammatory state in the patients discontinuing biological DMARDs and targeted synthetic DMARDs, such as JAK inhibitors, is mandatory. Reintroduction of the biological DMARD should be considered without delay if necessary. Moderate- to high-dose glucocorticoids may be systemically administered for severe cases along with therapeutic/prophylactic (tentative) antibiotics such as trimethoprim/sulfamethoxazole.

Among the 52 cases with detailed outcomes from 122 reported cases of new onset or exacerbation of ILD, secondary to administration of biological DMARDs [20], 15 (29%) patients died during the follow-up and the majority (70%) died

during the first 5 weeks after initiating biological DMARDs. Poor prognostic factors were age >65 years, a later onset of ILD, frequent immunosuppressive drugs, and a previous diagnosis of ILD. In Japan, fatal outcomes were observed in 7.5–33.3% of patients developing DLI [15–19].

12.4 Conclusion

DLI occurs in approximately 0.5% of patients within 6 months after starting major synthetic or biological DMARDs, and 5–33% of these cases are fatal. The pathogenesis of DLI caused by DMARDs, especially biological DMARDs, is complicated by having RA, the direct effects of DMARDs on the lungs, allergic reaction to DMARDs, and immunosuppressive effects by DMARDs. These complications lead to the variation in clinical, radiographic, and histopathological findings.

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Chapter 13
DLI Induced by Herbal Medicine: What Are the Characteristics of DLI due to Herbal Medicines?

Mitsuhiro Abe, Kenji Tsushima, and Koichiro Tatsumi

Abstract In many countries, herbal medicine has been developed and is currently practiced. Herbal medicine involves the use of the stalks, roots, leaves, flowers, and berries of several different plant species for medical treatment. Many practitioners believe that herbal medication has no side effects because of its natural origin. Thus, herbal medication has been used for a long time with little awareness of its side effects. However, there is an increasing incidence of interstitial pneumonia due to a drug-induced lung injury (DLI), which could be induced by common drugs. Moreover, increasing cases of bronchiolitis obliterans and pulmonary hypertension are being reported; further, these are drug-induced conditions. Clinicians should be more aware of DLI symptoms caused by herbal medication and interrogate patients regarding their use of herbal medication and supplements as well as prescription drugs.

Keywords Herbal medicine • Drug-induced lung injury (DLI) • Shosaikoto (SST)

13.1 Introduction

Generally, herbs are plants that are used for flavoring food and drugs. Broadly, "herbs" can be the leaves, roots, flowers, seeds, resin, bark, berries, or other segments of a plant. Some herbs have strong side effects and are toxic in large doses. "Herbal medicine" involves the use of herbs for medical treatment. Herbal medicine has a long tradition that has evolved independently over many years in different regions worldwide.

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Since the nineteenth century, the bioactive components of herbs used in herbal medicine have been identified and extracted to synthesize a drug formulation. In the twentieth century, evidence-based medical research to evaluate the effects of drugs in large clinical trials has become mainstream. Along with this development, the practice of conventional herbal medicine has decreased.

However, recently, the use of herbal medication to treat certain diseases has been increasing. For example, herbal medicine is being used increasingly to augment the efficacy of chemotherapy and reduce toxicity [1], extend the survival of patients with uterine cervical cancer [2], and reduce postoperative ileus [3].

Many herbs are not readily identified as medication. People can obtain these herbs without visiting a clinic or hospital. Therefore, it is difficult to accurately recognize the market size and side effects of herbal medicine.

Typically, herbal medication is considered a probable cause of adverse events [4]. For example, aconitum (monkshood), which is often used in Chinese herbal medicine, is highly toxic (lethal dose, 0.2–1 g). Aconitum is usually heat-detoxified. Many other herbal drug formulations also have some toxic properties.

As the practice of herbal medicine increases, side effects are being increasingly reported. In this regard, the consumption of healthy and natural foods is just as important as the ingestion of prescription drugs in influencing patient health. To diagnose side effects accurately, we should always consider these side effects. Moreover, we should ask patients sufficiently and understand the characteristics of DLI in each drug.

13.2 Diagnosis of DLI Related to Herbal Medication

There is no special method to diagnose a DLI associated with the use of herbal medication. The Japanese Respiratory Society has proposed five diagnostic criteria for a DLI [4] (Table 13.1): (1) a patient history of ingestion of a drug that induces a lung injury, (2) the clinical manifestations reported as drug-induced lung injury, (3) other causes of the clinical manifestations are excluded, (4) the clinical manifestations improve after drug discontinuation, and (5) the exacerbation of the clinical manifestations after resuming drug administration. Resuming drug administration to identify the causative drug is usually not recommended; however, it is acceptable if the patient requires the drug, and a reasonable level of safety is assured.

The drug lymphocyte stimulation test (DLST) is sometimes helpful in the diagnosis of a DLI. ^{3}H-thymidine uptake by lymphocytes is measured as a stimulating index. The DLST has a positivity rate of 66.9% in patients with drug-induced pneumonia [4, 5]. The rate of drug-induced pneumonia due to herbal medication is 67.6% [5]. However, the results of the DLST should be interpreted with caution for several reasons. First, the DLST is performed in vitro; therefore, the results may be inconsistent with the in vivo condition. Second, the administration procedure is not well established; therefore, the results of the DLST can be different at different institutions.

Table 13.1 Diagnostic criteria for DLIs [4]

1.	History of ingestion of a drug that is known to induce lung injury	Specifically inquire about the following when taking the patient's history: over-the-counter (OTC) drugs, health foods, and illegal narcotic drugs/antihypnotic drugs
2.	The clinical manifestations have been reported to be induced by a drug	The clinical manifestations include clinical findings, imaging findings, and pathological features
3.	Other causes of the clinical manifestations could be ruled out	Differentiation from infection, cardiogenic pulmonary edema, exacerbation of an underlying disease, etc.
4.	Improvement of the clinical manifestations after drug discontinuation	Spontaneous remission or remission in response to an adrenocorticosteroid
5.	Exacerbation of the clinical manifestations after resuming drug administration	Resuming drug administration to identify if the causative drug is not generally recommended but is acceptable if the patient requires the drug and safety is assured

Third, false-positive or false-negative reactions often occur when the DLST is used as a diagnostic test for a DLI, regardless of whether herbal medication is involved. Moreover, herbal medicine includes several plant components (Table 13.2). Some of these components cannot be absorbed in the intestine. A DLST test is performed in vitro; therefore, the component that is not present in the blood in vivo can react with the lymphocytes in vitro (i.e., a false-positive result). For example, Sho-Saiko-To (SST) can directly stimulate lymphocytes, thereby resulting in a false-positive result [4, 6]. Nakayama reported that a DLST for SST was positive in 27.5% of healthy controls [6]. Therefore, we need to carefully consider the result of a DLST in patients suspected with a DLI due to herbal medication.

13.3 DLI due to Herbal Medication

13.3.1 Characteristics of a DLI due to Herbal Medication

Generally, any unfavorable medical occurrence in a patient or a subject of clinical investigation administered a pharmaceutical product is referred to as an adverse event (AE). A DLI is an AE that occurs specifically in the pulmonary system [7]. A DLI can be classified into several different types based on clinicoradiological features such as the clinical course, laboratory findings, and radiological findings (Table 13.3) [4]. Several pathognomonic findings of a DLI have been reported in patients administered with herbal medication.

The most common pathognomonic of a DLI due to herbal medication is interstitial pneumonia. However, recently, other symptoms such as bronchiolitis obliterans and pulmonary arterial hypertension have been associated with herbal medication-related DLI [8, 9].

