

# Pulmonary Drug Toxicity: Radiologic and Pathologic Manifestations<sup>1</sup>

## CME FEATURE

See accompanying test at [http://www.rsna.org/education/rg\\_cme.html](http://www.rsna.org/education/rg_cme.html)

## LEARNING OBJECTIVES FOR TEST 2

After reading this article and taking the test, the reader will be able to:

- Identify the most common histopathologic processes underlying pulmonary drug toxicity.
- List the drugs that most commonly cause pulmonary drug toxicity.
- Describe the clinical and radiologic manifestations of the most common forms of pulmonary drug toxicity.

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Pulmonary drug toxicity is increasingly being diagnosed as a cause of acute and chronic lung disease. Numerous agents including cytotoxic and noncytotoxic drugs have the potential to cause pulmonary toxicity. The clinical and radiologic manifestations of these drugs generally reflect the underlying histopathologic processes and include diffuse alveolar damage (DAD), nonspecific interstitial pneumonia (NSIP), bronchiolitis obliterans organizing pneumonia (BOOP), eosinophilic pneumonia, obliterative bronchiolitis, pulmonary hemorrhage, edema, hypertension, or veno-occlusive disease. DAD is a common manifestation of pulmonary drug toxicity and is frequently caused by cytotoxic drugs, especially cyclophosphamide, bleomycin, and carmustine. It manifests radiographically as bilateral hetero- or homogeneous opacities usually in the mid and lower lungs and on high-resolution computed tomographic (CT) scans as scattered or diffuse areas of ground-glass opacity. NSIP occurs most commonly as a manifestation of carmustine toxicity or of toxicity from noncytotoxic drugs such as amiodarone. At radiography, it appears as diffuse areas of heterogeneous opacity, whereas early CT scans show diffuse ground-glass opacity and late CT scans show fibrosis in a basal distribution. BOOP, which is commonly caused by bleomycin and cyclophosphamide (as well as gold salts and methotrexate), appears on radiographs as hetero- and homogeneous peripheral opacities in both upper and lower lobes and on CT scans as poorly defined nodular consolidation, centrilobular nodules, and bronchial dilatation. Knowledge of these manifestations and of the drugs most frequently involved can facilitate diagnosis and institution of appropriate treatment.

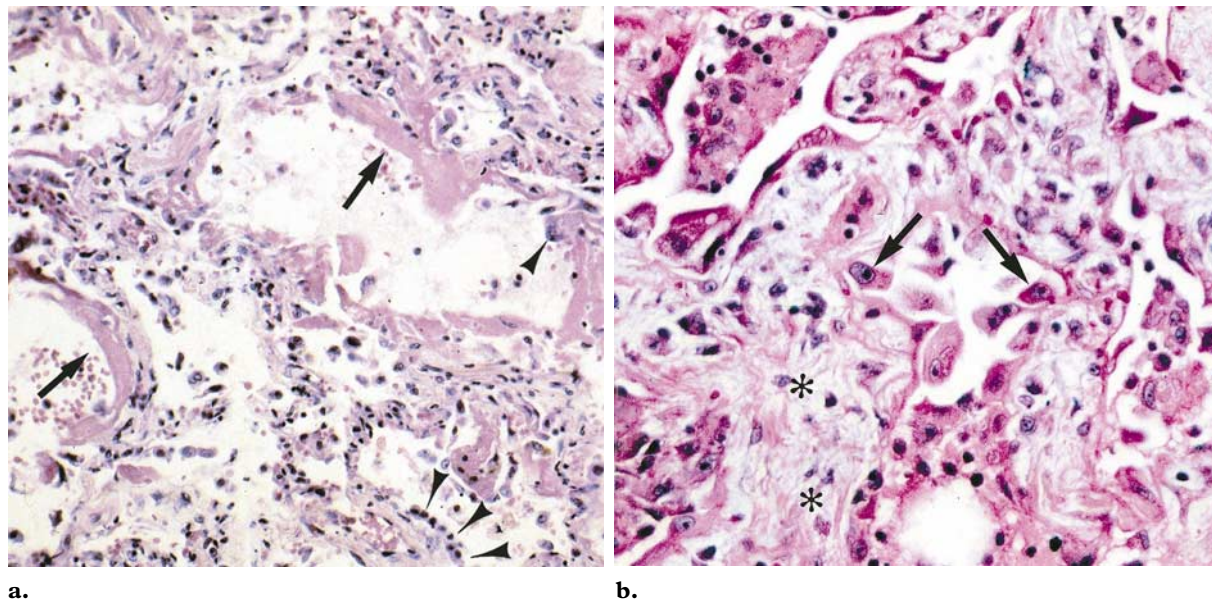
**Abbreviations:** BOOP = bronchiolitis obliterans organizing pneumonia, DAD = diffuse alveolar damage, NSIP = nonspecific interstitial pneumonia

**Index terms:** Drugs, toxicity, 60.64 • Lung, effects of drugs on, 60.64 • Lung, diseases, 60.21, 60.64 • Lung, hemorrhage, 60.4123

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**Figure 1.** DAD. (a) Photomicrograph (original magnification,  $\times 100$ ; hematoxylin-eosin stain) shows early exudative phase DAD characterized by prominent hyaline membranes (arrows), alveolar septal thickening, and hyperplastic change of type II pneumocytes (arrowheads). (b) Photomicrograph (original magnification,  $\times 200$ ; hematoxylin-eosin stain) shows late proliferative phase DAD characterized by interstitial and alveolar duct fibrosis (\*) and prominent reactive change in hyperplastic type II pneumocytes (arrows).



Principal Histopathologic Manifestations of Pulmonary Drug Toxicity	
Mechanism of Injury	Drugs
DAD	Bleomycin, busulfan, carmustine, cyclophosphamide, mitomycin, melphalan, gold salts
NSIP	Amiodarone, methotrexate, carmustine, chlorambucil
BOOP	Bleomycin, gold salts, methotrexate, amiodarone, nitrofurantoin, penicillamine, sulfasalazine, cyclophosphamide
Eosinophilic pneumonia	Penicillamine, sulfasalazine, nitrofurantoin, nonsteroidal anti-inflammatory drugs, para-aminosalicylic acid
Pulmonary hemorrhage	Anticoagulants, amphotericin B, cytarabine (ara-C), penicillamine, cyclophosphamide

## Introduction

Pulmonary drug toxicity is a common and possibly underdiagnosed cause of acute and chronic lung disease (1). There are numerous agents with potential toxic effects on the lungs. These agents include cytotoxic drugs such as bleomycin, methotrexate, and cyclophosphamide and noncytotoxic drugs such as nitrofurantoin, sulfasalazine, and amiodarone.

The histopathologic manifestations of pulmonary drug toxicity are protean but often stereo-

typical. These reactions include diffuse alveolar damage (DAD), nonspecific interstitial pneumonia (NSIP), bronchiolitis obliterans organizing pneumonia (BOOP), eosinophilic pneumonia, obliterative bronchiolitis, pulmonary hemorrhage, edema, hypertension, or veno-occlusive disease (Table). The clinical and radiologic manifestations of pulmonary drug toxicity generally reflect the underlying histopathologic processes. In this article, we review the most common histopathologic and radiologic manifestations of pulmonary drug toxicity and the agents that typically cause these abnormalities.

