Drug-Induced Lung Disease

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24.1 Overview

Drug-induced lung disease, also known as drug-induced lung damage, is the lung damage caused by drugs and their metabolites through direct cytotoxicity or allergic immune reactions, as a part of systemic adverse reactions caused by drugs. Previous studies have reported that lung damage accounts for 6–7% of adverse drug reactions [1]. More than 350 kinds of drugs can cause lung damage. Drugs with lung toxicity include chemotherapy drugs, antibiotics, cardiovascular drugs, nonsteroidal anti-inflammatory drugs, etc. Drug-induced lung damage caused by cytotoxic chemotherapy drugs is the most common. In recent years, drug-induced lung damage has been increasing year by year with the emergence of biological agents, new anti-tumor targeted drugs, and programmed death protein 1 (PD-1) immunotherapy.

Drug-induced lung damage has various clinical manifestations. It can be temporary and reversible. The damage can be recovered after drug withdrawal or become a permanent damage. Drug-induced lung damage has acute, subacute, or chronic course. Typical allergic and noncardiogenic pulmonary edema may occur within minutes or hours after administration, while alveolar injury, pulmonary hemorrhage, and organizing pneumonia often have subacute course, which occur within several days to several weeks after treatment. Chronic damage is manifested as interstitial pneumonia, which often occurs within months or years after administration. The most common clinical manifestations include cough, progressive dyspnea, and fever, with the severity ranging from asymptomatic or mild cough to respiratory failure and even death. Because of the lack of specificity of clinical symptoms, the disease is often missed or misdiagnosed.

Drug-induced lung damage can be involved from bronchi, alveoli, and interstitium to pleura, as well as mediastinum and pulmonary vessels. Interstitial pneumonia is the most common type of drug-induced lung damage, including diffuse alveolar damage, nonspecific interstitial pneumonia, organizing pneumonia, hypersensitivity pneumonitis, bronchiolitis obliterans, and so on. Anti-tumor drugs, cytotoxic drugs, cardiovascular drugs, and antibiotics are all common drugs that lead to interstitial pneumonia. The possible main pathogenesis is that drugs directly damage alveolar cells or drugs lead to immune dysregulation and immune-mediated lung injury. Drug-induced airway damage includes laryngeal edema, bronchospasm, cough, etc., and chest imaging may not be abnormal. Common drugs: antibiotics such as penicillins, cephalosporins or sulfonamides, biological products, cardiovascular drugs, and nonsteroidal anti-inflammatory drugs. Diffuse alveolar hemorrhage is rare. Besides anticoagulants and thrombolytic drugs, other drugs that cause damage to alveolar epithelial cells or capillary endothelial cells, such as amiodarone and cocaine, can also cause the above symptoms.

In addition to traditional cytotoxic drugs, lung damage caused by new anti-tumor targeted drugs has attracted more and more clinical attention. The lung damage caused by targeted drugs is mainly interstitial pneumonia, but with diverse and complex manifestations, including pulmonary infection, pulmonary hemorrhage, pulmonary embolism, pulmonary fibrosis, and so on [2]. The lung damage caused by common drugs is shown in Table 24.1.

Immune checkpoint blockade therapy is a high-profile tumor treatment method. Different from other previous treatment methods, immune checkpoint inhibitors target the immune system rather than tumor cells, aiming at restoring and promoting the function of effector T cells to specifically recognize and kill tumor cells, and systematically enhancing the whole body's anti-tumor immune response, which represents the transformation of current tumor treatment mode. At present, the known immune checkpoints include programmed death protein-1 (PD-1), cytotoxic T lymphocyte antigen-4 (CTLA-4), lymphocyte activation gene 3 (LAG3),

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H. Li et al. (eds.), *Radiology of Infectious and Inflammatory Diseases - Volume 3*,
https://doi.org/10.1007/978-981-99-4614-3_24