Table 13.2 The list of components of herbal medicines in Japan that has been reported to cause drug-induced IP

	bakumondoto	bofutsushosan	boiogito	daikenchuto	daisaikoto	gorinsan	goshajinkigan	hangeshashinto	hochuekkito	junchoto	keigairenngyoto
baimo											
bakumondo	○										
biwayou											
boi			○								
bofu		○									○
bosho		○									
botampi							○				
borei											
bukuryo						○	○				
bushi							○				
byakugo											
byakujutu		○									
byakushi											○
chikujo											
chimo											
chimpi									○		
chotoko											
daio					○					○	
gomin											
goshitsu							○				
hakka											○
hange	○				○			○			
ireisen											
jikoppi											
jio						○	○			○	○

kankyo				○				○			
karokon											
kasseki						○					
kanzo	○		○			○		○	○	○	○
keigai											○
keihi							○				
kikyou											○
kijitsu					○					○	○
kobei	○										
kobushi											
koboku										○	
kujin											
kyokatsu											
kyonin										○	
mao		○									
mashin										○	
mokutsu						○					
ninjin	○			○				○	○		
obaku											○
ogi			○						○		
ogon		○			○	○		○		○	○
oren								○			○
renniku											
rengyo											○
ryukotsu											

(continued)

Table 13.2 (continued)

	bakumondoto	bofutsushosan	boiogito	daikenchuto	daisaikoto	gorinsan	goshajinkigan	hangeshashinto	hochuekkito	junchoto	keigairenngyoto
ryutan											
saiko					○				○		○
saishin											
sanshishi						○					○
sansho				○							
sanshuyu							○				
sanyaku							○				
sekko		○									
senkyu											○
shakuyaku					○	○					○
shazenshi						○	○				
shishi											
shokyo			○		○				○		
shoma									○		
sohakuhi											
sojutsu			○						○		
soyo											
takusha						○	○				
taiso	○		○		○			○	○		
temmondo											
tennansho											
toki						○			○	○	○
tonin										○	

	nijutsuto	otsujito	orengedokuto	ryutanshakanto	saibokuto	saikokaryukotsuboreito	saikokeisikannkyoto	saikokeishito	sammotsuogonto
baimo									
bakumondo									
biwayou									
boi									
bofu				△					
bosho									
botampi									
borei						○	○		
bukuryo	○				○	○			
bushi									
byakugo									
byakujutu	○								
byakushi									
chikujo									
chimo									
chimpi	○								
chotoko									
daio		○				△			
gomin									
goshitsu									
hakka				△					
hange	○				○	○		○	
ireisen	○								
jikoppi									
jio				○					○

(continued)

Table 13.2 (continued)

	nijutsuto	otsujito	orengedokuto	ryutanshakanto	saibokuto	saikokaryukotsuboreito	saikokeisikannkyoto	saikokeishito	sammotsuogonto
kankyo							○		
karokon							○		
kasseki									
kanzo	○	○		○	○		○	○	
keigai									
keihi						○	○	○	
kikyou									
kijitsu									
kobei									
kobushi	○								
koboku					○				
kujin									○
kyokatsu	○								
kyonin									
mao									
mashin									
mokutsu				○					
ninjin					○	○		○	
obaku			○	△					
ogi									
ogon	○	○	○	○	○	○	○	○	○
oren			○	△					
renniku									
rengyo				△					
ryukotsu						○			

ryutan				○					
saiko		○			○	○	○	○	
saishin									
sanshishi			○	○					
sansho									
sanshuyu									
sanyaku									
sekko									
senkyu				△					
shakuyaku				△				○	
shazenshi				○					
shishi									
shokyo	○				○	○		○	
shoma		○							
sohakuhi									
sojutsu	○								
soyo					○				
takusha				○					
taiso					○	○		○	
temmondo									
tennansho	○								
toki		○		○					
tonin									

(continued)

Table 13.2 (continued)

	sanoshashinto	seihaito	seishinrenshiin	shakuyakukanzoto	shin'iseihaito	shosaikoto	shoseiryuto	unseiin	yokukansan
baimo		○							
bakumondo		○	○		○				
biwayou					○				
boi									
bofu									
bosho									
botampi									
borei									
bukuryo		○	○						○
bushi									
byakugo					○				
byakujutu									
byakushi									
chikujo		○							
chimo					○				
chimpi		○							
chotoko									○
daio	○								
gomin		○					○		
goshitsu									
hakka									
hange						○	○		
ireisen									
jikoppi			○						
jio								○	

kankyo							○		
karokon									
kasseki									
kanzo		○	○	○		○	○		○
keigai									
keihi							○		
kikyou		○							
kijitsu									
kobei									
kobushi									
koboku									
kujin									
kyokatsu									
kyonin		○							
mao							○		
mashin									
mokutsu									
ninjin			○			○			
obaku								○	
ogi			○						
ogon	○	○	○		○	○		○	
oren	○							○	
renniku			○						
rengyo									
ryukotsu									

(continued)

Table 13.2 (continued)

	sanoshashinto	seihaito	seishinrenshiin	shakuyakukanzoto	shin'iseihaito	shosaikoto	shoseiryuto	unseiin	yokukansan
ryutan									
saiko						○			○
saishin							○		
sanshishi					○			○	
sansho									
sanshuyu									
sanyaku									
sekko					○				
senkyu								○	○
shakuyaku				○			○	○	
shazenshi			○						
shishi		○			○				
shokyo		○				○			
shoma					○				
sohakuhi		○							
sojutsu									○
soyo									
takusha									
taiso		○				○			
temmondo		○							
tennansho									
toki		○						○	○
tonin									

○ always including, △ sometimes including

Table 13.3 Main clinical types and histological diagnoses of DLIs (in contrast to common diffuse pulmonary diseases)

Main lesion site	Clinical disease type	Histological diagnosis
1. Alveolar and interstitial regions	Acute respiratory distress syndrome (ARDS)	Diffuse alveolar damage (DAD)
	Idiopathic interstitial pneumonias (IIPs)	
	Acute interstitial pneumonia (AIP)	Diffuse alveolar damage (DAD)
	Idiopathic pulmonary fibrosis (IPF)	Usual interstitial pneumonia (UIP)
	Nonspecific interstitial pneumonia (NSIP)	Nonspecific interstitial pneumonia (NSIP)
	Desquamative interstitial pneumonia (DIP)	Desquamative interstitial pneumonia (DIP)
	Cryptogenic organizing pneumonia (COP)	Organizing pneumonia (OP)
	Eosinophilic pneumonia (EP)	Eosinophilic pneumonia (EP)
	Hypersensitivity pneumonia (HP)	Hypersensitivity pneumonia (HP)
	Granulomatous interstitial lung diseases	Granulomatous interstitial pneumonia
	Pulmonary edema	Pulmonary edema
	Capillary leak syndrome	Pulmonary edema
	Pulmonary alveolar proteinosis	Alveolar proteinosis
	Diffuse alveolar hemorrhage	Alveolar hemorrhage
	Bronchial asthma	Bronchial asthma
2. Airway	Bronchiolitis obliterans syndrome (BOS)	Bronchiolitis obliterans (BO)
	Pulmonary artery embolism	Pulmonary artery embolism
3. Blood vessels	Vasculitis	Vasculitis
	Pulmonary hypertension	Pulmonary hypertension
	Pulmonary veno-occlusive disease	Pulmonary veno-occlusive disease
4. Pleura	Pleuritis	Pleuritis

In Japan, approximately 140 types of herbal drug formulations have been covered by insurance. Many herbal medicines that are used to treat chronic diseases are sometimes ineffective. Nonetheless, herbal medication has been generally considered an unlikely cause of adverse reactions [4]. The first case of interstitial pneumonia due to herbal medication was reported in 1989 [10]. This patient was administered Sho-Saiko-To (SST) for treatment of chronic hepatitis. Thereafter, interstitial pneumonia has been diagnosed in an increasing number of patients receiving herbal medication.

13.3.2 Interstitial Pneumonia (IP)

Drug-induced IP is the most common characteristic of a DLI and is classified into two types: cytotoxic and allergic drug-induced IP [11].

Cytotoxic drug-induced IP involves multiple mechanisms, including reactive oxygen species (ROS) synthesis, decreased deactivation of metabolites in the lung, impaired alveolar-repair mechanisms, and release of various cytokines [12]. Additionally, cytotoxic drug-induced IP shows a diffuse alveolar damage (DAD) pattern and often presents as a severe clinical manifestation with a lethal outcome. Chemotherapeutic agents, antirheumatic drugs, and amiodarone are typical agents that cause cytotoxic drug-induced IP. However, cytotoxic drug-induced IP due to herbal medication has not been reported. Cases of allergic drug-induced IP often improve with corticosteroid treatment. However, some cases of allergic drug-induced IP have resulted in deaths; therefore, some of these cases may involve conditions other than allergic drug-induced IP.

As mentioned previously, the first report of IP due to herbal medication involved SST in 1989 [10], which occurred in Japan. SST consists of seven types of herbs, saiko (*Bupleurum scorzonerifolium*), ogon (*Scutellaria baicalensis*), hange (*Pinellia ternata*), shokyo (*Zingiber officinale*), taiso (*Ziziphus jujube*), ginseng (*Panax ginseng*), and kanzo (*Glycyrrhiza uralensis*). SST improved liver function in patients with chronic active hepatitis in a double-blind randomized study [13]. Some studies report that only two SST components (ogon and hange) were positive in a DLST [10, 14]. However, another study found that all seven components were positive in a DLST [15]. Shimodaira reported in 2000 that ogon, kanzo, and shokyo are commonly involved in lung injury after a review of 488 patients administered with herbal medication [16].