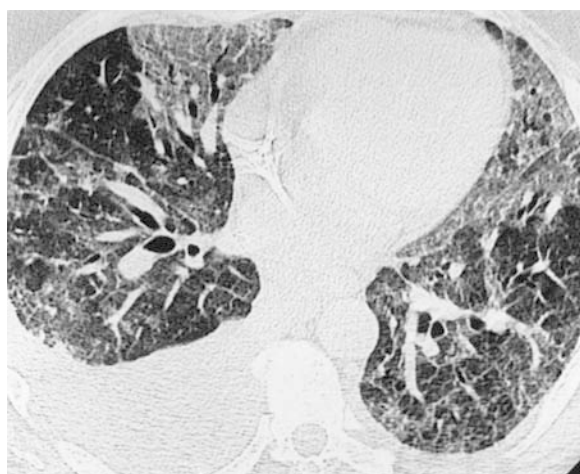
**Figures 2, 3.** (2) Cyclophosphamide-induced DAD in a 74-year-old woman with breast cancer, progressive dyspnea, and decreased  $D_LCO$ . Anteroposterior chest radiograph shows bilateral heterogeneous and homogeneous opacities typical for DAD. Diagnosis was confirmed with transbronchial biopsy. (3) Daunorubicin-induced DAD in a 43-year-old man with osteosarcoma, fever, dyspnea, and decreased  $D_LCO$ . High-resolution CT scan shows diffuse thickening of interlobular septa and scattered areas of ground-glass opacity, findings typical of early DAD. No organisms were cultured from transbronchial lavage specimens, and biopsy revealed findings consistent with DAD.



2.



3.



**Figure 4.** Bleomycin-induced DAD in a 39-year-old man with a germ cell malignancy, nonproductive cough, and dyspnea. High-resolution CT scan shows scattered areas of ground-glass opacity and thickening of interlobular septa. Architectural distortion and traction bronchiectasis suggest fibrosis due to late-stage DAD. Note right pleural effusion. Transbronchial biopsy revealed findings consistent with late proliferative phase DAD.

## Histopathologic and Radiologic Findings

### Diffuse Alveolar Damage

DAD is a common manifestation of drug-induced lung injury that results from necrosis of type II pneumocytes and alveolar endothelial cells (2).

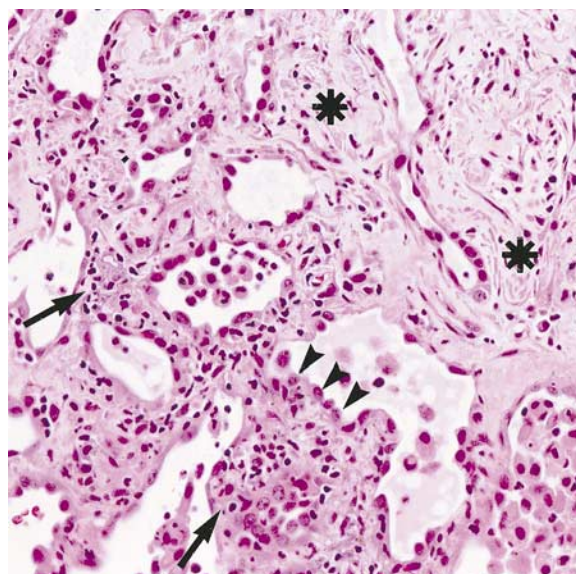
Histopathologically, DAD is divided into an acute exudative phase and a late reparative or proliferative phase (3,4). The exudative phase, which is characterized by alveolar and interstitial edema and hyaline membranes, is most prominent in the 1st week after lung injury (2–4) (Fig 1a). The reparative phase, which is characterized by proliferation of type II pneumocytes and interstitial fibrosis, typically occurs after 1 or 2 weeks (2–5) (Fig 1b). Depending on the severity of the injury, fibrosis can improve significantly, remain stable, or progress to honeycomb lung (2). Drugs that most commonly cause DAD are bleomycin, busulfan, carmustine (BCNU), cyclophosphamide, melphalan, mitomycin, and gold salts (2,4).

Affected patients present with dyspnea, cough, and occasionally fever. Diffusing capacity for carbon monoxide ( $D_LCO$ ) is characteristically decreased.

Chest radiographs show bilateral heterogeneous or homogeneous opacities, often in a mid and lower lung distribution (Fig 2). Progression to diffuse opacification is common. High-resolution computed tomography (CT) in early DAD typically shows scattered or diffuse areas of ground-glass opacity (Fig 3). Fibrosis typically develops within 1 week but initially may not be evident on chest radiographs (Fig 4). With progressive fibrosis, however, marked architectural distortion and honeycomb lung can occur (2).



**Figure 5.** NSIP. Photomicrograph (original magnification,  $\times 100$ ; hematoxylin-eosin stain) shows patchy expansion of the interstitium by mononuclear inflammatory cells (arrows), mild interstitial fibrosis (\*), and reactive hyperplastic type II pneumocytes (arrowheads).



### Nonspecific Interstitial Pneumonia

Although all forms of interstitial pneumonia have been reported as manifestations of pulmonary drug toxicity, the most commonly encountered form does not fulfill the diagnostic criteria for usual interstitial pneumonia or desquamative interstitial pneumonia and is called nonspecific interstitial pneumonia (NSIP) or chronic interstitial pneumonia. NSIP and chronic interstitial pneumonia are histologically indistinguishable, and, although the terms are often used interchangeably, some authors reserve the use of NSIP for inflammation and fibrosis that is idiopathic or associated with connective tissue diseases (2).

NSIP is characterized by areas of scattered expansion of the interstitium by mononuclear inflammatory cells, mild interstitial fibrosis, and re-

active hyperplastic type II pneumocytes (4) (Fig 5). Interstitial inflammation is typically more homogeneous and more cellular than that seen in cases of usual interstitial pneumonia. NSIP occurs most commonly as a manifestation of amiodarone, methotrexate, or carmustine toxicity (2–8). Gold salts and chlorambucil toxicity are less common causes of NSIP (2).

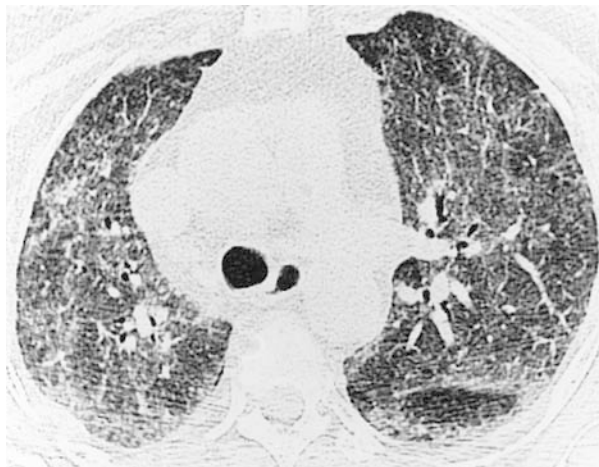
Affected patients present with insidious onset dyspnea and nonproductive cough, usually within several months of initiating therapy. Low-grade fever and malaise are common constitutional complaints (9). Levels of  $D_LCO$  are characteristically decreased. Chest radiographs usually show diffuse heterogeneous opacities (2,8,9). Early high-resolution CT scans may show only scattered or diffuse areas of ground-glass opacity (8,10) (Fig 6). Later, findings of fibrosis (traction bronchiectasis, honeycombing) predominate in a basal distribution (Fig 7).