Table 24.1 Lung damage caused by common drugs

Drugs	Common pathological and imaging types
Methotrexate	Nonspecific interstitial pneumonia, hypersensitivity pneumonitis
Amiodarone	Diffuse alveolar damage, nonspecific interstitial pneumonia, organizing pneumonia, and hyperdensities (iodine) in lung lesions
Nitrofurantoin	Nonspecific interstitial pneumonia, organizing pneumonia
Sulfasalazine	Eosinophilic pneumonia, organizing pneumonia, hypersensitivity pneumonitis
Bleomycin	Diffuse alveolar damage, organizing pneumonia, nonspecific interstitial pneumonia
Busulfan	Nonspecific interstitial pneumonia, diffuse alveolar damage
Cyclophosphamide	Diffuse alveolar injury, nonspecific interstitial pneumonia
Cocaine	Pulmonary edema, pulmonary hemorrhage, organizing pneumonia
Gefitinib	Interstitial pneumonia, diffuse alveolar damage, alveolar hemorrhage, pulmonary fibrosis
TNF inhibitor	Interstitial pneumonia
PD-1 antibody	Organizing pneumonia, nonspecific interstitial pneumonia, hypersensitivity pneumonitis, pulmonary sarcoidosis-like changes

etc. The side effect caused by blockade of CTLA-4 antibody and PD-1/PD-L1 antibodies is called immune-related adverse event (irAE) [3], which involves multiple organs or systems, including skin, gastrointestinal tract, liver, endocrine system, lung, etc. The incidence of immune checkpoint inhibitor-associated pneumonia is not high, but it may be life-threatening. The most common pathological type is organizing pneumonia, followed by NSIP, hypersensitivity pneumonitis, etc. Some severe patients may also have diffuse alveolar damage.

In addition to some typical manifestations of pneumonia, pulmonary sarcoidosis-like changes may also occur, including subpleural nodules and hilar lymphadenectasis [4].

In recent years, biological agents for treating autoimmune diseases have been widely used in clinical practice. If using biological agents, tuberculosis should be paid attention to especially tumor necrosis factor (TNF) inhibitors. The most common noninfectious lung lesions when using TNF inhibitors are interstitial pneumonia, acute exacerbation of original interstitial lung diseases, and sarcomatoid lesions. The most common ILD types of interstitial pneumonia are UIP, NSIP, and organizing pneumonia. The main clinical manifestations are dyspnea and cough [5].

Drug-induced lung damage requires exclusion diagnosis, which is generally determined by the relationship between medication and the onset and improvement of lung damage. However, due to the great differences between different individuals and drugs in the onset time, dosage, and clinical manifestations of lung damage, clinical diagnosis is difficult. Clinical diagnosis of drug-induced lung damage should meet the following criteria [6]:

1. Patients should have a history of taking drugs known to cause drug-induced lung damage.
2. The clinical manifestations are consistent with those reported in the literature.
3. Other causes that can lead to the same clinical manifestations have been excluded.
4. Clinical manifestations are improved after drug withdrawal.
5. The clinical manifestations deteriorate after taking the medicine again.

Cell classification of bronchoalveolar lavage fluid (BALF) is helpful to analyze the types of drug-induced lung damage [6]. If lymphocytes > 15%, it indicates the possibility of NSIP, organizing pneumonia, hypersensitivity pneumonitis, bronchiolitis obliterans, or lymphocytic interstitial pneumonia.

If neutrophils > 50%, it indicates diffuse alveolar damage.

If eosinophils > 25%, it indicates eosinophilic pneumonia.

24.2 Pathological Manifestations

The histopathological changes of drug-induced lung damage are nonspecific, similar to those of various acute and chronic lung diseases, and can be manifested as various histological types (Table 24.2): diffuse alveolar damage, diffuse alveolar hemorrhage, nonspecific interstitial pneumonia, hypersensitivity pneumonitis, organizing pneumonia (bronchiolitis obliterans accompanied by organizing pneumonia), and eosinophilic pneumonia.

