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5

Acute Lung Injury

Oi-Yee Cheung, MD, Paolo Graziano, MD, and Kevin O. Leslie, MD

A wide variety of insults can produce acute lung damage, inclusive of those that injure the lungs directly. Early terms for diffuse acute lung injury occurring indirectly in the setting of overwhelming nonthoracic trauma accompanied by hypovolemia were "shock lung," "postperfusion lung," "traumatic wet lung," and "congestive atelectasis."[1,2]

In 1967, Ashbaugh and coworkers formally described a syndrome characterized by acute onset of severe respiratory distress after an identifiable injury. Clinical signs included dyspnea, reduced lung compliance, diffuse chest radiographic infiltrates, and hypoxemia refractory to supplementary oxygen.[3] Today this sequence of clinical events is referred to as the *acute respiratory distress syndrome* (ARDS). The clinical course is rapid and the mortality rate is high, with more than one half of affected patients dying of respiratory failure within days to weeks.[2,4,5] A recent meta-regression analysis performed by Zambon and Vincent[6] of mortality rates from 72 published studies of ARDS identified a decrease of 1.1% per year for the period 1994 to 2006, with an overall pooled mortality rate for all studies of 43%.

The American-European Consensus Conference (AECC) formally defined ARDS in 1994 using the following criteria: acute onset; bilateral chest radiographic infiltrates; hypoxemia regardless of the positive end-expiratory pressure oxygen concentration, an arterial partial pressure of oxygen to inspired oxygen fraction ratio less than 200, and no evidence of left atrial hypertension.[7] The AECC also agreed that ARDS represents the most severe form on a spectrum of disease conditions encompassed under the general term *acute lung injury*.

The histopathologic counterpart of ARDS is distinctive and referred to as *diffuse alveolar damage* (DAD). DAD is the most extreme manifestation of lung injury and can occur as a result of a large number of direct injuries to the lungs (e.g., infection). In this chapter, the emphasis is on DAD and less severe manifestations of acute lung injury. Some authors have considered organizing pneumonia to be a form of acute lung injury, but we and others believe that organization is a subacute phenomenon with a more protracted clinical course (extending over several days to weeks). Subacute organizing pneumonia of unknown etiology (previously known as idiopathic bronchiolitis obliterans organizing pneumonia)[8] is discussed with the chronic diffuse diseases (see Chapter 7).

Diffuse Alveolar Damage: The Morphologic Prototype of Acute Lung Injury

The causes of acute lung injury are numerous (Box 5-1). The lung reacts to various types of insults in similar ways, regardless of etiology. The resultant endothelial and alveolar epithelial cell injury is attended by fluid and cellular exudation. Subsequent reparative fibroblastic proliferation is accompanied by type II pneumocyte hyperplasia.[4,9] The microscopic appearance depends on the time interval between insult and biopsy, and on the severity and extent of the injury.[2] DAD is the usual pathologic manifestation of ARDS and is the best-characterized prototype of acute lung injury. From studies of ARDS, the pathologic changes appear to proceed consistently through discrete but overlapping phases (Fig. 5-1)—an early exudative (acute) phase (Fig. 5-2A and B), a subacute proliferative (organizing) phase (see Fig. 5-2C), and a late fibrotic phase (Fig. 5-3).[2,4,5,8,10] The exudative phase is most prominent in the first week of injury. The earliest changes include interstitial and intra-alveolar edema with variable amounts of