Since the first report in 1989, the number of reports of drug-induced IP due to SST has increased. More than 100 cases have been reported in 10 years [17]. Ten people with SST-induced IP have died, and this condition has become a serious social problem in Japan. Suzuki reported the clinical characteristics of SST-induced IP (Table 13.4) [17]. The period of onset of SST-induced IP was longer (78.9 ± 121.0 days) than that for non-herbal drug-induced IP. The proportion of SST-induced IP patients that was positive for the hepatitis C virus (HCV) antibody was 75.7%. Laboratory findings indicated high lactic dehydrogenase enzyme (LDH) and C-reactive protein (CRP) levels, hypoxemia, and a high proportion of lymphocytes in the bronchoalveolar lavage fluid. Chest computed tomography (CT) findings indicated that ground-glass opacity was 29.2% and air-space consolidation was 45.8%.

Additionally, Sato characterized patients with SST-induced IP [18]. A comparison of the survivors and non-survivors revealed a significant difference in the prevalence of pulmonary complications such as idiopathic pulmonary fibrosis, duration of treatment after onset, degree of hypoxemia, prevalence of liver cirrhosis, positive proportion of HCV antibody, and CRP values.

Table 13.4 Clinical features of Sho-Saiko-To-induced interstitial pneumonia

Age (years)		64.5 ± 8.2
Male/female		69/31
Underlying disease	Chronic hepatitis	52 (52%)
	Cirrhosis of the liver	29 (29%)
	Liver dysfunction	18 (18%)
	Others	1 (1%)
Period to onset (day)		78.9 ± 121.0 (n = 80)
Duration of administration after the onset (day)		6.9 ± 9.3 (n = 84)
First symptom	Cough	87.6%
	Dyspnea	85.9%
	Fever	79.8%
Laboratory findings	Hematology/serology	
	White blood cell	7823 ± 3324/mm^3 (n = 77)
	Eosinophils	246 ± 288/mm^3 (n = 56)
	LDH	681 ± 310 IU/L (n = 74)
	CRP	5.3 ± 4.9 mg/dL (n = 53)
	Arterial blood gas	
	PaO_2	48.5 ± 13.0 Torr (n = 76)
	$PaCO_2$	33.5 ± 6.3 Torr (n = 71)
	Bronchoalveolar lavage (n = 17)	
	Macrophage	38.0 ± 28.6%
	Lymphocytes	46.2 ± 29.2%
	Neutrophils	12.4 ± 16.6%
	Eosinophils	3.2 ± 3.5%
	CD_4/CD_8 ratio	0.61 ± 0.51%
Radiological findings	Chest X-ray (n = 41)	
	Ground-glass opacity	58.5%
	Infiltration	26.8%
	Ground-glass opacity + infiltration	14.6%
	Chest CT (n = 24)	
	Ground-glass opacity	29.2%
	Air-space consolidation	45.8%
	Ground-glass opacity + air-space consolidation	4.2%
	Nodular shadow	16.7%

LDH lactic dehydrogenase enzyme, *CRP* C-reactive protein, *CT* computed tomography

A delay in the discontinuation of SST administration can result in death. Although the treatment response for allergic drug-induced IP is generally positive, cytotoxic mechanisms may result in death.

Fibroblasts produce inflammatory cytokines (such as IL-1, IL-6, and IL-8) in vitro in response to stimulation by SST, and this reaction is stronger in fibroblasts from the lungs of patients with idiopathic pulmonary fibrosis (IPF) than in healthy

individuals [19]. Furthermore, the proportion of patients with SST-induced IP that were positive for HCV antibody was high. Interferon (IFN) production due to viral infection either may be involved in the onset of drug-induced IP or may increase its severity.

In Japan, SST is frequently reported as the causative agent of an AE involving IP compared to other herbal medicines. An AE that involved IP has been reported for 25 species of herbal medicines, including SST [20]. Some IP patients use multiple herbal medicines, while others develop IP after herbal medicine use was discontinued. We should recognize that all herbal medicines pose a risk for developing drug-induced IP.

13.3.3 Bronchiolitis Obliterans

An outbreak of bronchiolitis obliterans in association with *Sauropus androgynus* (*Sauropus albicans*) was reported in Taiwan in *Lancet* in 1996 [8]. *Sauropus androgynus* (SA) is a plant from the *Euphorbiaceae* family. This plant grows to a height of approximately 1.5 m. The leaves of this plant are eaten as a vegetable particularly in Malaysia, Indonesia, and Vietnam. SA has been imported into Taiwan from these countries since 1982. Some people believe that SA can be used for weight management, especially young and middle-aged women in Southeast Asia who regularly consume SA. The characteristic DLI due to herbal medicine is reported as only IP. Therefore, the 1996 report of bronchiolitis obliterans as a new pathognomonic of a DLI due to SA was of interest of many researchers.

The mean age of the 23 women in this 1996 report by Lai [8] was 39 years (range, 21–52 years). SA is usually cooked in most Southeast Asian countries; however, 23 patients drank juice from uncooked SA. The mean estimated total amount of ingested SA per person was 8–16 kg (range, 2–21 kg) over a mean of approximately 10 weeks (range, 2–13 weeks). Table 13.5 shows the clinical features of SA-induced bronchiolitis obliterans. Progressive dyspnea (23 patients) and persistent cough (21 patients) were the predominant symptoms on presentation; these features developed approximately 14 weeks after SA ingestion. Physical examination revealed decreased breathing sounds and tachypnea with wheezing in 3 patients and crackles in 17 patients. The use of the accessory muscles was observed in 19 patients. No abnormality was detected in the complete blood count, serum biochemistry, serum alpha-1 antitrypsin concentration, urine analysis, and electrocardiography.

Malaysians have consumed SA for a long time; however, there are no reports of related side effects. In contrast, in Taiwan, several side effects have been reported, which may be due to a difference in the amounts of consumed SA [21]. Taiwanese people consume about 150 g of SA as opposed to about 100 ~ 200 g consumed by Malaysians.

One study reported that papaverine, which is a component of SA, results in the development of bronchiolitis obliterans [22]; however, this is questionable. Wang

Table 13.5 Clinical features of *Sauropus androgynous*-induced bronchiolitis obliterans

Total number	23 (male 0/female 23)	
Mean age (range)	39 (21–52)	
	Number (proportion)	
Symptoms		
Progressive dyspnea	23 (100%)	
Cough	21 (91%)	
Sputum	8 (34%)	
Oral ulcer	9 (39%)	
Palpitation	17 (73%)	
Insomnia	12 (52%)	
Physical examination		
Decreased breath sounds	3 (13%)	
Tachypnea	3 (13%)	
Wheezing	3 (13%)	
Crackles	17 (73%)	
Using of accessory muscles	19 (82%)	
	Mean (SD)	% predicted
Blood arterial gas		
pH	7.43 (±0.03)	
$PaCO_2$ (Torr)	39.0 (±6.7)	
PaO_2 (Torr)	72.0 (±12.0)	
SpO_2 (%)	94 (±3)	
Spirometry		
FEV_1 (L)	0.66 (±0.20)	26%
FVC (L)	1.52 (±0.36)	51%
TLC (L)	4.12 (±0.51)	95%
RV (L)	2.34 (±0.45)	177%
DL_{CO} (mL min^{-1} $mmHg^{-1}$)	12.1 (±4.1)	49%

SD standard deviation, FEV_1 forced expiratory volume in 1 s, *FVC* forced vital capacity, *TLC* total lung capacity, *RV* residual volume

reported that a more accurate histopathological classification of SA-associated lung disease is constrictive obliterative bronchitis/bronchiolitis with the participation of T-lymphocytes, macrophages, mast cells, eosinophils, and fibroblasts in its morphogenesis of the bronchioles or bronchi. The persistent accumulation of inflammatory cells was predominantly mediated by continued blood flow to the site of injury, eventually resulting in the irreversible fibrosis of the bronchioles and bronchi <3 mm in diameter. Obliterative arteriopathy was suspected of being only an indirect contributing factor [23].

In SA-induced bronchiolitis obliterans, respiratory failure sometimes progresses after SA ingestion has been discontinued. Moreover, corticosteroid therapy and immunosuppressive agents are usually administered; however, the condition is often resistant. Therefore, lung transplantation should be considered for treatment [24, 25]. This clinical course is not typically recognized as a DLI.

Table 13.6 Risk factors for pulmonary arterial hypertension

Definite	Possible	Likely	Unlikely
Aminorex	Cocaine	Amphetamines	Oral contraceptives
Fenfluramine	Phenylpropanolamine	L-tryptophan	Estrogen
Dexfenfluramine	St. John's Wort	Methamphetamines	Cigarette smoking
Toxic rapeseed oil	Chemotherapeutic agents	Dasatinib	
Benfluorex	Interferon α and β		
SSRI	Amphetamine-like drugs		

SSRI selective serotonin reuptake inhibitor

13.3.4 Pulmonary Arterial Hypertension

The Evian Conference in 1998 [9] reported that some drugs are the risk factors for the development of pulmonary arterial hypertension (PAH). In addition, these drugs were categorized into four types based on their incidence rate.