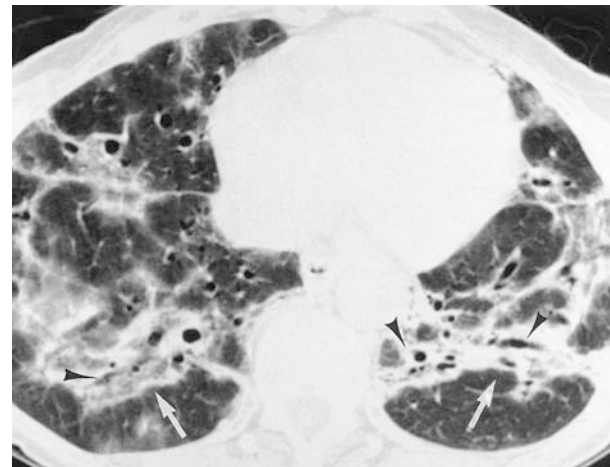
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7a.



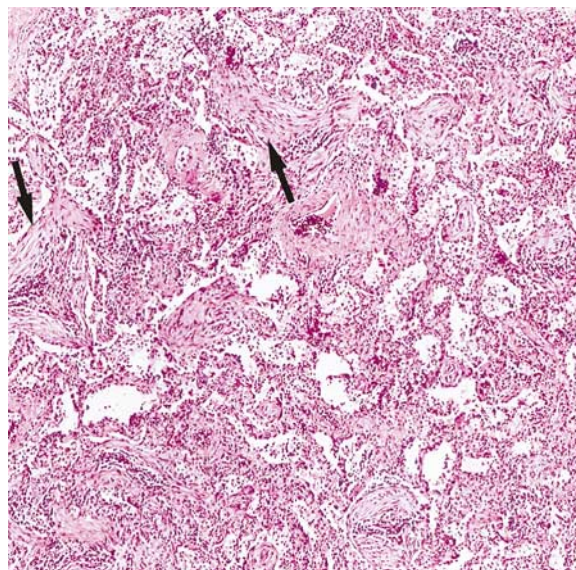
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7b.

**Figures 6, 7.** (6) Vincristine and adriamycin-induced NSIP in a 68-year-old woman with myeloma, dyspnea, and fever. (a) Posteroanterior chest radiograph shows bilateral heterogeneous opacities in a lower lung distribution. (b) High-resolution CT scan reveals scattered areas of ground-glass opacity and thickening of interlobular septa. Note minimal architectural distortion. Transbronchial biopsy of the right lower lobe revealed mild, immature fibrosis and mononuclear interstitial infiltrate, findings consistent with NSIP. (7) Nitrofurantoin-induced NSIP in a 77-year-old woman with chronic urinary tract infection, progressive dyspnea, and cough. (a) Posteroanterior chest radiograph shows bilateral coarse linear opacities in a lower lung distribution. (b) CT scan shows basal areas of conglomerate fibrosis (arrows) and traction bronchiectasis (arrowheads). Transbronchial biopsy showed findings of NSIP, and chest radiography performed 1 month later after discontinuation of nitrofurantoin therapy showed radiologic improvement.

**Figure 8.** BOOP. Photomicrograph (original magnification,  $\times 40$ ; hematoxylin-eosin stain) shows patchy interstitial inflammation and occlusion of terminal bronchioles and alveolar ducts with plugs of loose edematous connective tissue (arrows).



### **Bronchiolitis Obliterans Organizing Pneumonia**

BOOP is a nonspecific histopathologic pattern of lung injury that can be a manifestation of pulmonary drug toxicity. BOOP is characterized by the proliferation of immature fibroblastic plugs (Masson bodies) within the respiratory bronchioles, alveolar ducts, and adjacent alveolar spaces (2,10) (Fig 8). Bleomycin, gold salts, cyclophosphamide, and methotrexate are the most common drugs that cause this form of lung injury (2,4,11). Amiodarone, nitrofurantoin, penicillamine, and sulfasalazine are less common causes of drug-induced BOOP (11).

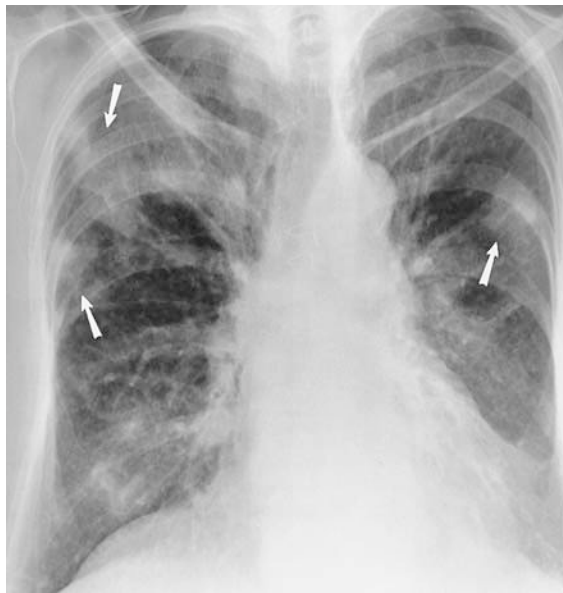
Affected patients present with progressive dyspnea, dry cough, and fever. Chest radiographs demonstrate bilateral scattered heterogeneous and homogeneous opacities. These areas are typi-

cally peripheral in distribution and are equally distributed between the upper and lower lobes (10) (Fig 9). CT often shows associated poorly defined nodular areas of consolidation (Fig 10), centrilobular nodules and branching linear opacities ("tree-in-bud opacities"), and bronchial dilatation (10,12). BOOP caused by pulmonary drug toxicity typically responds well to cessation of drug therapy, but the patient may also require the administration of corticosteroids.

### **Eosinophilic Pneumonia**

Eosinophilic pneumonia is characterized by the accumulation of eosinophils and macrophages in the alveoli (Fig 11). Alveolar septa are thickened and infiltrated by eosinophils, lymphocytes, and plasma cells (3). Causative drugs include penicillamine, sulfasalazine, nitrofurantoin, para-aminosalicylic acid, and nonsteroidal anti-inflammatory drugs (2-4,11).

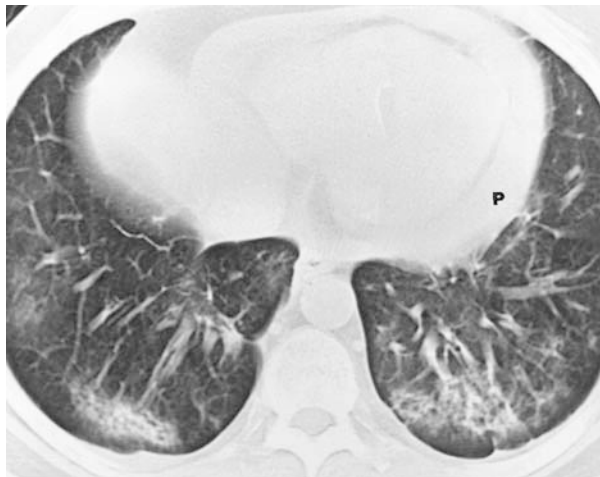




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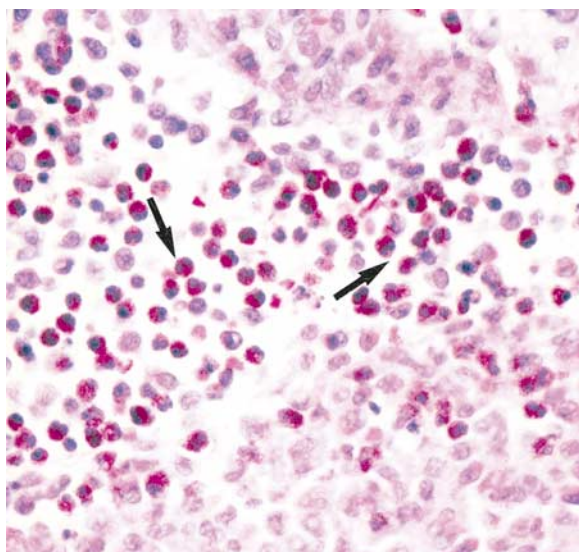