Box 5-1. Etiology of Diffuse Alveolar Damage

- Idiopathic
  - Acute interstitial pneumonia (Hamman-Rich syndrome)
- Infection
  - Any infection in the immunosuppressed patient, especially *Pneumocystis jiroveci* infection
  - Viral infection: adenovirus, influenzavirus, herpesvirus, CMV, and hantavirus infections; SARS; coronavirus and RSV infections, others
  - *Legionella* infection
  - *Mycoplasma*/*Chlamydia* infection
  - Rickettsial infection
- Drugs
  - Chemotherapeutic drugs: busulfan, bleomycin, methotrexate, azathioprine, BCNU, cytoxan, melphalan, mitomycin-C
  - Amiodarone
  - Gold
  - Nitrofurantoin
  - Hexamethonium
  - Placidyl
  - Penicillamine
- Collagen vascular disease
  - Systemic lupus erythematosus
  - Rheumatoid arthritis
  - Polymyositis/dermatomyositis
  - Scleroderma
  - Mixed connective disease
- Pulmonary hemorrhage syndrome and vasculitis
  - Goodpasture syndrome
  - Microscopic polyangiitis
  - Polyarteritis nodosa
  - Wegener granulomatosis
  - Vasculitis associated with collagen vascular disease
- Ingestants
  - Paraquat
  - Kerosene
  - Denatured rapeseed oil
- Inhalants
  - Oxygen
- Inhalants—cont'd
  - Amitrole-containing herbicide
  - Ammonia and bleach mixture
  - Chlorine gas
  - Hydrogen sulfide
  - Mercury vapor
  - Nitric acid fumes
  - Nitrogen dioxide
  - Paint remover
  - Smoke
  - Smoke bomb
  - Sulfur dioxide
  - War gases
- Shock
  - Traumatic
  - Hemorrhage
  - Neurogenic
  - Cardiogenic
- Sepsis
- Radiation exposure
- Other etiologic factors/conditions
  - Acute massive aspiration
  - Acute pancreatitis
  - Burn
  - Cardiopulmonary bypass
  - Heat
  - High altitude
  - Intravenous administration of contrast material
  - Leukemic cell lysis
  - Molar pregnancy
  - Near-drowning
  - Peritoneal-venous shunt
  - Post-lymphangiography
  - Toxic shock syndrome
  - Transfusion therapy
  - Uremia
  - Venous air embolism

BCNU, carmustine; CMV, cytomegalovirus; RSV, respiratory syncytial virus; SARS, severe acute respiratory syndrome.
Modified from Katzenstein A, Askin F, eds. *Katzenstein and Askin's Surgical Pathology of Non-Neoplastic Lung Disease,* 3rd ed. Philadelphia: Saunders; 1997:16.

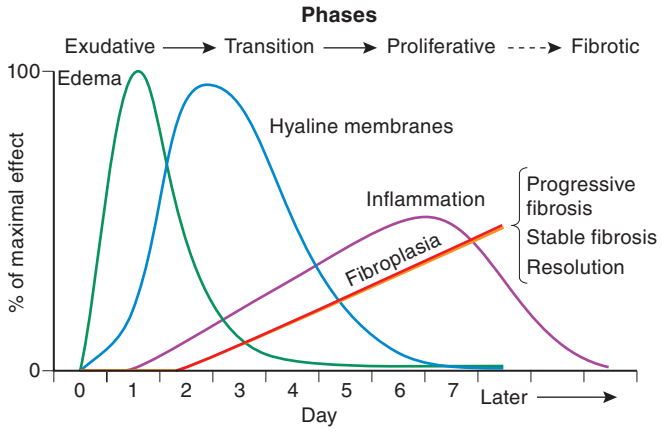

Figure 5-1. Acute respiratory distress syndrome (ARDS) timeline. The phases of ARDS are reproducible and reflect the global mechanisms of wound repair (exudation, proliferation, variable fibrogenesis). The indefinite relationship between proliferation and fibrogenesis is depicted as a *hashed line* in the sequence at the top of the figure. In experimental ARDS, the exact time of injury is known, and the entire lung proceeds through the phases at the same time. In a patient who develops diffuse alveolar damage from any cause, the acute lung injury may begin in different areas at different times, so a biopsy specimen may demonstrate injury at various phases in this sequence. (Modified from Katzenstein A: Acute lung injury patterns: diffuse alveolar damage and bronchiolitis obliterans–organizing pneumonia. In: Katzenstein A, Askin F, eds. *Katzenstein and Askin's Surgical Pathology of Non-Neoplastic Lung Disease,* 3rd ed. Philadelphia: Saunders; 1997.)