This categorization was followed by additional modification at the Venice meeting in 2003 [26], the Dana Point conference in 2008, and the Nice meeting in 2013 (Table 13.6) [27]. In this drug categorization scheme, "definite" indicates the demonstration of an association between a drug and PAH in large multicenter epidemiologic studies. "Likely" indicates the demonstration of such an association by a single-center case-control study or a multiple-case series. "Possible" indicates a demonstration of such an association based on case series, registries, or expert opinions. Finally, "unlikely" indicates that a drug has been studied in epidemiological studies and an association with PAH was not demonstrated [26–28].

Some of these drugs that pose a risk for the development of PAH are related to herbal medication (e.g., toxic rapeseed oil, cocaine, St. John's wort, and methamphetamine).

13.3.4.1 Toxic Rapeseed Oil

In 1981, in Madrid, Spain, the outbreak of toxic oil syndrome (TOS) was caused by the ingestion of a type of oil that was fraudulently sold as olive oil [29]. More than 15,000 children and adults were hospitalized in Madrid, complaining of fever, dyspnea, cough, skin rash, and a spectrum of gastric and neurologic symptoms. Approximately 300 died shortly after the onset of the disease, and a larger number developed a chronic disease [30].

PAH is one of the symptoms of TOS, showing an estimated frequency of 1 ~ 3% [30]. Garcia-Dorado D studied 38 patients with PAH due to toxic rapeseed oil [31], where the mean pulmonary arterial pressure of the patients was 40 ± 9 mmHg and the mean pulmonary to systemic vascular resistance ratio (Rp/Rs) was three times that of normal individuals (0.45 versus 0.15). However, cardiac index, pulmonary capillary wedge pressure, and left ventricular end-diastolic pressure remained within the normal range.

13.3.4.2 Cocaine

Long-term cocaine abuse causes left ventricular hypertrophy and systolic dysfunction [32]. In addition, many adverse cardiovascular events have been reported (e.g., dysrhythmias, endocarditis, and aortic dissection or rupture) [33, 34].

Moreover, pulmonary granulomatosis and pulmonary artery hypertension have been documented in chronic users of cocaine [35–37].

Significant reduction of the pulmonary vascular bed owing to the granulomatous process may result in pulmonary hypertension. The granulomatous process may be caused by insoluble agents that adulterate the addictive drug [36, 37].

Yakel DL Jr. (1995) measured the systolic pulmonary artery pressure (PAP) of 13 chronic intravenous cocaine users (aged 33.3 years; range, 23–41 years). Eight subjects had an elevated PAP (>30 mm Hg), three of whom had a PAP >40 mmHg [37].

13.3.4.3 St. John's Wort (*Hypericum perforatum*)

St. John's wort (*Hypericum perforatum*) is an herb of European origin that is perennial, bears yellow flowers, and is available worldwide.

St. John's wort is currently used for treating depression. A meta-analysis in 1996 [38] revealed that extracts of St. John's wort are more effective than placebo for the treatment of mild to moderately severe depression. Further, a double-blind randomized controlled trial [39] carried out in the United States was unable to demonstrate the efficacy of St. John's wort compared to placebo and sertraline—a selective serotonin reuptake inhibitor [SSRI]).

Hyperforin, one of the main components of the St. John's wort, increases synaptic serotonin and norepinephrine concentrations via an indirect and yet unknown mechanism [40]. Increasing synaptic serotonin and norepinephrine concentrations may be related to PAH, similar to SSRIs. In fact, an SSRI is categorized as a "definite" cause of PAH [28, 41].

13.3.4.4 Methamphetamine

Methamphetamine is synthesized from ephedrine extracted from *Ephedra sinica*. This plant has been used in China for more than 5000 years to stimulate circulation and for its antipyretic and antitussive properties. Ephedrine, which is the main ingredient of *Ephedra sinica*, was discovered by N. Nagai in 1885.

Ephedrine acts on parts of the sympathetic nervous system (SNS). The main mechanism of ephedrine is an indirect stimulation of the adrenergic receptor system through increasing the activity of norepinephrine at the postsynaptic α-adrenergic and β-adrenergic receptors. Although the action of ephedrine is less potent than that of adrenaline, its activation time is 7–10 times longer. Hence, ephedrine is used as a bronchodilator and vasopressor.

In contrast, methamphetamine is a strong agonist of trace amine-associated receptor 1 (TAAR1). Activated TAAR1 increases cyclic adenosine monophosphate (cAMP) production and completely inhibits the uptake of the dopamine transporter (DAT), norepinephrine transporter (NET), and serotonin transporter (SERT) in the plasma membrane [42, 43]. Moreover, methamphetamine induces efflux of neurotransmitters via the vesicular monoamine transporters (VMAT) [44]. Currently, methamphetamine is used to treat conditions such as narcolepsy and depression; however, it is strictly restricted worldwide because of its addictive nature and irritation to the central nervous system.

The proportion of stimulant use (amphetamines, methamphetamines, or cocaine) was investigated in 340 patients with idiopathic PAH, chronic thromboembolic PH (CTEPH) or PAH that was associated with other risk factors. A history of stimulant use was found in 28.9% of the patients diagnosed with idiopathic PAH, compared to 3.8% for the patients with PAH and a known risk factor, and 4.3% for patients with CTEPH [45].

Methamphetamines potently act on norepinephrine and dopamine transporters and rarely affect the serotonin transporter. Both serotonin and norepinephrine have vasoconstrictive and growth-modulating effects on smooth muscle cells, suggesting a possible involvement of methamphetamines in the development of PAH [46, 47].

Y. Sakurai reported a case of pulmonary hypertension due to bofutsushosan. Ephedra is a component of bofutsushosan [48]; thus, ephedra is probably involved in the development of PAH.

13.3.5 Pulmonary Arterial Thrombosis

Demonstrating a relationship between an administered drug and the development of pulmonary arterial thrombosis is difficult.

Yigit M reported a 41-year-old woman with a pulmonary embolism while on a high-dose course of panax tablets that contain extracts of *Tribulus terrestris*, *Avena sativa*, and *Panax ginseng* [49]. However, the pathophysiological mechanism of pulmonary embolism has not been demonstrated.

13.4 Therapy and Prognosis of a DLI due to Herbal Medication

There is no special treatment to protect against a DLI due to herbal medication. The Japanese Respiratory Society has proposed a treatment for DLI [4]. Any drug that is suspected of causing a DLI should be immediately discontinued in all cases. If continued treatment is necessary, the suspected drug should be replaced by one that is less likely to induce a lung injury.

Table 13.7 Proposed classification and treatment strategy for drug-induced interstitial pneumonia and acute lung injury [4]

Degree of severity	PaO_2	Treatment[a]
Mild	≧80 Torr	Discontinuation of the suspected drug
Moderate	≧60 Torr, <80 Torr	Discontinuation of the suspected drug
		Adrenocorticosteroid therapy
Severe	<60 Torr (PaO_2/FiO_2 < 300)	Discontinuation of the suspected drug mPSL pulse therapy for 3 days and then continuous adrenocorticosteroid administration

[a]The treatment information is provided for reference only. When a patient rapidly resolves after discontinuation of the suspected drug or responds to adrenocorticosteroid therapy, the dose of the steroid should be reduced

Regarding drug-induced IP, treatment should be determined using PaO_2 (Table 13.7). The most common type of drug-induced IP due to herbal medication is the allergic type; thus, most patients will have a good response to steroid therapy. However, ten patients with SST-induced IP have died in Japan [17]. Therefore, it is important to note that delayed diagnosis and treatment of a drug-induced IP due to herbal medication could result in death.

Bronchiolitis obliterans due to *Sauropus androgynus* is irreversible and resistant to treatment, similar to idiopathic bronchiolitis obliterans. Lung transplantation is the only solution for patients in the advanced stage of this disease. Some patients with bronchiolitis obliterans due to *Sauropus androgynous* have successfully received a lung transplant [24, 25]. Therefore, early detection and treatment are important.

13.5 Conclusion

Herbal medication is rarely suspected to be involved in a DLI. A detailed inquiry of the patients is important because some DLIs resulting from the use of herbal medication are irreversible.

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Chapter 14
DLI Induced by Antiarrhythmic Drug and Antimicrobial Drug: What Are the Characteristics of DLI in Antiarrhythmic Drugs and Antimicrobial Drugs?