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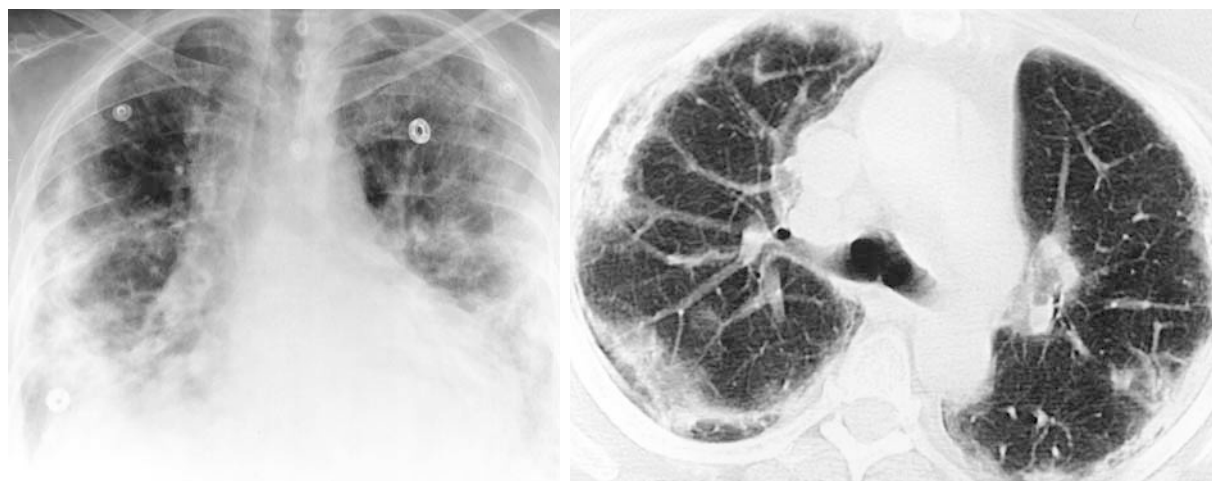


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**Figures 9, 10.** (9) Cyclophosphamide-induced BOOP in a 72-year-old woman with malignant thymoma, fever, nonproductive cough, and dyspnea. (a) Posteroanterior chest radiograph shows scattered, poorly defined peripheral opacities (arrows). (b) Follow-up posteroanterior chest radiograph obtained 2 weeks later shows progressive peripheral consolidation. Wedge resection biopsy of the middle lobe revealed findings of BOOP. (10) Cyclophosphamide-induced BOOP in a 42-year-old man with nodular sclerosing Hodgkin disease who presented with low-grade fever and decreased  $D_LCO$ . Chest CT scan shows peripheral, poorly defined areas of focal consolidation and bronchial wall thickening. Note moderate pericardial effusion (*P*). Transbronchial biopsy showed findings of BOOP.



**Figure 11.** Eosinophilic pneumonia. Photomicrograph (original magnification,  $\times 200$ ; hematoxylin-eosin stain) shows filling of alveolar space by infiltrate of eosinophils (arrows) and macrophages.



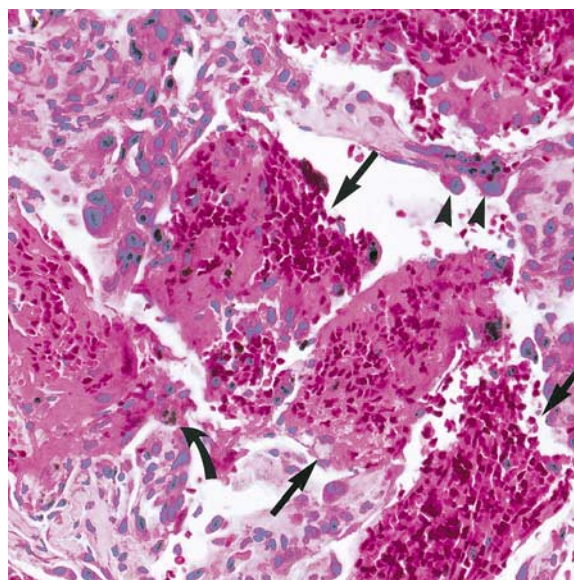
**Figure 12.** Indomethacin-induced eosinophilic pneumonia in a 76-year-old woman with cough and fever. **(a)** Posteroanterior chest radiograph shows bilateral, peripheral homogeneous opacities. **(b)** CT scan helps confirm the peripheral distribution of the radiographic findings. Transbronchial biopsy of the right lower lobe showed filling of the alveoli with eosinophils and macrophages, findings consistent with eosinophilic pneumonia.

Affected patients typically present with progressive dyspnea, dry cough, and occasionally fever. Peripheral eosinophilia and elevated IgE levels are common. Chest radiographs show homogeneous opacities that typically have a peripheral and upper lobe distribution (Fig 12). The “reverse pulmonary edema” pattern is uncommon. CT can be useful for demonstrating the peripheral nature of the pulmonary opacities. Eosinophilic pneumonia caused by drug therapy usually responds well to cessation of the therapy but the administration of corticosteroids may also be required.

### Pulmonary Hemorrhage

Diffuse pulmonary hemorrhage is an uncommon complication of drug therapy, with potentially significant morbidity and mortality (Fig 13). Typical agents that cause diffuse pulmonary hemorrhage include anticoagulants, amphotericin B, high-dose cyclophosphamide, mitomycin, cytarabine (ara-C), and penicillamine (2,4,11).

Affected patients can present with acute respiratory distress. Hemoptysis is uncommon. Chest radiographs typically show bilateral heterogeneous and homogenous opacities. Focal consolidation is a less common finding. High-resolution CT usually shows bilateral, scattered, or diffuse areas of ground-glass opacity (Fig 14). Prognosis depends on the causative agent.