hemorrhage and fibrin deposition (Fig. 5-4). Hyaline membranes (Fig. 5-5), the histologic hallmark of the exudative phase of ARDS, are most prominent at 3 to 7 days after injury. Minimal interstitial mononuclear inflammatory infiltrates (Fig. 5-6) and fibrin thrombi in small pulmonary arteries (Fig. 5-7) also are seen. Type II pneumocyte hyperplasia (Fig. 5-8) begins by the end of this phase and persists through the proliferative phase. The reactive type II pneumocytes may demonstrate marked nuclear atypia, with numerous mitotic figures (Fig. 5-9). The proliferative phase begins at 1 week after the injury and is characterized by fibroblastic proliferation, seen mainly within the interstitium but also focally in the alveolar spaces (Fig. 5-10). The fibrosis consists of loose aggregates of fibroblasts admixed with scattered inflammatory cells (Fig. 5-11); collagen deposition is minimal. Reactive type II pneumocytes persist. Immature squamous metaplasia may occur (Fig. 5-12) in and around terminal bronchioles. The degree of cytologic atypia in this squamous epithelium can be so severe as to mimic malignancy (Fig. 5-13). The hyaline membranes are mostly resorbed by the late proliferative stage, but a few remnants may be observed along alveolar septa. Some cases of DAD resolve completely, with few residual morphologic effects, but in other cases, fibrosis may progress to extensive structural remodeling and honeycomb lung. As might be expected, a recent review of outcomes for 109 survivors of ARDS revealed persistent functional disability at 1 year after discharge from intensive care.[11]

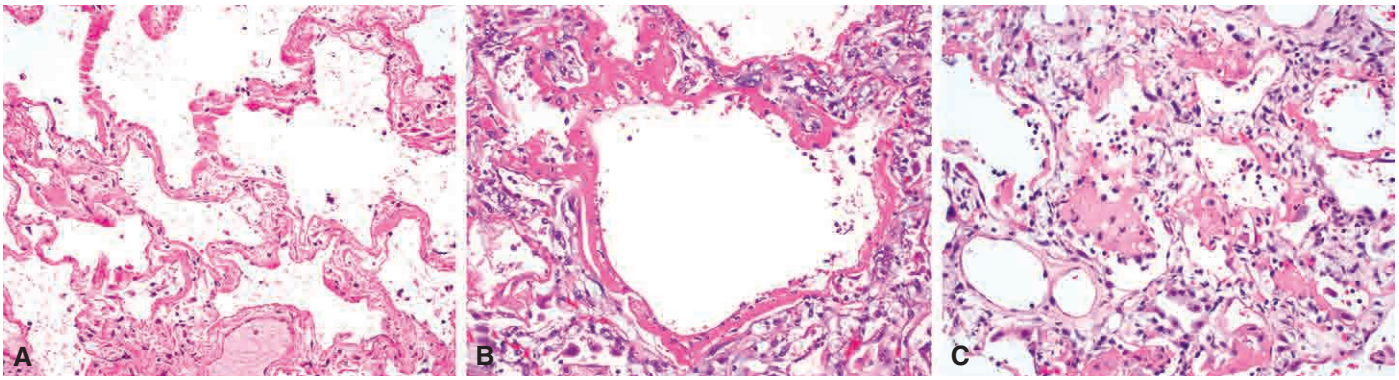

Figure 5-2. Acute respiratory distress syndrome (ARDS): exudative and proliferative phases. The early exudative phase of ARDS, characterized by some edema, cellular debris, and early hyaline membrane formation (**A**) evolves to include well-defined hyaline membranes (**B**). Note the increased cellularity in the interstitium, with some spindled fibroblast-like cells evident. **C,** Organization of hyaline membranes occurs in the early proliferative phase. Another feature specific to this stage is increased air space cellularity.