Fumio Sakamaki

Abstract In this chapter, lung injury induced by antiarrhythmic and antimicrobial drugs is described. Amiodarone-induced lung injury is especially reported in detail, as amiodarone-induced lung injury has significant diversity in its pathogenesis and clinical features, causing a lot of diagnostic and therapeutic problems. The mechanisms of amiodarone-induced lung injury may consist of both direct and indirect mechanisms, and especially the direct mechanisms may be related to the drug accumulation in lung tissue, making the clinical course complex. Similar to the DLI induced by other agents, amiodarone-induced lung injury should not be diagnosed by just one biological, physiological, or radiological parameter, but by multidisciplinary points including clinical course, radiographic findings, physiological and biochemical parameters, and exclusion of other etiologies including pulmonary infection, congestive heart failure, and malignancy. Even if the characterized radiological or histopathological findings are found in patients who take amiodarone, drug-induced lung injury may not be confirmed. Lung toxicity or injury induced by antiarrhythmic drugs other than amiodarone and antimicrobial drugs are also described with regard to their onset rates and types of lung injury.

Keywords Antiarrhythmic drugs • Antimicrobial drugs • Interstitial pneumonia • Acute lung injury • Organizing pneumonia

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14.1 Introduction

Various kinds of antiarrhythmic and antimicrobial drugs have the possibility to cause drug-induced lung injury (DLI) including interstitial pneumonia, organizing pneumonia, acute respiratory distress syndrome (ARDS) or diffuse alveolar damage (DAD), acute or chronic alveolar hemorrhage, pleural effusion, solitary pulmonary mass, and hypoventilation syndrome. In contrast to other kinds of drugs, there are often not alternatives to the use of antiarrhythmic and antimicrobial drugs, and they cannot be easily interrupted without resulting in adverse outcomes in patients. DLI induced by antiarrhythmic and antimicrobial drugs has significant diversity in its pathogenesis and clinical features, leading to diagnostic and therapeutic challenges. In particular, amiodarone-induced lung injury has been widely reported and reviewed since the 1980s, whereas reports of DLI due to other antiarrhythmic and antimicrobial drugs have not been so well outlined. Therefore, in this chapter, we will mainly discuss amiodarone-induced lung injury, including our case reports, and DLI induced by antiarrhythmic drugs other than amiodarone, as well as antimicrobial drugs, will be reviewed with regard to their onset rates and types of lung injury.

14.2 DLI Induced by Antiarrhythmic Drugs

14.2.1 Amiodarone-Induced Lung Toxicity

14.2.1.1 Incidence Rate and Risk Factors of Amiodarone-Induced Lung Toxicity

Amiodarone has a significant beneficial effect on fatal arrhythmia including severe ventricular arrhythmia, selected refractory atrial fibrillation, or supraventricular arrhythmias, as well as severe congestive heart failure. However, several clinical forms of severe pulmonary toxicity sometimes occur. In past investigations, amiodarone pulmonary toxicity occurred with an incidence in the range of 0.1–17% [1], and case fatality rates were in the range of 1–50% [2–4].

In one investigation, a 9.1% cumulative risk of pulmonary toxicity occurred between 6 days and 60 months of treatment, with the highest incidence occurring during the first 12 months [4], while another report found the occurrence of lung injury over 10 years after the start of amiodarone administration [5]. There is evidence that a daily amiodarone dose of less than 200 mg is associated with a lower risk of toxicity [6]. However, pulmonary toxicity can occur at lower doses, and the total cumulative dose and serum levels of amiodarone and its metabolite, desethylamiodarone, do not reliably predict toxicity [7].

It has been reported that amiodarone is associated with episodes of acute noncardiogenic pulmonary edema (acute respiratory distress syndrome, ARDS), which occurs mainly after pulmonary angiography and cardiac or noncardiac surgery.

Table 14.1 Proposed risk factors for lung injuries induced by amiodarone (Refs. [4, 6, 14])

1. Gender	Male
2. Age	Rare in males ≤40 years of age, while patients >50 years of age are at relatively high risk
3. Underlying lesions and conditions	(1) Presence of abnormal chest X-ray findings, especially interstitial lung parenchymal change (2) Lung surgery and reduced pulmonary function: Abnormal pulmonary function including DLco <80% before the administration of amiodarone is likely a risk factor for amiodarone-induced lung injuries. Unilateral pneumonectomy increases the risk of amiodarone-induced lung injuries (3) An increased inspiratory oxygen fraction (4) Use of iodinated contrast medium in CT or angiography (5) The incidence of lung injury, especially ARDS, may be relatively higher after cardiac or noncardiac surgery
4. Dose	(1) A low dose (≤200 mg/day) of amiodarone produces a low risk for developing lung injury, but the severity of injury may vary (2) The incidence rate varies from approximately 0.1% in patients administered with a low dose of amiodarone to 50% in those given a high dose (≥1200 mg/day) (3) The incidence rate ranges from 5 to 15% in patients administered amiodarone at a dose of >500 mg/day and from 0.1 to 0.5% in those given amiodarone at a dose of 200 mg/day (4) High-level serum concentration of desethylamiodarone (DEA) (>2.34 ± 0.18 μg)

One retrospective investigation showed a much higher incidence of ARDS in patients taking amiodarone who had undergone cardiac surgery than in very similar control groups [8, 9].

The value of baseline pulmonary function tests or radiographic abnormalities before the start of amiodarone is also controversial [10]. Several recent studies in patients treated with amiodarone showed that a reduction in diffusing capacity is a poor indicator of amiodarone-induced pulmonary toxicity [10]. Serum levels of KL-6, a mucin-like high molecular weight glycoprotein secreted by proliferating type II pneumocytes, are now frequently used in assessing the activity of interstitial pneumonia [11]. Several studies, mainly from Japan, have demonstrated that KL-6 is a useful marker for the disease activity and severity of amiodarone-induced DLI [5, 12]. However, in our study, serial measurement of serum KL-6 did not predict amiodarone-induced lung injury, especially for ARDS [13]. The risk factors for amiodarone pulmonary toxicity have not been fully investigated, although the factors listed in Table 14.1 are considered to be important in clinical situations [4, 6, 14].

14.2.1.2 Pathogenesis of Amiodarone-Induced Lung Toxicity [3, 15]

Many drugs are thought to damage the lung parenchyma as a result of direct cytotoxicity to susceptible target lung cells. Amiodarone is an iodine-containing amphipathic compound with high solubility and can be directly toxic to cultured pulmonary

endothelial cells by phospholipid accumulation, which can induce direct cell injury and cell death because amiodarone is a potent inhibitor of phospholipase A [16].

The mechanism of amiodarone toxicity has not yet been determined; however, several possibilities have been considered [15, 16]. First, the cellular phospholipidosis induced by amiodarone may cause direct cellular injury, which results in secondary pulmonary inflammation. Second, cell-mediated immunologic response to amiodarone, mainly presented as CD8-positive (T-suppression/cytotoxic) lymphocytosis in the bronchoalveolar lavage fluid, may occur in many patients. Third, amiodarone may be capable of generating toxic oxygen metabolites, and there is some evidence that the lung injury may be due, in part, to damage caused by these toxic oxidants. In addition, one study in vitro suggests that amiodarone and its metabolites caused dose-dependent apoptosis, necrosis, and net cell loss of human and rat alveolar epithelial cells [17]. Another study indicated that amiodarone induces apoptosis of alveolar epithelial cells in vivo that is inhibited by angiotensin antagonists and that blockade of angiotensin formation or function may attenuate amiodarone-induced lung fibrosis, irrespective of the severity of alveolitis [18]. In summary, the mechanisms of amiodarone-induced lung toxicity may consist of both direct and indirect mechanisms. One indirect mechanism is an allergic reaction and can be alleviated through drug discontinuation and steroid treatment, while a direct mechanism is drug accumulation in lung tissue, and thus may not be detected until long after the start of amiodarone treatment and will continue even after drug discontinuation.

14.2.1.3 Diagnosis and Clinical Features of Amiodarone-Induced Lung Toxicity

Similar to DLI induced by other kinds of drugs, the diagnosis of amiodarone-induced lung injury is made using the following criteria:

1. A new pulmonary lesion is detected during the amiodarone treatment as well as after treatment has been completed.
2. Other causes of clinical respiratory manifestations, including pulmonary infection, malignant disease (e.g., carcinomatous lymphangitis), and pulmonary congestion due to left-sided heart failure, which is most important in patients taking amiodarone, are ruled out.
3. Improvement of the clinical manifestation after drug discontinuation and/or exacerbation after resuming drug administration, independent of corticosteroid administration as a treatment [14].