Diffuse alveolar damage can undergo the early acute exudation stage and the chronic rehabilitation stage. The acute exudation stage is mainly characterized by alveolar and interstitial edema, while the chronic rehabilitation stage is characterized by type II alveolar cell proliferation and interstitial fibrosis. Some severe cases may progress to end-stage honeycomb lung. The histological features of nonspecific

Table 24.2 Common drugs causing different histopathological types of drug-induced lung damage

Histopathological type	Common drugs
Diffuse alveolar damage	Busulfan, cyclophosphamide, carmustine (BCNU), bleomycin, paclitaxel, docetaxel, amiodarone, aspirin, anesthetics, low-dose methotrexate or cocaine, colchicine, sulfasalazine
Diffuse alveolar hemorrhage	Anticoagulants, amphotericin, amiodarone, cyclophosphamide, gefitinib, carbamazepine, methotrexate, mitomycin, nitrofurantoin, penicillamine, phenytoin sodium, propylthiouracil
Hypersensitivity pneumonitis	Methotrexate, cyclophosphamide, mesalazine, fluoxetine, amitriptyline, paclitaxel, and docetaxel
Organizing pneumonia	Bleomycin, cyclophosphamide, methotrexate, amiodarone, acetabinolol, minocycline, nitrofurantoin, gold potassium cyanide, penicillamine, phenytoin, carbamazepine, hydralazine, interferon, mesalazine
Eosinophilic Pneumonia	Amiodarone, bleomycin, nitrofurantoin, phenytoin sodium, β-receptor blocker, nonsteroidal anti-inflammatory drugs, antidepressants, hydrochlorothiazide, minocycline, sulfonamides, sulfasalazine, mesalazine
Nonspecific interstitial Pneumonia	Bleomycin, busulfan, BCNU, methotrexate and other cytotoxic drugs, amiodarone, sulfasalazine, hydrochlorothiazide, cyclophosphamide, phenytoin sodium
Pulmonary edema	Amphotericin, cocaine, hydrochlorothiazide, naloxone, high-dose aspirin, amlodipine, and others

interstitial pneumonia are different degrees of interstitial inflammation and fibrosis, which can be divided into cellular NSIP, fibrous NSIP, or both according to different components. Obliterative bronchiolitis accompanied by organizing pneumonia is histologically manifested as patchy organizing pneumonia involving alveolar ducts and alveoli, with or without organizing obliteration of fibroblast granuloma in bronchioles. The histopathological manifestations of eosinophilic pneumonia include the infiltration of inflammatory cells such as eosinophils, lymphocytes, and plasma cells in alveolar space or pulmonary interstitium. The pathological features of hypersensitivity pneumonitis are cellular bronchiolitis, non-caseous granuloma, and bronchial central interstitial pneumonia mostly with lymphocyte infiltration.

24.3 Imaging Manifestations

The imaging manifestations of drug-induced lung damage are various, similar to those of other interstitial or parenchymal lung diseases, depending on the histopathological types of lung damage. CT is the best noninvasive examination to evaluate drug-induced lung damage at present, which can usually reflect its histopathological types, and some cases may have more than one histopathological type.

1. Diffuse alveolar damage.
   (a) X-ray: The density of both lungs may be uniform or uneven, mainly distributed in the middle and lower lungs, and the lesions often progress to diffuse opacities in both lungs.
   (b) CT: Patchy or fused ground-glass opacities of both lungs, which may be accompanied by thickened interlobular septa and show "paving stone" sign. It can also be accompanied by patchy consolidation. In the chronic organizing stage, structural distortion and traction bronchiectasis can be found, showing reticular opacities and honeycomb changes (Fig. 24.1).
2. Diffuse alveolar hemorrhage.
   (a) X-ray: Patchy uneven hyperdensities of both lungs with or without consolidation.
   (b) CT: Extensive patchy ground-glass opacities in both lungs. 2–3 days after acute onset of pulmonary hemorrhage, the ground-glass opacities decrease and centrilobular nodules with blurred edges occur. Thickened interlobular septa are rare.
3. Hypersensitivity Pneumonitis.
   (a) X-ray: Ground-glass opacities of both lungs, sometimes accompanied by small nodules with blurred edges.
   (b) CT: Diffuse ground-glass opacities or centrilobular nodules with blurred edges in acute stage; irregular stripe-like and reticular opacities in both lungs in the chronic stage (Fig. 24.2).
4. Organizing Pneumonia.
   (a) X-ray: Bilateral or unilateral pulmonary patchy consolidation, mainly distributed in subpleural area and outer zone of lung field.
   (b) CT: Patchy consolidation distributed under pleura or around bronchi, often asymmetrically distributed. Consolidation around lobules is also common, and centrilobular nodules are rare (Fig. 24.3).
5. Eosinophilic pneumonia.
   (a) X-ray: Consolidation distributed in the nonsegmental area of both lungs, mainly in upper lungs and periphery.
   (b) CT: Consolidation and ground-glass opacities distributed in the periphery of both lungs, mainly distributed in the middle and upper lung fields and peripheral areas.
6. Nonspecific interstitial pneumonia.
   (a) X-ray: Uneven patchy opacities in both lungs, mainly in the middle and lower lung fields and subpleural area.