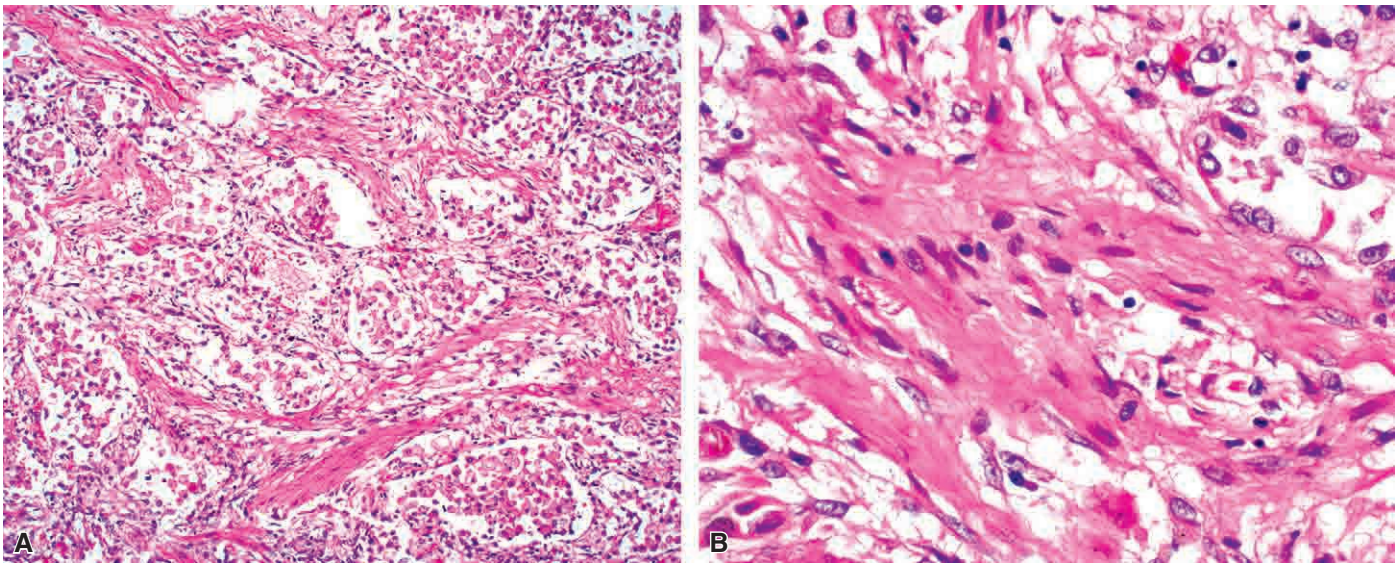

Figure 5-3. Acute respiratory distress syndrome (ARDS): late proliferative and fibrotic stages. The late proliferative phase of ARDS (**A**) may evolve to fibrosis (**B**), with cellular fibroblastic proliferation and collagen deposition.

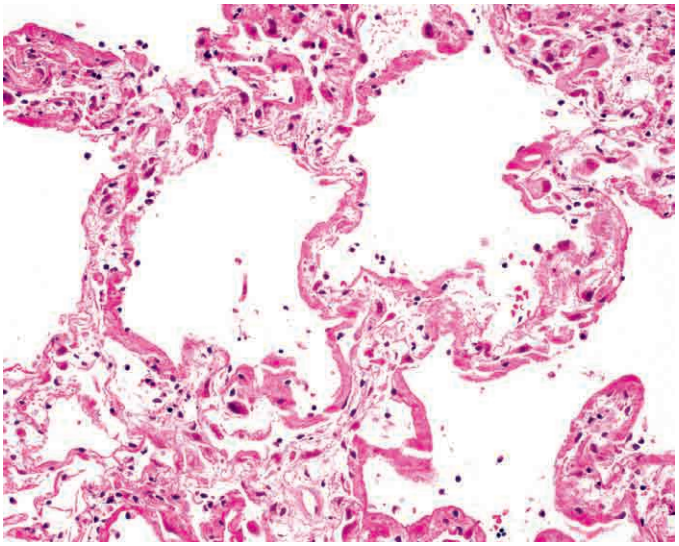

Figure 5-4. Acute respiratory distress syndrome: early exudative phase. Mild interstitial edema with hyaline membranes outlining alveolar spaces is characteristic.