Representative symptoms and signs of amiodarone-induced lung injury include a nonproductive cough, dyspnea, pleuritic pain, weight loss, fever, and bilateral inspiratory crackles without clubbing finger in a physical examination.

In laboratory tests, peripheral blood findings are nonspecific, although elevations have been reported in white blood cell counts, the serum lactate dehydrogenase

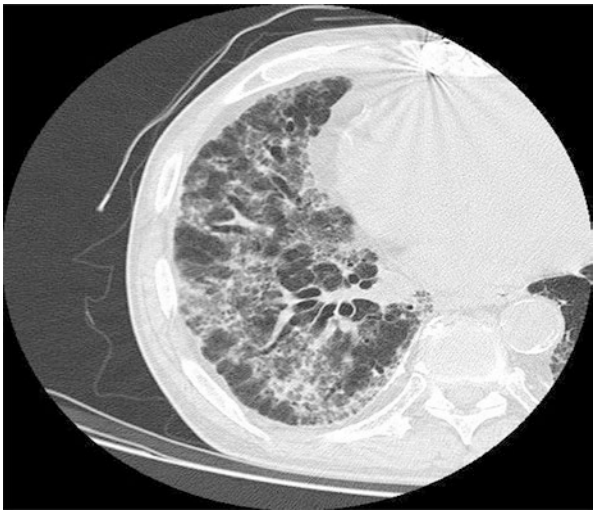

Fig. 14.1 Chest CT scan of a patient with chronic alveolitis/fibrotic lung disease who was diagnosed with amiodarone-induced lung injury (the author's attended case) at the exacerbated phase. A 77-year-old man with chronic heart failure due to coronary artery disease had been treated with amiodarone (100 mg/day) as a maintenance dose. Two years after the start of amiodarone, bilateral pulmonary interstitial shadows with fibrosis were exacerbated, as shown in this figure

level, and the erythrocyte sedimentation rate [3]. Peripheral eosinophilia and antinuclear antibodies are uncommon as compared with other allergic pneumonitis [3].

Amiodarone-induced lung toxicity has several forms of clinical presentations. Radiographic features in X-ray and computed tomography (CT) scans of the chest can be classified as follows:

1. Chronic alveolitis/fibrotic lung disease (Fig. 14.1)
   Chronic fibrotic lung disease is the most common type and occurs in approximately two-thirds of patients and is characterized by the incidental onset of cough, dyspnea on exertion associated with interstitial infiltrates in a chest radiograph, and restrictive ventilator impairment. Chronic fibrotic lung disease is usually recognized after 2 months of therapy, especially in patients in whom the daily dose exceeds 400 mg/day [3].
2. Subacute organizing pneumonia (Fig. 14.2)
   An organizing pneumonia with or without bronchiolitis obliterans is seen in one-third to one-fourth of patients with amiodarone-induced lung injury [19]. Symptoms of the relatively acute form include: fever, cough, chest pain, dyspnea, and focal alveolar infiltration or consolidation with or without an interstitial shadow in a chest X-ray or CT. These findings may mimic infectious pneumonitis, especially when it is seen as lobar or segmental infiltrations.

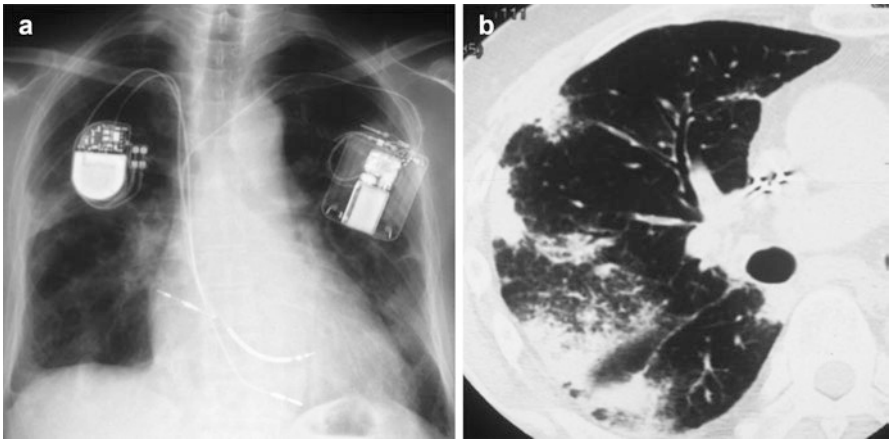

Fig. 14.2 Panel (**a**) Chest X-ray and (**b**) CT scan of a patient with subacute organizing pneumonia who was diagnosed with amiodarone-induced lung injury (the author's attended case). A 65-year-old man with ventricular tachycardia due to an old myocardial infarction had been treated with amiodarone (200 mg/day) as a maintenance dose. One year after the start of amiodarone, patchy consolidation of bilateral lungs developed accompanied by the progression of dyspnea on exertion. An increased ratio of lymphocytes in bronchoalveolar lavage fluid analysis was seen. Prednisolone (40 mg/day as starting dose) was started, and the patient's symptom and chest radiographic finding improved

3. Acute noncardiogenic pulmonary edema (acute respiratory distress syndrome/acute lung injury, ARDS/ALI; Fig. 14.3)
   Noncardiogenic pulmonary edema, often culminating in ARDS, is a rare and fatal form of amiodarone-induced pulmonary toxicity. In almost all cases, ARDS complication occurs after pulmonary angiography, as well as various cardiac and noncardiac surgeries, and is characterized by a fulminant course [8, 20]. There is often a 1–4-day delay between the surgical procedure and the onset of ARDS. However, in one report, two patients with ARDS after pulmonary angiography suffered from deteriorating respiratory symptoms within 30 min of the procedure [21].
4. Pulmonary solitary mass (Fig. 14.4) and others
   Pulmonary solitary nodules or pleura-based or parenchymal mass lesions, which mimic lung cancer, have also been reported as types of amiodarone-induced pulmonary complication [22]. Isolated or unilateral pleural effusions were also described as less common radiographic manifestations [8].

Both localized and diffuse areas of very high CT attenuation can often be seen in amiodarone-induced pulmonary toxicity (Fig. 14.5), as well as in the liver and spleen. This lesion may indicate areas of focal accumulation of foamy macrophages, which contain large doses of amiodarone including 37% iodine by weight and are presented as high CT attenuation areas [23]. The presence of these high attenuation areas on CT scans is not definitively diagnostic of actual pulmonary toxicity because

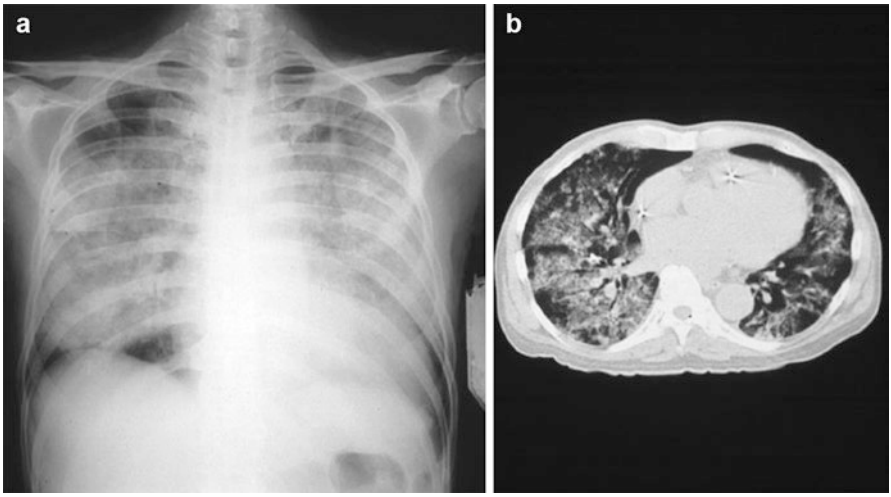

Fig. 14.3 Panel (**a**) Chest X-ray and (**b**) CT scan of a patient with ARDS/ALI who was diagnosed with amiodarone-induced lung injury (the author's attended case). A 64-year-old man with congestive heart failure had been treated with amiodarone (200 mg/day) as a maintenance dose. Four years after the start of amiodarone, the patient suffered from a nonproductive cough, dyspnea, high-grade fever, and bilateral diffuse alveolar shadows in a chest radiograph, suggesting pulmonary edema. Right heart catheterization demonstrated a normal pulmonary venous pressure; mean right atrium pressure = 0 mmHg, mean pulmonary arterial pressure = 16 mmHg, mean pulmonary arterial wedge pressure = 10 mmHg, cardiac output = 5.4 L/min