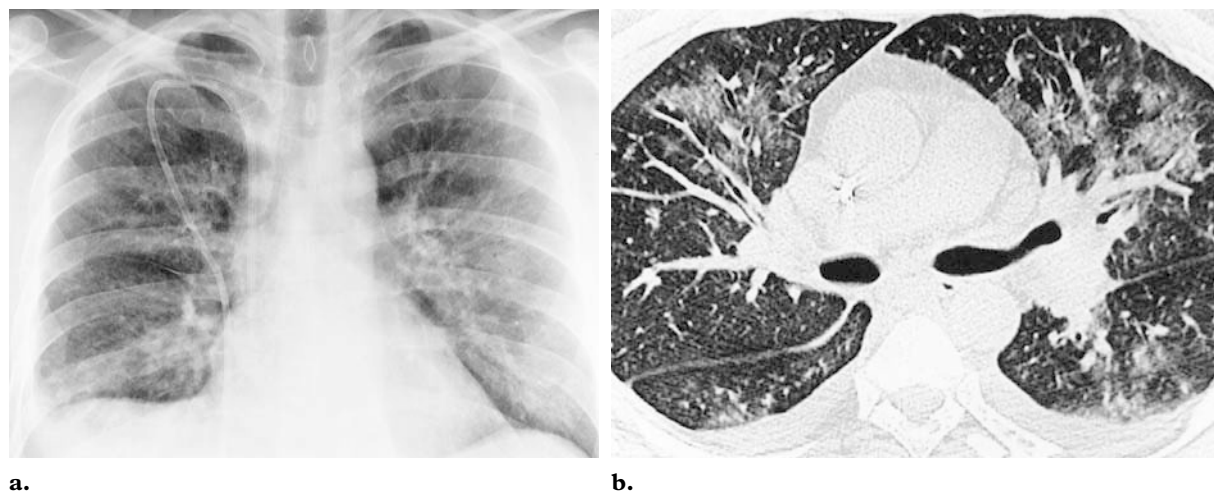


**Figure 13.** Diffuse alveolar hemorrhage. Photomicrograph (original magnification,  $\times 200$ ; hematoxylin-eosin stain) shows acute and organizing intraalveolar hemorrhage (straight arrows), hemosiderin-laden macrophages (curved arrow), and reactive type II pneumocytes (arrowheads).

### Specific Agents

Although more than 100 drugs are known to adversely affect the lungs, some of the most frequently encountered drugs that cause pulmonary toxicity are discussed herein (13).





**Figure 14.** Cytarabine-induced pulmonary hemorrhage in a 30-year-old man with acute leukemia, severe dyspnea, and decreased  $D_LCO$ . **(a)** Posteroanterior chest radiograph shows bilateral heterogeneous opacities. **(b)** High-resolution CT scan shows scattered areas of ground-glass opacity and small bilateral pleural effusions. Transbronchial biopsy of the right upper lobe showed organizing hemorrhage and mild interstitial fibrosis.



**Figure 15.** Acute carmustine pulmonary toxicity in a 23-year-old woman with grade 3 astrocytoma, dyspnea, and decreased  $D_LCO$ . High-resolution CT scan filmed with narrow window settings (level, -675; window, 650) accentuates the areas of ground-glass opacity present bilaterally. Diagnosis of drug toxicity was presumed because sputum cultures were negative for infection, and the patient's symptoms resolved with cessation of carmustine therapy and administration of corticosteroids.

### Cytotoxic Drugs

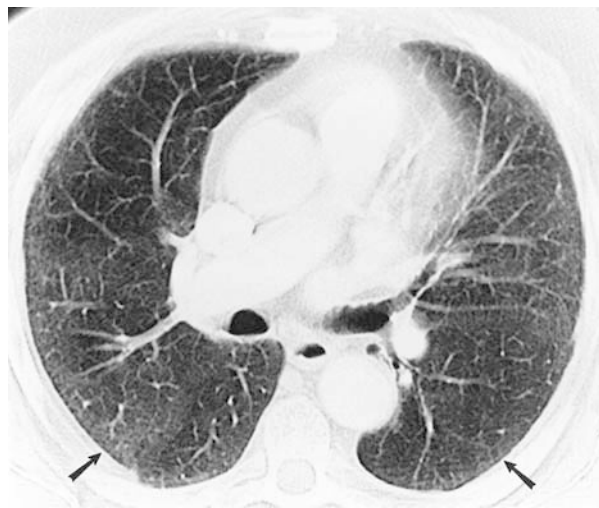
Cytotoxic drugs constitute the largest and most important group of agents associated with lung toxicity (2,8,14,15). In this group, cyclophosphamide and busulfan are the most common drugs that cause lung injury; chlorambucil and melphalan are uncommon causes of lung injury.

Cyclophosphamide is most frequently used to treat a variety of malignancies but is also used to treat nonmalignant conditions such as glomerulonephritis and Wegener granulomatosis. Toxicity occurs from 2 weeks to 13 years (mean, 3.5 years) after cyclophosphamide administration (2,8). There is no relationship between development of lung injury and dose and duration of therapy. Discontinuation of therapy is typically associated with a good prognosis. DAD is the

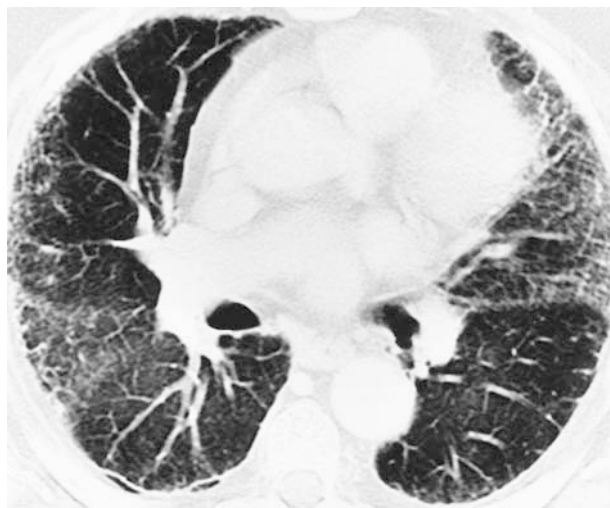
most common manifestation of cyclophosphamide-induced lung disease (2,16–18), with NSIP and BOOP being less common (2) (Figs 2, 9, 10).

Carmustine is primarily used to treat central nervous system malignancies. Carmustine is one of the few drugs for which there is a clear relationship between cumulative dose and lung injury (8,19). Carmustine-induced lung injury occurs in 20%–30% of treated patients overall, but the incidence increases to 50% if the cumulative dose is more than 1.5 g/m<sup>2</sup> (20). In addition, lung injury can occur at low doses if the patient has previously undergone thoracic radiation therapy. DAD is the most common manifestation of carmustine-induced lung disease (20) (Fig 15), with NSIP being less common (7).

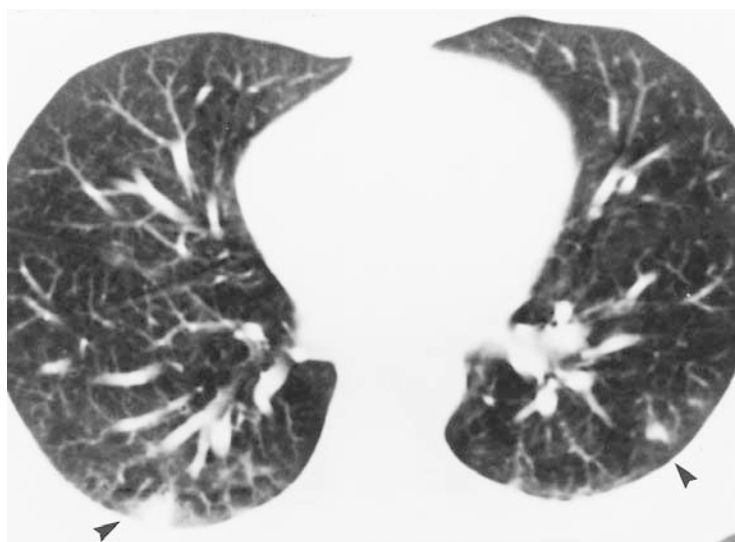
**Figures 16, 17.** (16) Bleomycin-induced pulmonary toxicity in a 63-year-old man with nonseminomatous germ cell malignancy, nonproductive cough, dyspnea, and decreased  $D_LCO$ . (a) Chest CT scan demonstrates subtle, subpleural areas of ground-glass and linear opacity (arrows), particularly in the posterior lung bases. (b) Follow-up chest CT scan obtained 3 months later shows increasing subpleural areas of reticular and ground-glass opacity, findings compatible with progressive fibrosis. Diagnosis of drug toxicity was based on clinical findings and the temporal relationship to bleomycin therapy. (17) Bleomycin-induced pulmonary toxicity in a 35-year-old man with nonseminomatous germ cell malignancy, cough, dyspnea, and decreased  $D_LCO$ . Chest CT scan shows peripheral, poorly defined pulmonary nodules (arrowheads) that were not seen on prior CT scans. Transthoracic needle aspiration biopsy was negative for malignancy, and the nodules resolved after cessation of bleomycin therapy.