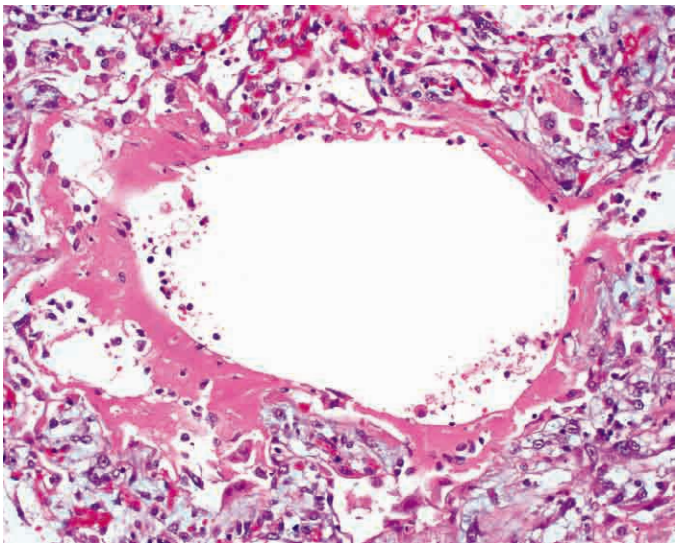

Figure 5-5. Acute respiratory distress syndrome: hyaline membranes. Proteinaceous alveolar exudates accumulate along the periphery of alveoli, closely adherent to alveolar wall–air space interface.

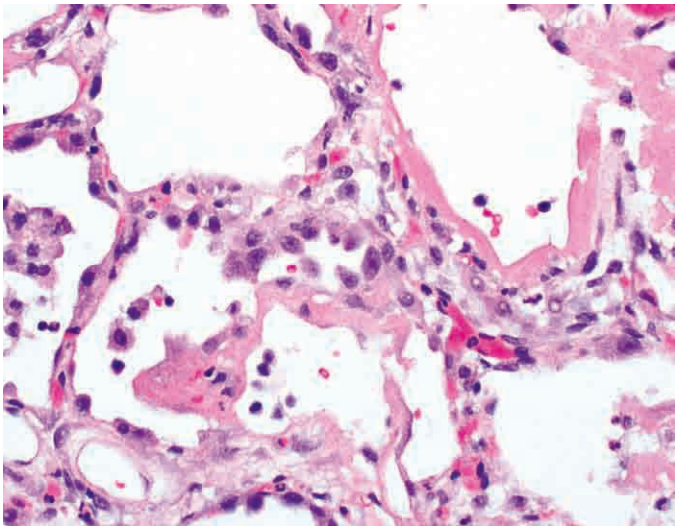

Figure 5-6. Acute respiratory distress syndrome (ARDS): mild interstitial inflammation. In ARDS, the inciting event is frequently extrathoracic, and lung injury is therefore superimposed on normal pre-existing structure.

By definition, ARDS has a known inciting event. The foregoing description is based on a model of ARDS due to oxygen toxicity, wherein the evolution of histopathologic abnormalities can be studied over a defined time period.[2,5] In practice, lung biopsy most often is performed in patients without a known cause or specific time of onset of injury. Moreover, with some causes of acute lung injury, the damage evolves over a protracted period of time, or the lung may be injured in repetitive fashion (e.g., with drug toxicity). In such circumstances, the pathologic changes do not necessarily progress sequentially through defined stages as in ARDS, so both acute and organizing phases may be encountered in the same biopsy specimen. The basic histopathologic elements of acute lung injury are presented in Box 5-2.