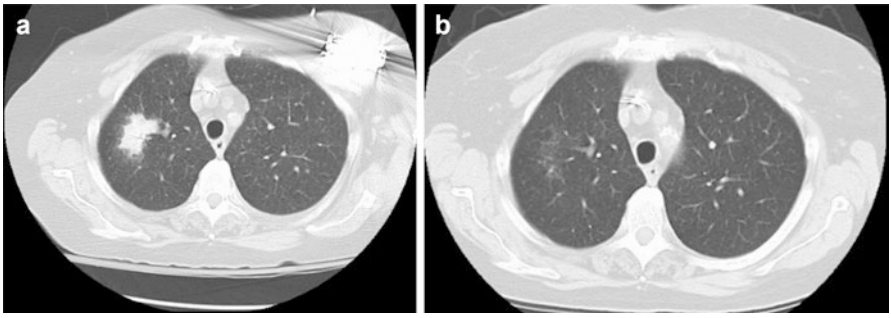

Fig. 14.4 Chest CT of a patient with a pulmonary solitary mass type, "amiodaronoma" who was diagnosed with amiodarone-induced lung toxicity (cited from reference [22]). A 66-year-old woman with non-sustained ventricular tachycardia had been treated with 200 mg/day of amiodarone. Four years after the start of amiodarone, an irregular hyperdense mass in the right upper lobe appeared in a chest X-ray and CT scan (Panel (**a**)). Biopsy of the mass showed no malignancy and no specific pathological agents, but multiple lamellar bodies within macrophages in electron microscopy suggested amiodarone-induced pulmonary toxicity. This lesion showed resolution 3 months after the discontinuation of amiodarone (Panel (**b**))

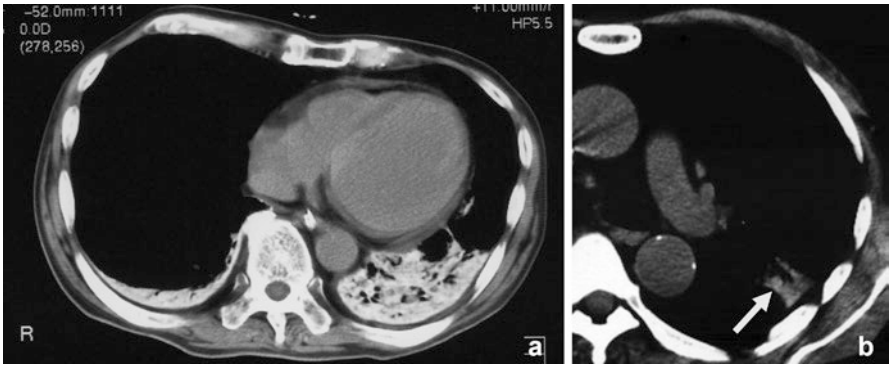

Fig. 14.5 High CT attenuation areas can be often seen in patients taking amiodarone for long periods. This lesion may indicate areas of focal accumulation of foamy macrophages, which contain large doses of amiodarone including iodine. However, the presence of this lesion is not definitively diagnostic of pulmonary toxicity. Panel (**a**) High CT attenuation areas coincided with bilateral lower lobe pulmonary consolidation that was not amiodarone-induced lung injury, but rather bacterial pneumonia, which improved with antimicrobial drugs and the continuation of amiodarone (the author's attended case). Panel (**b**) High CT attenuation nodular (*arrow*) in the organizing pneumonia lesion that was diagnosed as amiodarone-induced lung injury (the author's attended case)

this finding is also normal in drug accumulation seen in patients taking amiodarone without pulmonary toxicity [23].

A report by Vernhet and colleagues of high-resolution CT (HRCT) patterns in symptomatic patients with amiodarone-induced lung toxicity indicated that reversible lung injury is characterized by ground-glass opacities associated with a crazy-paving pattern and/or subpleural consolidations with bronchial abnormalities [24]. HRCT in prone positions can provide important information for the diagnosis of amiodarone-induced pulmonary toxicity by differentiating it from pulmonary congestion due to left-sided heart failure by countering the effects of gravity on pulmonary vascularity [25].

Gallium scanning is a sensitive test of amiodarone-induced pneumonitis because it shows positive findings in most cases of pulmonary toxicity. However, a few studies in patients diagnosed with amiodarone-induced pulmonary toxicity have shown that the uptake of gallium in the lung, after discontinuation of amiodarone, continued to elevate despite the absence of clinical worsening, radiographic abnormalities, and bronchoalveolar lavage [26]. A positive gallium scan along with other supportive clinical evidence of inflammatory and immune response-associated pulmonary toxicity may be helpful in excluding other diagnostic entities such as interstitial edema associated with congestive heart failure. However, this is rarely performed due to its high cost, high radiation dose, and the long duration of the test (48–72 h) [3].

Pulmonary function testing is not specifically diagnostic for amiodarone-induced pulmonary toxicity because it is frequently abnormal in patients with chronic heart

disease with or without amiodarone treatment, although a reduced total lung capacity of 15% or above, or a lung diffusion capacity (DLco) of 20% or above, may suggest interstitial change in the lung caused by amiodarone [3].

Serum marker levels of KL-6, surfactant protein-D (SP-D), or SP-A are now frequently used in assessing the activity of interstitial pneumonia [11, 27]. Several studies have demonstrated that KL-6 may be a useful marker for the disease activity and severity of amiodarone-induced DLI [5, 12]. One report indicated that two patients with amiodarone-induced pulmonary toxicity showed abnormally increased serum SP-D levels, while their KL-6 level were normal [28]. The author and colleagues reviewed 15 patients with clinical amiodarone-induced pulmonary toxicity. They were divided into five patients with ARDS and ten patients with chronic alveolitis/fibrotic lung disease (FLD). In the ARDS group, DLco and serum KL-6 levels before the onset of clinical symptoms were normal, and the increase in serum KL-6 after the onset was relatively small. Whereas in the FLD group, decreased DLco and increased KL-6 levels appeared before the onset of clinical symptoms, and KL-6 increased further after the onset, reflecting the clinical disease activity. The pulmonary lesions in patients in the ARDS group were severe, but quickly improved after the initiation of glucocorticoid therapy, whereas the improvement of pneumonitis in the FLD group was relatively slow or poor, and one patient died from opportunistic infection. In amiodarone-induced pulmonary toxicity, the course of DLco and serum KL-6 levels, as well as the response to glucocorticoid therapy, may show a different pattern between the ARDS type and subacute/chronic FLD type [13].

Bronchoalveolar lavage (BAL) findings in amiodarone-induced pneumonitis are highly variable and include a normal BAL cellular profile in many patients, neutrophilia and elevated red blood cells in the early phase, eosinophilia, and lymphocytosis. In some cases, lymphocytosis in BAL is associated with an increase in lymphocytes bearing the CD8 surface marker. Foamy macrophages can often be seen in BAL, but this can also be detected in subjects taking amiodarone who have no clinical evidence of lung toxicity. Therefore, the presence of foamy macrophage is neither pathognomonic nor diagnostic of amiodarone-induced pulmonary toxicity, although the absence of foamy macrophage makes the diagnosis of amiodarone lung injury unlikely [3].

The pathologic features of amiodarone-induced pulmonary toxicity are variable. Intra-alveolar hemorrhage, type II alveolar epithelial cell proliferation, and hyaline membrane formation can be seen in acute patterns. Chronic patterns are characterized by alveolar septal thickening due to infiltration with lymphocytes, monocytes, and plasma cells. Alveolar and septal fibrosis occurs in the later stages. Transbronchial or surgical lung biopsy is often useful to identify the typical change, foamy cells, neutrophilic alveolitis, and an increased phospholipid content, in the lungs of patients taking amiodarone, similar to that of BAL. Electron microscopic examination can detect the cytoplasm of foamy macrophages containing "lamellar" inclusions filled with undigested phospholipids. These findings are normally seen in the lungs of patients taking amiodarone without lung toxicity, and thus their presence is not diagnostic of amiodarone-induced "toxicity" [3, 8].

14.2.1.4 Treatment and Prognosis of Amiodarone-Induced Lung Toxicity

Although no evidence-based strategy has been established, the treatment of amiodarone-induced lung toxicity is usually begins with discontinuation of the drug and consideration of alternative medications and procedures for arrhythmia or heart failure. An implantable cardiovascular defibrillator has recently been used as an alternative to amiodarone for preventing life-threatening ventricular arrhythmias.

Corticosteroid therapy, such as prednisone 40–60 mg/day (0.5–1.0 mg/kg), with a taper over 2–6 months, can be used for moderate-to-severe cases. Intravenous high-dose methylprednisolone 15–30 mg/kg/day for 3–7 days can be experientially used for patients with severe respiratory failure or ARDS. The use of immunosuppressing agents, but not steroids, including cyclophosphamide, azathioprine, cyclosporine A, and others, may be not recommended due to the lack of evidence and experience in patients with amiodarone-induced lung injury.