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16b.

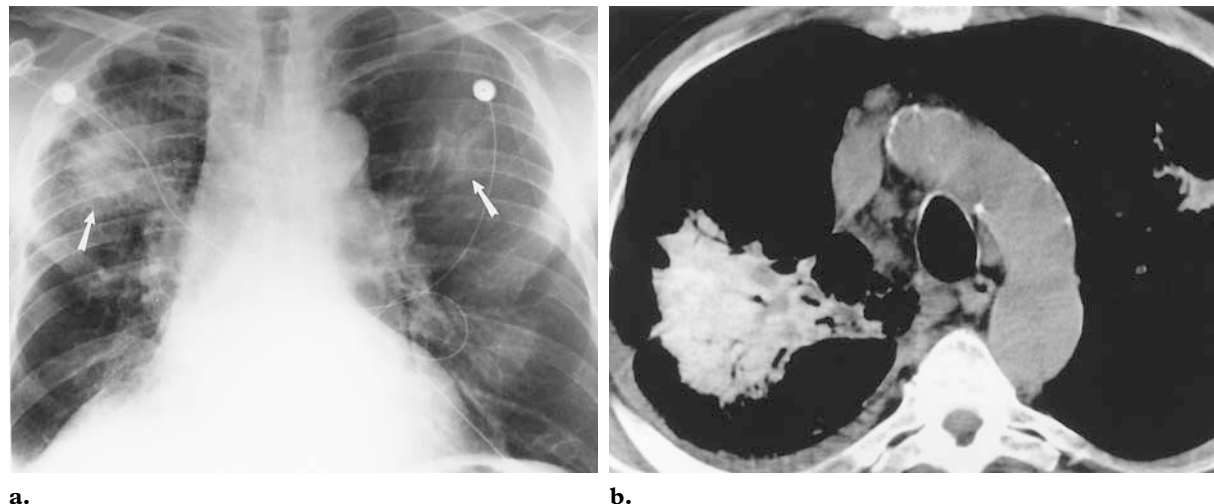


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Bleomycin is commonly used, either alone or in combination with other chemotherapeutic agents, in the treatment of squamous cell carcinomas (of the head and neck, cervix, and vagina), testicular carcinomas, and Hodgkin lymphoma. Bleomycin-induced lung injury usually occurs in 3%–5% of treated patients, although there is a marked increased risk if the total cumulative dose is more than 450 units (8,14). The risk of developing lung injury is increased in the elderly and in patients receiving oxygen therapy,

with a history of prior thoracic irradiation, or in whom therapy is reinstituted within 6 months of discontinuation. The prognosis is poor, with most patients dying of respiratory failure within 3 months of onset of symptoms (2). DAD is the most common manifestation of bleomycin-induced lung disease (21) (Figs 4, 16), with NSIP and BOOP being less common. Unlike patients with bleomycin-induced DAD, patients with bleomycin-induced BOOP can be asymptomatic at presentation. In such cases, pulmonary nodules may be seen on chest radiographs and CT scans (Fig 17). The nodules range from 5 mm to

**Figure 18.** Amiodarone-induced pulmonary toxicity in a 71-year-old man with a history of refractory ventricular arrhythmia and cough. **(a)** Posteroanterior chest radiograph shows scattered heterogeneous opacities in the lower lobes and focal homogeneous opacities in the upper lobes (arrows). **(b)** Non-contrast material-enhanced CT scan reveals high-attenuation consolidation in the right upper lobe, consistent with amiodarone-induced lung injury. (Reprinted, with permission, from reference 26.)



3.0 cm in diameter, are usually subpleural in location, and can be sharply or poorly margined (8,10,22,23). Differentiation of these nodules from metastases can be difficult, and biopsy may be required.

### Noncytotoxic Drugs

Amiodarone is commonly used to treat refractory ventricular tachyarrhythmias. Pulmonary toxicity occurs in approximately 5%–10% of patients, usually within months of starting therapy (2,9, 24). Although there is no correlation between the development of drug toxicity and the duration of therapy or total accumulative dose, the risk is increased if the daily maintenance dose is greater than 400 mg and if the patient is elderly (2). The prognosis is good, with most patients improving after discontinuation of therapy. A minority of patients experience acute, severe lung injury culminating in death (25). NSIP is the most common manifestation of amiodarone-induced lung disease (9). Pleural inflammation is an accompanying feature and can manifest as pleural effusion. BOOP is less common and typically occurs in association with NSIP.

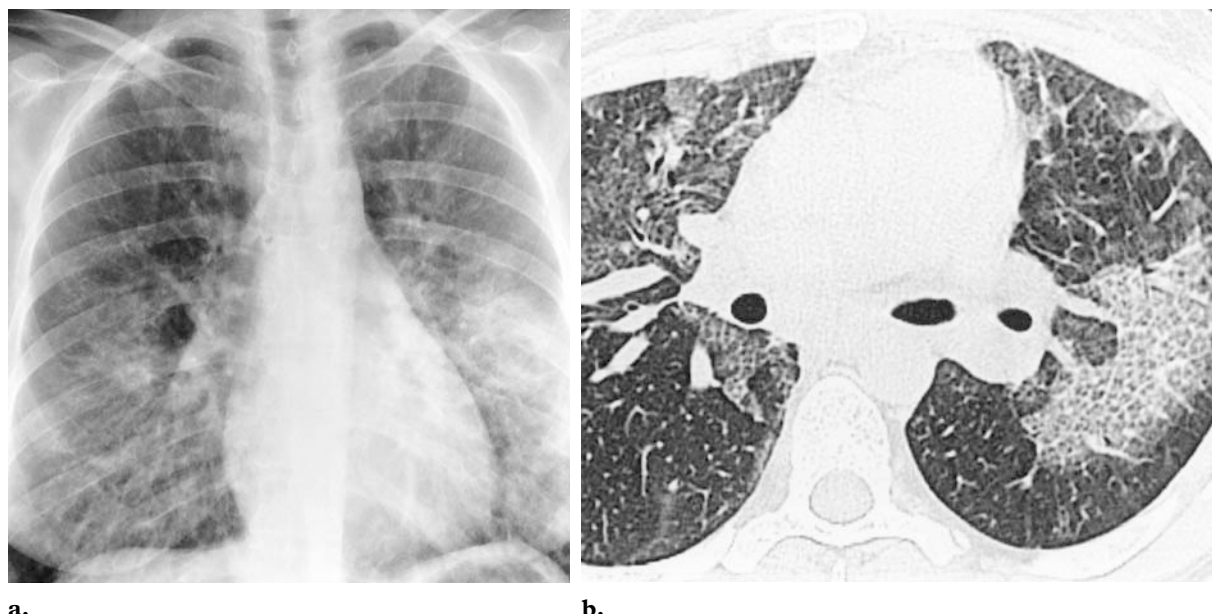
A distinctive feature of amiodarone toxicity is the occurrence of focal, homogeneous pulmonary opacities (25). These opacities are typically peripheral in location and of high attenuation at CT due to incorporation of amiodarone into the type II pneumocytes (6,24) (Fig 18). The combination of high-attenuation abnormalities within

the lung, liver, or spleen are characteristic of amiodarone toxicity.