Acute fibrinous and organizing pneumonia (AFOP) is a recently recognized histologic pattern of acute lung injury with a clinical presentation similar to that of classic DAD, in terms of both potential etiologic disorders and outcome. It differs from DAD in that hyaline membranes are absent. The dominant feature is intra-alveolar fibrin "balls" or aggregates, typically in a patchy distribution. Organizing pneumonia in the form of luminal loose fibroblastic tissue is present surrounding the fibrin. The alveolar septa adjacent to areas of fibrin deposition show a variety of changes similar to those of DAD, such as septal edema, type II pneumocyte hyperplasia, and acute and chronic inflammatory infiltrates. The intervening lung shows minimal histologic changes. AFOP may represent a fibrinous variant of DAD. In some patients, both DAD and AFOP disease patterns may be present simultaneously.[12,13]

Specific Causes of Acute Lung Injury

Infection

Infection is one of the most common causes of acute lung injury. Among infectious organisms, viruses most consistently produce DAD.[2,5] Occasionally, fungi (e.g., *Pneumocystis*) and bacteria (e.g., *Legionella*) also can cause infections manifesting as DAD. Some of the organisms that are well known to cause acute lung injury with characteristic histopathologic changes are discussed next.

Viral Infection

Influenza is a common cause of viral pneumonia. The histopathology ranges from mild organizing acute lung injury (resembling organizing pneumonia) in nonfatal cases to severe DAD with necrotizing tracheobronchitis (Fig. 5-14) in fatal cases.[14,15] Specific viral cytopathic effects are not identifiable by light microscopy. On ultrastructural examination, intranuclear fibrillary inclusions may be seen in epithelial and endothelial cells.[16]

The *coronavirus* responsible for severe acute respiratory syndrome (SARS) produces the acute lung injury associated with this disorder.[17–20] Both DAD and AFOP patterns have been identified in affected patients. On ultrastructural examination, involved lung tissue revealed numerous to moderate numbers of cytoplasmic viral particles in pneumocytes, many within membrane-bound vesicles.[21–23] The virus particles were spherical and enveloped, with spike-like projections on the surface and coarse clumps of electron-dense material in the center. Most had sizes ranging from 60 to 95 nm in diameter, but some were as large as 180 nm.

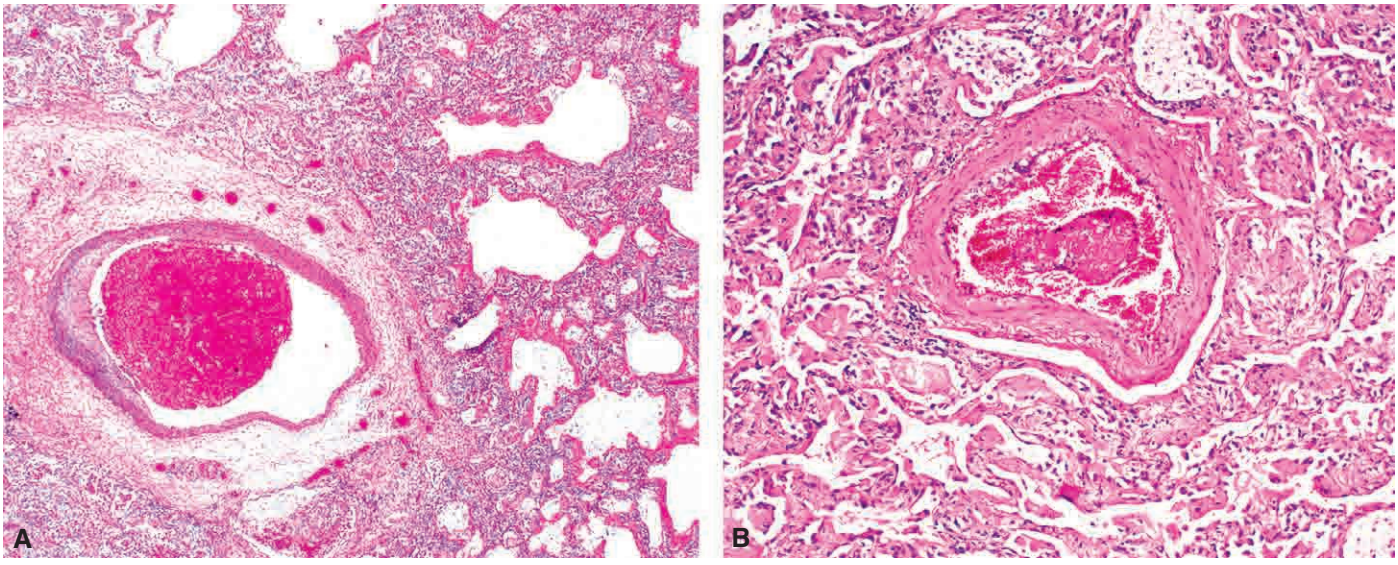

Figure 5-7. Acute respiratory distress syndrome: fibrin thrombi in arteries. Acute lung injury results in local conditions that lead to arterial thrombosis. Thrombi in various stages of organization may be seen (larger pulmonary artery in part **A,** smaller pulmonary artery in part **B**).