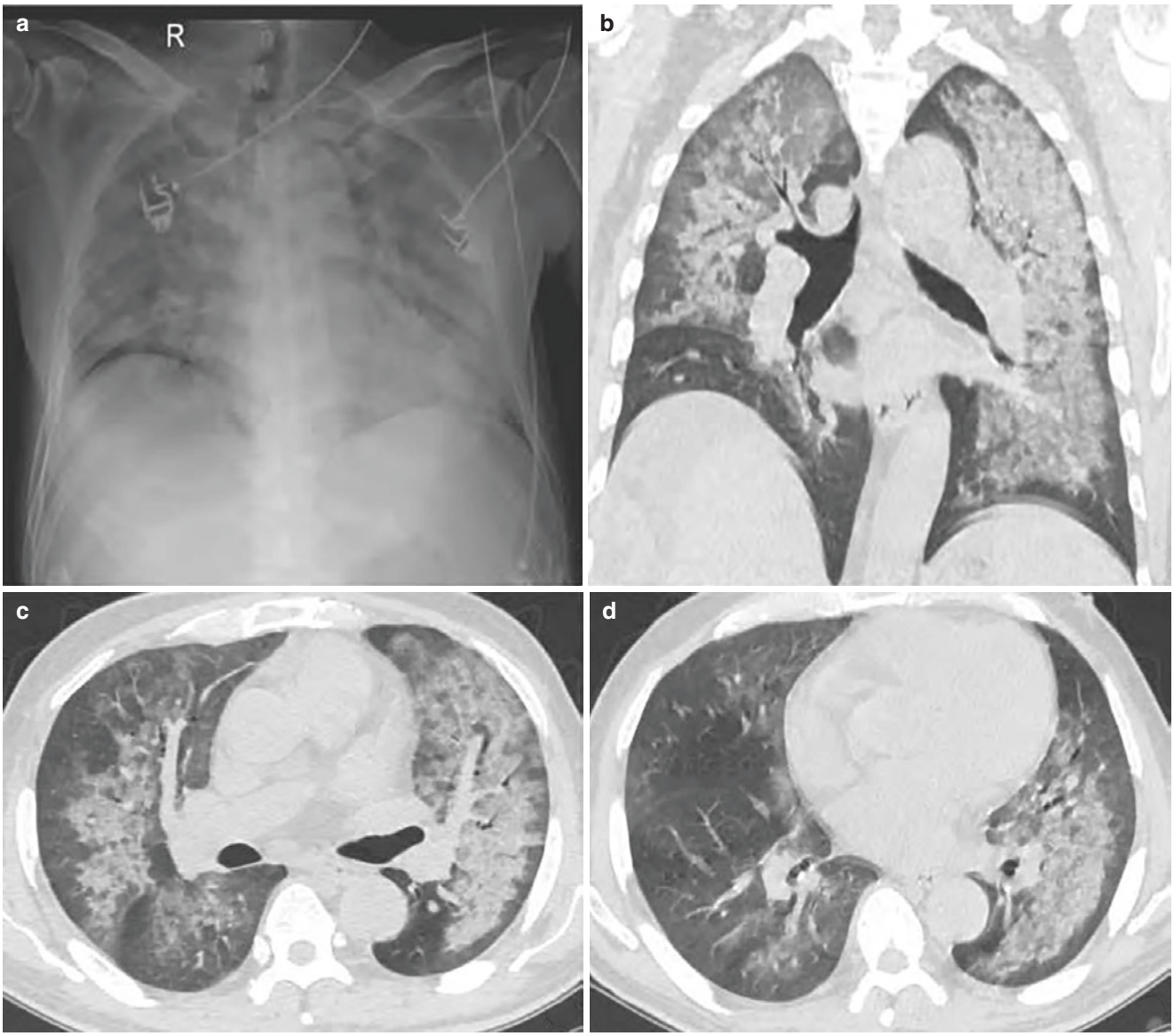

Fig. 24.1 Diffuse alveolar damage caused by bleomycin. (**a–d**) CT showed diffuse patchy ground-glass opacities in both lungs and thickened interlobular septa, manifested as "paving stone" sign

(b) CT: Symmetrical ground-glass opacities in both lungs, sometimes accompanied by reticular opacities, mainly distributed in the middle and lower lung fields and subpleural area (Figs. 24.4 and 24.5). In the advanced stage, traction bronchiectasis and lung consolidation can be found. Honeycomb changes are rare.