Mortality rates of amiodarone-induced lung injury have been reported to be 9–50%, and this large difference may depend on the condition of the medical service available and the disease type. The prognosis of amiodarone-induced lung toxicity is generally not poor, although patients with ARDS have a much higher mortality rate (approximately 50%) [29]. In one study three to four patients stabilized or improved after discontinuation of amiodarone with or without corticosteroid therapy [30]. In our experience, only 1 patient among 15 died from opportunistic infection [13]. The causes of death in past reports include fatal ventricular arrhythmia or worsened heart failure after discontinuation of amiodarone [4].

Recent reports have demonstrated that the mortality of 46 patients with amiodarone-induced pulmonary toxicity at 90 days was 37% and was linked to the speed of symptoms and a high HRCT alveolar score [31]. Furthermore, angiotensin system antagonist treatment was prescribed significantly more in surviving patients [30]. As mentioned previously in this chapter (Sect. 14.2.1.2), amiodarone-induced alveolar epithelial cell apoptosis in vivo is inhibited by angiotensin antagonists, and blockade of angiotensin formation or function may attenuate amiodarone-induced lung fibrosis [18]. Previous angiotensin antagonists for the treatment of heart disease may have favorable effects on the outcome of amiodarone-induced lung toxicity.

14.2.2 Other Antiarrhythmic Drugs

14.2.2.1 Bepridil

Bepridil is a class IV antiarrhythmic drug that inhibits the Na+, K+, and Ca2+ channels in cardiomyocytes and reduces the maximum depolarization rate of atrial or ventricular cardiac muscles and atrioventricular nodes. This drug is used for the treatment of ventricular arrhythmia, angina pectoris, and atrial fibrillation.

Although bepridil-induced lung injury is considered to be a relatively uncommon adverse effect of the drug, the number of case reports has gradually increased to date [32–34]. Yamasaki and colleagues evaluated the incidence of bepridil-induced pulmonary toxicity [33]. Eight of the 222 evaluable patients (3.6%) showed bepridil-induced pulmonary toxicity. Other studies have reported that the radiographic pattern on CT scans demonstrated almost bilateral reticular, ground-glass shadows and/or patchy consolidation, with a few cases of diffuse small granular infiltration or diffuse dense consolidation predominantly peribronchial in distribution [34]. Almost all patients' conditions improved or became stable after the discontinuation of bepridil with or without corticosteroid therapy.

14.2.2.2 Mexiletine

Mexiletine, which is frequently used for the treatment of ventricular arrhythmia, can cause drug-induced pulmonary toxicity; however, the incidence rate of this is rare (below 1 in 10,000). Chest imaging studies have shown the disease type in almost all patients to be chronic interstitial pneumonia or fibrosis syndrome with reticulonodular infiltrates. The prognosis is considered to be good, although several instances of death from respiratory failure have been reported [8, 35].

14.2.2.3 Tocainide and Flecainide

It has been reported that tocainide, used to treat refractory ventricular arrhythmias, caused over 100 cases of acute interstitial pneumonia 3 weeks to several months after starting the drug. After discontinuation of the drug with or without corticosteroid therapy, the prognosis is largely good [36]. It has been reported that flecainide, another antiarrhythmic drug, may cause ARDS and interstitial lymphocytic pneumonitis [35, 37].

14.2.2.4 Procainamide

Procainamide has been used to treat both supraventricular and ventricular arrhythmias. The main adverse effect of procainamide is drug-induced systemic lupus erythematosus (SLE)-like symptoms or signs. Positive titers of serum antinuclear antibodies (ANA) are found in 50–90% of patients taking procainamide, in whom 10–20% will develop symptomatic drug-induced SLE. Forty to eighty percent of symptomatic SLE patients will suffer from pulmonary manifestations [8]. Pleural effusion and pleuritic chest pain are the main pulmonary manifestation of adverse events due to procainamide. Pulmonary parenchymal infiltrates or injury is also seen in up to 40% of patients with procainamide-induced lung impairment. The discontinuation of procainamide is not needed in patients with a positive titer of ANA alone. When rheumatologic or pulmonary symptoms develop, the drug should

be discontinued promptly. After the discontinuation of the drug, symptoms are often resolved within 2–3 weeks, while adding corticosteroids administration will further speed up this improvement, sometimes to within several days [8].

14.2.2.5 Adverse Pulmonary Effects of Antiarrhythmic Drugs Other than Interstitial Lung Disease

Quinidine has been used for many decades to treat ventricular and supraventricular arrhythmias. Patients using quinidine sometimes develop positive titers of ANA and in rare cases pulmonary manifestations, mainly presented as pleuritic chest pain and pleural effusions. Drug discontinuation with or without corticosteroid therapy is usually effective to improve symptoms [8, 38].

Bronchoconstriction has been reported after acute or chronic adenosine, used in the treatment of supraventricular tachycardia, and sotalol, which is a class III antiarrhythmic that has nonselective β-adrenoreceptor blocking effects and is used against ventricular and selected supraventricular arrhythmias. β-adrenergic receptor blockers have been known to have bronchoconstricting effects. These drugs should not be used for patients with uncontrolled bronchial asthma or COPD with acute exacerbation status, although the use of β-adrenergic receptor blockers does not worsen the prognosis of COPD patients complicated with cardiovascular disease, but rather has a favorable effect [39].

14.3 DLI Induced by Antimicrobial Drugs

Although clinicians should take caution that all kinds of antimicrobial drugs may cause drug-induced lung injury, the incidence is extremely low despite the wide use of these agents. Tetracyclines [40], erythromycin derivatives, beta-lactams, and fluoroquinolones, of which several reports have been written, appear to be the causative antimicrobial drugs. Lung injury due to the antituberculosis drug, isoniazid, has been reported, as well as rifampicin and ethambutol. Additionally, sulfamethoxazole-trimethoprim combination [41], voriconazole, oseltamivir, and mefloquine have been suggested to be causative of lung injury. The pathogenesis of antimicrobial drug-induced lung injury is considered to be mainly an allergic reaction related to type III/IV or type I hypersensitivity [14]. The symptoms, including fever, nonproductive cough, and dyspnea, occur about 1–2 weeks after the start of treatment with antimicrobial drugs. Laboratory data may show an increase in blood eosinophils or IgE levels. In chest radiographic findings, diffuse ground-glass opacity, fine granulo-nodular shadow, or patchy infiltration appears, similar to that of eosinophilic pneumonia. Analysis of bronchoalveolar lavage fluid often reveals an increase in eosinophils or low levels of CD4/CD8 ratio in T-lymphocytes and may be helpful for diagnosis [14]. Drug discontinuation with or without corticosteroid therapy is usually effective, and instances of death are rare.

Antibiotics, especially aminoglycoside and polymyxin can cause neuromuscular blockade and induce alveolar hypoventilation and further acute hypercapnic respiratory failure [8, 36]. Tetracyclines, ampicillin, fluoroquinolones, and amphotericin B [42] were reported to cause this type of toxicity in very rare cases. This toxicity is related to special conditions, such as renal insufficiency and concomitant use of other neuromuscular blocking agents. This phenomenon is caused by a decrease in acetylcholine release at the presynaptic site at respiratory muscles and blocking the effect of acetylcholine at the postsynaptic receptor itself [43]. Treatment consists of mainly respiratory support including mechanical ventilation as needed and cholinesterase inhibitors such as neostigmine and pyridostigmine [8, 36].

14.4 Conclusion

Drug-induced lung injury by antiarrhythmic drugs, especially amiodarone, and antimicrobial drugs shows significant diversity in its pathogenesis and clinical features, resulting in diagnostic and therapeutic problems. We have found no definitive diagnostic laboratory, radiological, or pathological examinations. Similar to lung injury induced by other kinds of drugs, diagnosis should be made using the following criteria: (1) a new pulmonary lesion is detected during the drug administration; (2) other causes, including pulmonary infection, malignant diseases (e.g., carcinomatous lymphangitis), and pulmonary congestion due to heart failure, are ruled out; and (3) improvement of the clinical manifestation after drug discontinuation. The above condition (2) is very important for these drugs, for which alternative drugs cannot be used and interruption of usage may lead to adverse outcomes in patients. Indeed, a major cause of death is fatal ventricular arrhythmia or worsened heart failure after discontinuation of amiodarone. As is known for amiodarone, drugs and their toxicity can be accumulated in lung tissue and cells over long period of use. Therefore, antiarrhythmic drug-induced lung injury may occur long after the start of drug use and can continue even after discontinuation of drug use. Several months of corticosteroid therapy and long-term follow-up are needed in these patients.

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