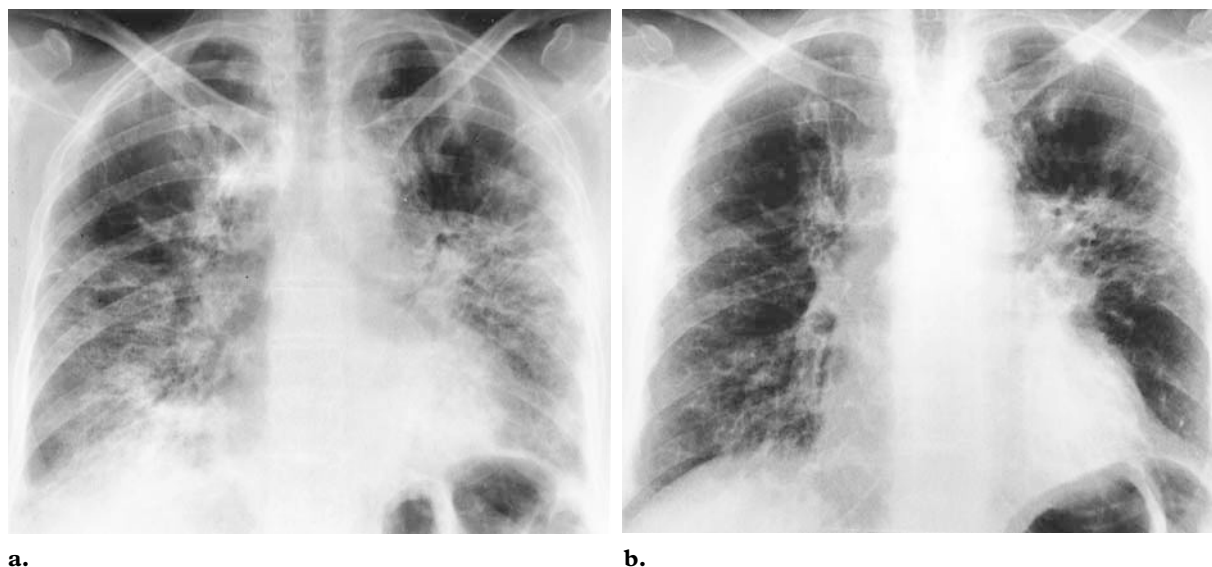
Gold salts are sometimes used to treat inflammatory arthritis. Gold-induced drug toxicity is uncommon, occurring in 1% of patients (24). Toxicity occurs within 2–6 months after therapy and is associated with mucocutaneous lesions in 30% of patients. The prognosis is good, with most patients improving after discontinuation of therapy. DAD and NSIP are the most common manifestations of gold-induced lung disease, with BOOP being less common (27).

Methotrexate is used alone or in combination with other chemotherapeutic agents to treat a wide variety of malignancies including lung cancer, breast cancer, head and neck epidermoid cancers, nonmetastatic osteosarcoma, and advanced-stage non-Hodgkin lymphoma. Methotrexate can also be used in the control of recalcitrant psoriasis and severe rheumatoid arthritis that responds poorly to first-line therapy. Methotrexate-induced pulmonary drug toxicity occurs in 5%–10% of patients. Symptoms typically manifest within months of starting therapy (8,15). There is no correlation between the development of drug toxicity and the duration of therapy or total cumulative dose (8). The prognosis is good, with most patients improving despite continuation of therapy. NSIP is the most common manifestation of methotrexate-induced lung disease





**Figure 19.** Methotrexate-induced pulmonary toxicity in a 41-year-old woman with rheumatoid arthritis, dyspnea, and decreased  $D_LCO$ . **(a)** Posteroanterior chest radiograph shows bilateral heterogeneous opacities in the mid to lower lung zones. **(b)** High-resolution CT scan shows scattered areas of ground-glass opacity, with thickened interlobular septa—the so-called crazy-paving appearance. Lung biopsy showed NSIP consistent with methotrexate-induced pulmonary toxicity.

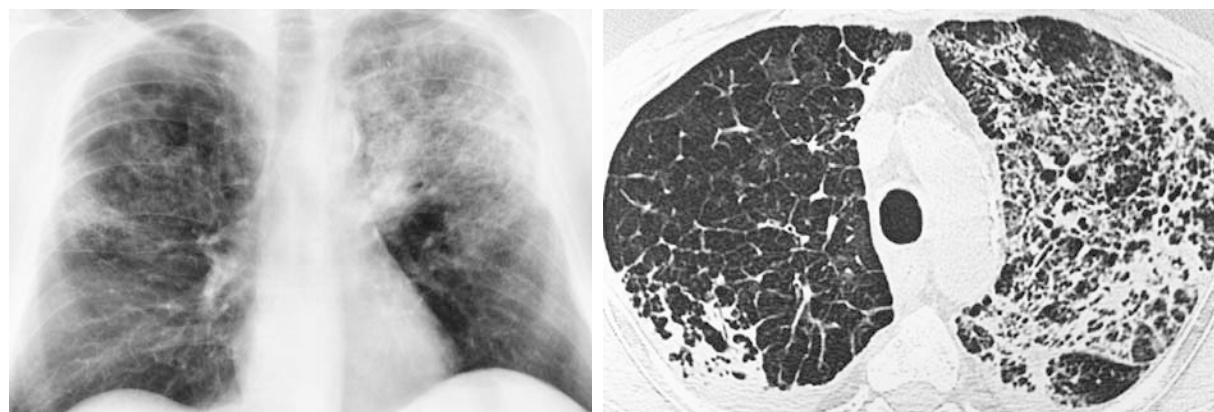


**Figure 20.** Nitrofurantoin-induced pulmonary toxicity in a 63-year-old woman with chronic ureteropelvic junction obstruction and acute respiratory distress. Diagnosis of drug toxicity was based on clinical presentation and exclusion of infection. **(a)** Posteroanterior chest radiograph shows bilateral heterogeneous opacities. **(b)** Follow-up posteroanterior chest radiograph obtained 2 months later shows marked improvement in pulmonary opacities after cessation of nitrofurantoin therapy and administration of corticosteroids.