7. Pulmonary edema.
   (a) X-ray: Cardiogenic pulmonary edema is manifested as thickened vascular markings in both lungs, thickened interlobular septa, pleural effusion, and enlarged cardiac shadow. In severe cases, consolidation or ground-glass opacities can be found in both lungs. Noncardiogenic pulmonary edema caused by increased pulmonary capillary permeability is often manifested as patchy ground-glass opacities or consolidation of both lungs, which is distributed around the hilum, but there is no interlobular septal thickening, pleural effusion, and cardiac shadow enlargement.
   (b) CT: Multiple ground-glass opacities or fused ground-glass opacities in both lungs, which may be accompanied by smooth interlobular septa and thickened intralobular septa, showing the "paving stone" sign.

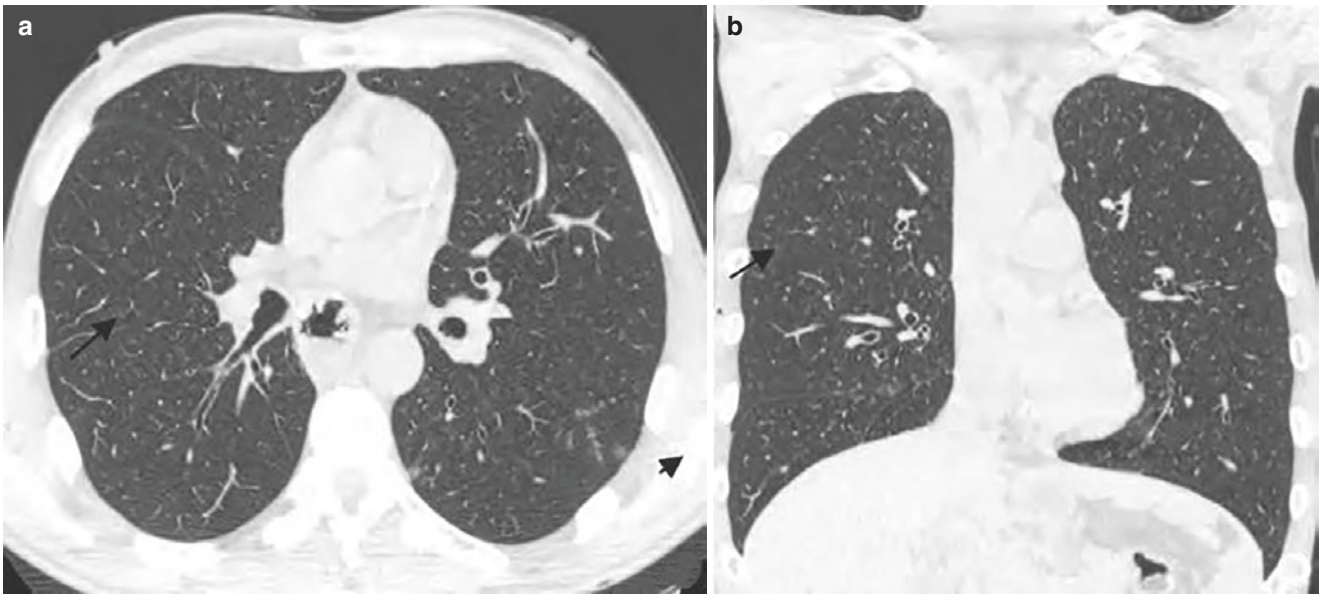

Fig. 24.2 Hypersensitivity pneumonitis caused by methotrexate. (**a** and **b**) CT lung window shows scattered centrilobular nodules with blurred edges (long arrow) and a few small patchy ground-glass opacities (short arrow) in both lungs