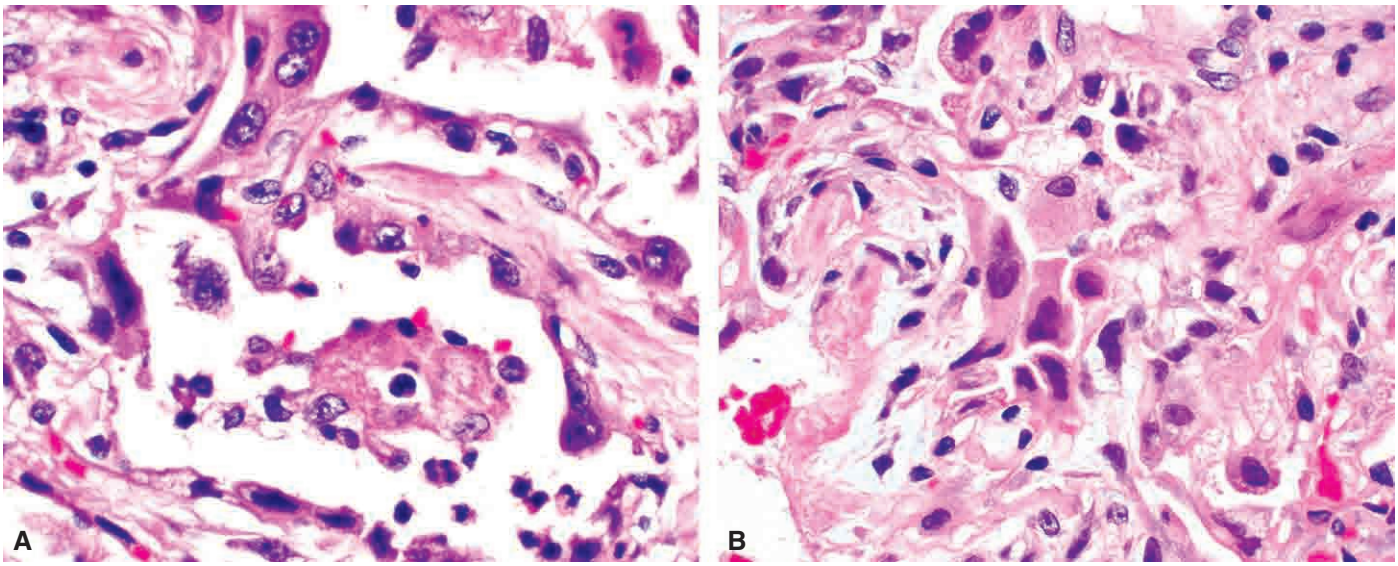

Figure 5-8. Acute respiratory distress syndrome (ARDS): type II cell hyperplasia. Cuboidal type II cells are nearly always prominent in the late exudative phase and throughout the proliferative phase of ARDS. These hyperchromatic and enlarged epithelial cells repopulate the damaged type I cell lining of the alveolar spaces. Depending on the mechanism of injury, atypia of regenerating type II cells may be mild, moderate, or severe. **A,** Prominent type II cells have a "hobnail" appearance simulating viropathic change. **B,** Brightly eosinophilic type II cells are aggregated at the center of a collapsed alveolus. Considerable structural remodeling may take place after ARDS as these atelectatic spaces fuse to form consolidated areas of lung parenchyma at the microscopic level.