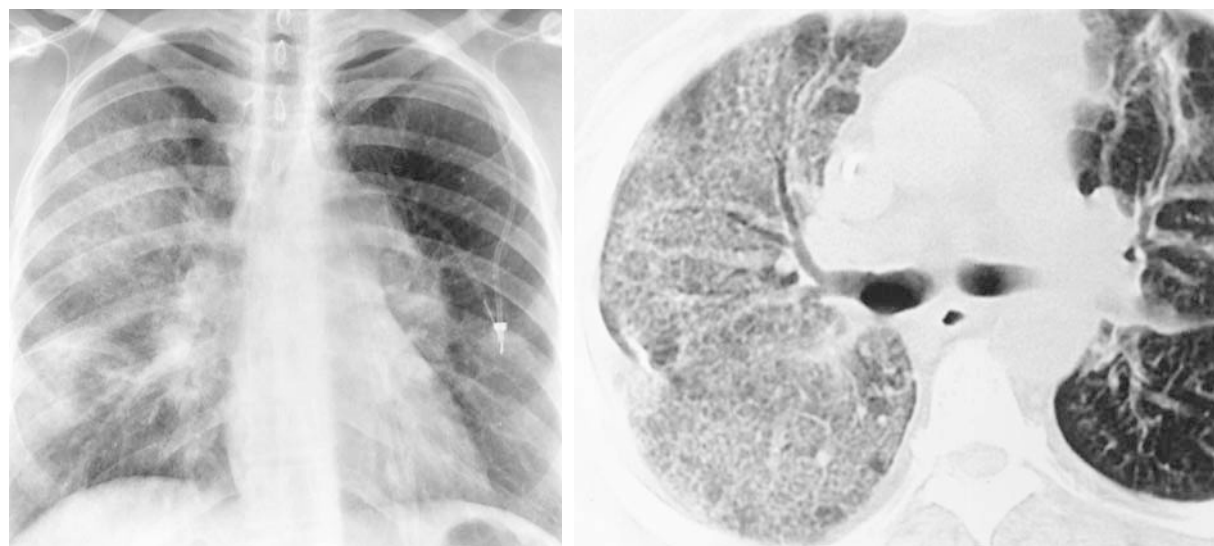
(28,29) (Fig 19). Histopathologic changes resembling hypersensitivity pneumonitis and BOOP are seen less frequently (30).

Nitrofurantoin is used to treat urinary tract infections. Nitrofurantoin-induced lung injury is uncommon, and the large number of cases reported reflects the widespread use of the drug rather than the incidence of the complication

(24). Both acute and chronic drug-induced injury have been described, with acute toxicity being more common. Acute toxicity usually occurs within 2 weeks of administration of nitrofurantoin (13). Clinical findings include fever, dyspnea, cough, and peripheral eosinophilia (2). Prognosis is good, with most patients recovering after discontinuation of nitrofurantoin therapy. Acute pulmonary toxicity manifests radiologically with



**Figure 21.** Carboplatin-induced pulmonary toxicity in a 62-year-old man with small cell lung cancer, progressive dyspnea, and fever. **(a)** Posteroanterior chest radiograph shows new heterogeneous opacities in the left and right upper lobes. **(b)** High-resolution CT scan shows predominantly left-sided areas of consolidation, thickening of interlobular septa, and traction bronchiectasis. Diagnosis of drug toxicity was based on clinical history, presentation, and exclusion of infection. The patient's symptoms improved following institution of corticosteroid therapy.



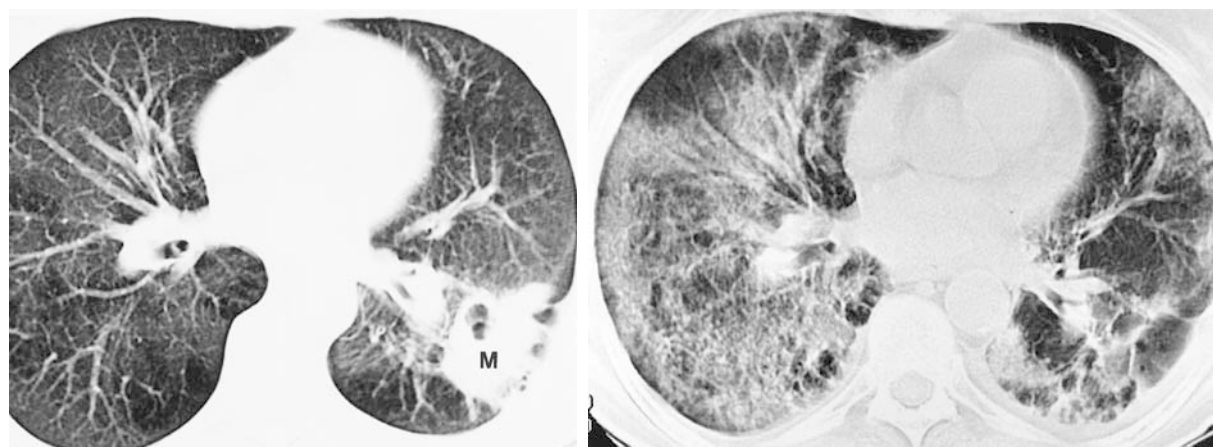
**Figure 22.** Topotecan-induced pulmonary toxicity in a 45-year-old woman with small cell lung cancer and increasing dyspnea. **(a)** Posteroanterior chest radiograph shows new heterogeneous opacities in the right lung. Note the mediastinal mass, consistent with small cell lung cancer. **(b)** Chest CT scan shows areas of ground-glass and linear opacity in the right lung and scattered opacities in the left lung. Wedge resection biopsy of the right upper lobe revealed findings of BOOP.

diffuse bilateral, predominantly basal heterogeneous opacities (31) (Fig 20). Chronic toxicity is less common and usually occurs after months or years of nitrofurantoin administration. Chronic pulmonary toxicity typically manifests clinically with insidious onset dyspnea and cough. NSIP is the most common histopathologic manifestation of chronic toxicity (30) (Fig 7).

### New Chemotherapeutic Agents

New antineoplastic agents are being added to the oncologist's armamentarium almost daily. Among these new agents are the taxoid derivatives pacli-

taxel and docetaxel, gemcitabine, topotecan, and vinorelbine. These agents have demonstrated activity against malignancies of the breast, lung, and ovary (32). Although experience is limited, it appears that many of these agents may have pulmonary toxicity (Figs 21–23). For instance, preliminary data suggest that paclitaxel administered at doses higher than 100 mg/m<sup>2</sup> may commonly cause pulmonary toxicity (32,33). The histopathologic features of pulmonary toxicity caused by these agents are not well described.



**a.** **b.**  
**Figure 23.** Pulmonary drug toxicity in a 60-year-old woman with non-small cell lung cancer treated with carboplatin and vinorelbine. She presented with progressive dyspnea. **(a)** CT scan shows a left lower lobe mass (*M*), mild emphysematous lung disease, and subtle areas of ground-glass opacity in the left lung adjacent to the mass. **(b)** Follow-up CT scan obtained 5 weeks later shows marked increase in diffuse ground-glass and reticular opacity. Note marked interval improvement in the left lower lobe mass. Diagnosis of drug toxicity was based on clinical history and exclusion of infection. The patient's symptoms and radiologic abnormalities resolved following institution of corticosteroid therapy.

### Conclusions

The prevalence of drug-induced pulmonary toxicity is increasing, and more than 100 drugs are now known to cause lung injury. Because this lung injury can be progressive and fatal, early recognition is important. The diagnosis of pulmonary drug toxicity should be considered in any patient with a history of drug therapy who presents with new or progressive respiratory complaints. Drug-induced pulmonary toxicity can be difficult to diagnose; therefore, knowledge of the drugs most frequently involved, together with an understanding of the typical histopathologic and radiologic manifestations of toxicity caused by those drugs, are necessary for institution of appropriate treatment.

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