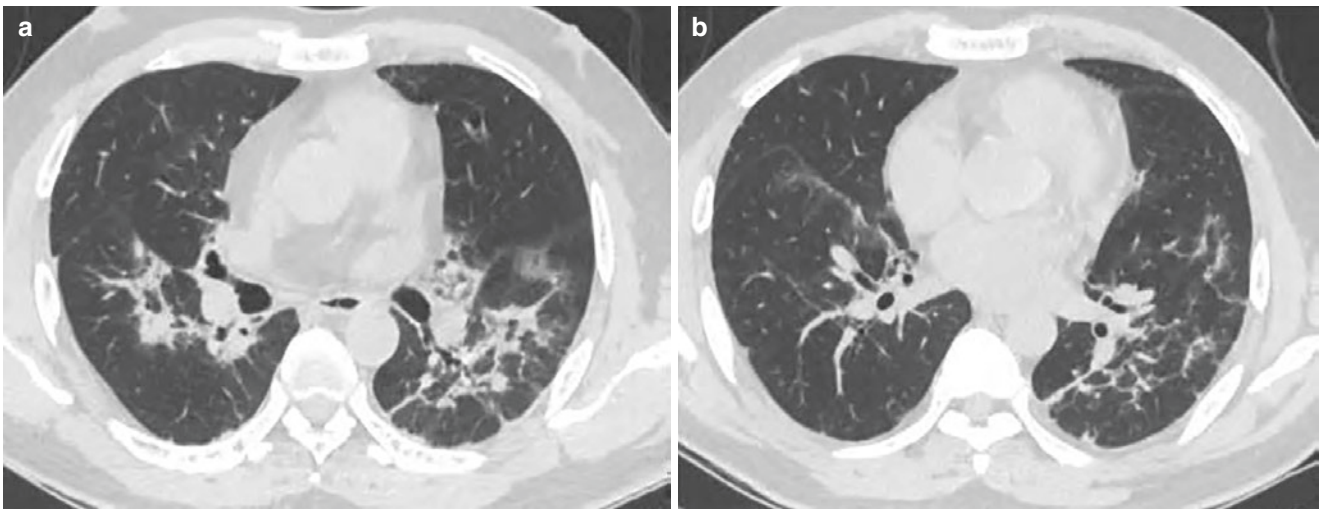

Fig. 24.3 Organizing pneumonia caused by bleomycin. (**a** and **b**) CT lung window showed multiple asymmetric patchy lung consolidations around bronchi and subpleural

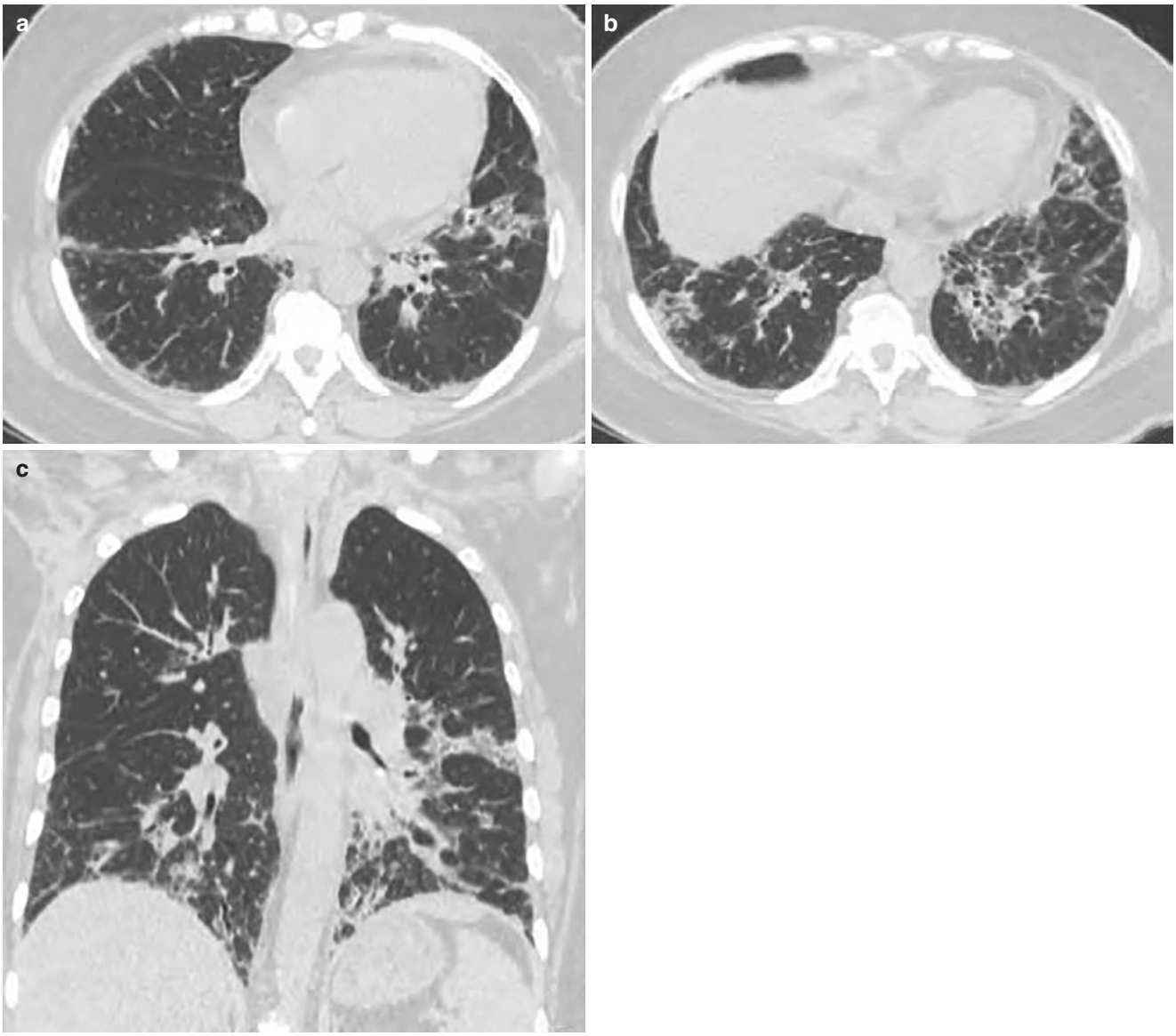

Fig. 24.4 Nonspecific interstitial pneumonia caused by nitrofurantoin. (**a–c**) CT lung window showed multiple thickened interlobular septa and reticular opacities, accompanied by patchy ground-glass opacities under the pleura of both lower lobes of the lungs

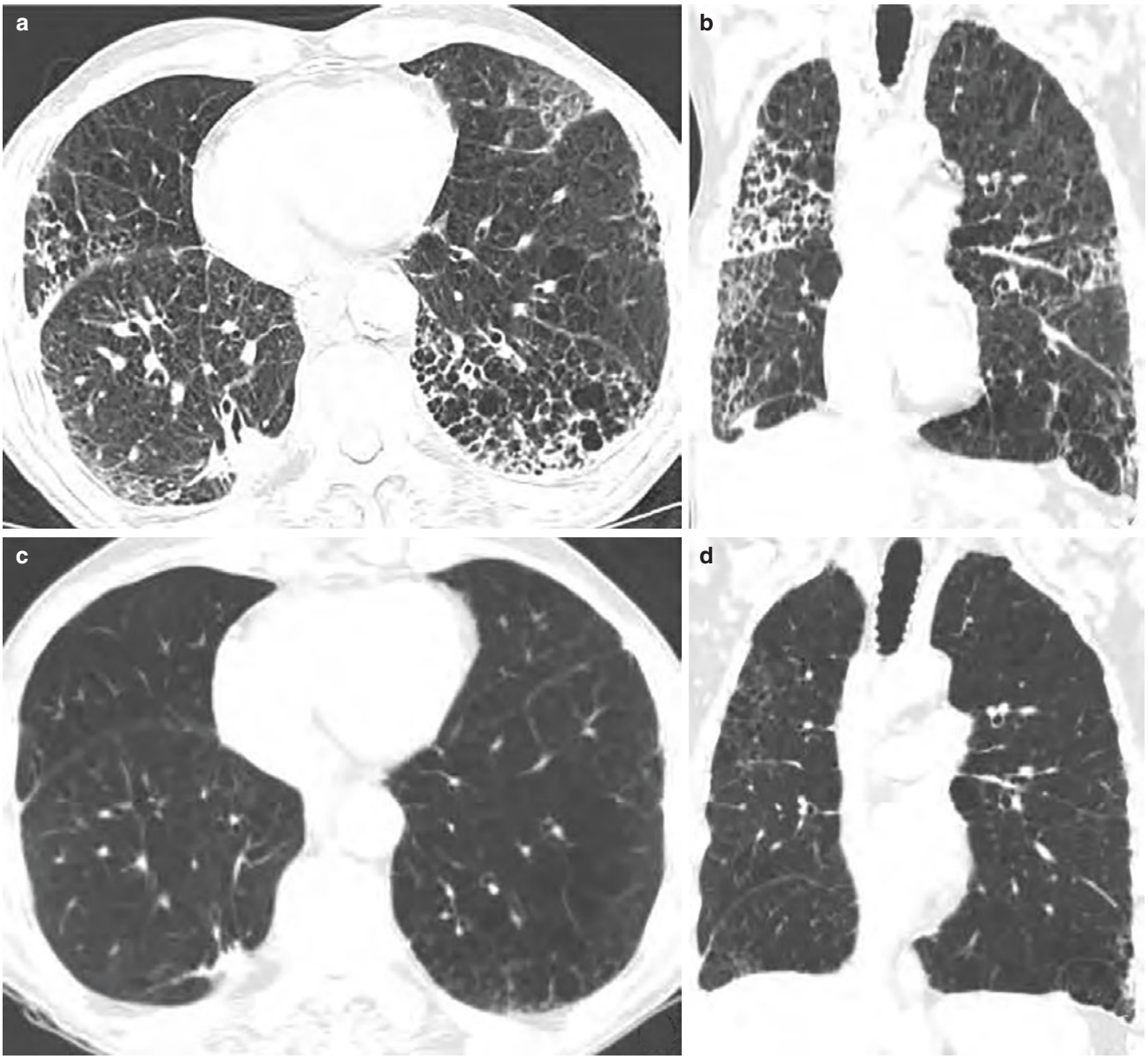

Fig. 24.5 Nonspecific interstitial pneumonia caused by PD-1 inhibitor (Sintilimab). (**a** and **b**) CT lung window showed thickened subpleural interlobular septa, accompanied by a small amount of patchy ground-glass opacities; and (**c** and **d**) 2 weeks after hormone therapy, reexamination showed most of the lesions absorbed and improved

24.4 Diagnostic Key Points

1. Patients have a history of taking drugs known to cause drug-induced lung damage.
2. Common pathological and imaging types include nonspecific interstitial pneumonia, diffuse alveolar damage, organizing pneumonia, eosinophilic pneumonia, hypersensitivity pneumonitis, alveolar hemorrhage, and pulmonary edema.
3. Other causes that can lead to the same clinical manifestations have been ruled out.
4. The clinical manifestations can be improved after drug withdrawal and deteriorated after taking the drug again.

24.5 Differential Diagnosis

1. Pulmonary infection: The main manifestation of drug-induced lung damage is interstitial pneumonia, and the pathological and imaging changes are nonspecific, so it is necessary to exclude lung infection, such as mycoplasma pneumonia, Pneumocystis jirovecii pneumonia, and viral

pneumonia, which are usually manifested as interstitial pneumonia. Analysis in combination with clinical characteristics, laboratory examination, or cell classification of bronchoalveolar lavage fluid is helpful for differential diagnosis.
2. Progress of primary disease: Lung lesions of patients treated with tumor drugs need to be differentiated from primary disease, especially for patients with lung tumors.
3. Eosinophilic pneumonia: Drug reaction is a common cause of eosinophilic pneumonia, which needs to be distinguished from other causes of eosinophilia clinically, such as parasitic infection, fungal infection, and immune or systemic diseases.

24.6 Research Status and Progress

Some studies have reported the diagnostic value of ^{18}F-FDG PET/CT in lung damage induced by lymphoma chemotherapy. CT can show diffuse ground-glass changes, patchy consolidation, subpleural reticular opacities, and slightly increased FDG uptake in both lungs [7].

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