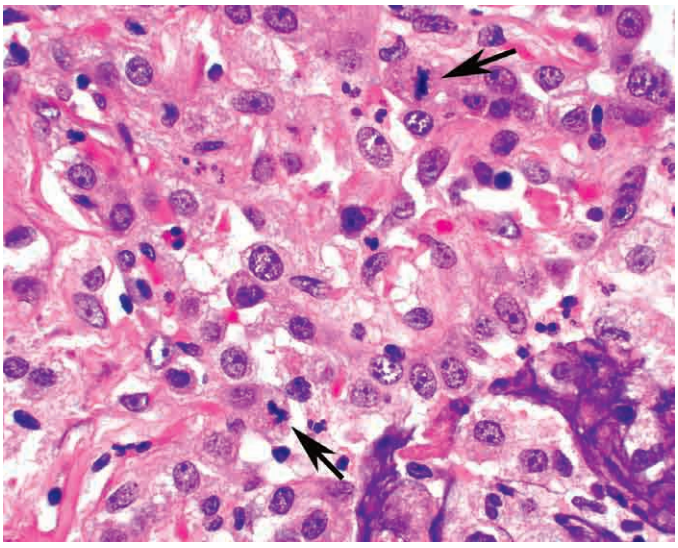

Figure 5-9. Acute respiratory distress syndrome: mitotic figures in type II cells. Mitotic activity can be quite brisk in all forms of acute lung injury (mitotic figures at *arrows*).

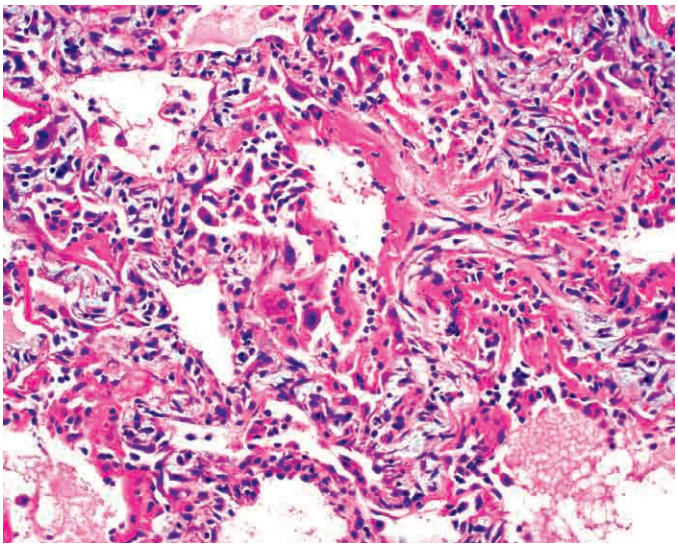

Figure 5-10. Acute respiratory distress syndrome (ARDS): fibroblastic proliferation. Fibroblastic proliferation occurs to a variable degree both in the interstitium and within air spaces in the proliferative and early fibrotic phases of ARDS.

Measles virus produces a mild pneumonia in the normal host but can cause serious pneumonia in immunocompromised children. Histopathologic features of such infection include interstitial pneumonia, bronchitis and bronchiolitis, and DAD.[24] The characteristic histologic feature is the presence of multinucleated giant cells (Fig. 5-15A) with characteristic eosinophilic intranuclear and intracytoplasmic inclusions.[24–28] These cells are found in the alveolar spaces and within alveolar septa (see Fig. 5-15B). Viral inclusions are seen on ultrastructural examination as tightly packed tubules.[28]

Adenovirus is an important cause of lower respiratory tract disease in children,[29,30] although adults (particularly those who are immunocompromised)[31] and military recruits also are occasionally affected.[32] The lung shows necrotizing bronchitis, or bronchiolitis, accompanied by DAD. The pathologic changes are more severe in bronchi, bronchioles, and peribronchiolar regions (Fig. 5-16A). Two types of inclusions can be observed in lung epithelial cells: An eosinophilic intranuclear inclusion with a halo usually is less conspicuous than the more readily identifiable "smudge cells" (see Fig. 5-16B). These latter cells are larger than normal and entirely basophilic, with no defined inclusion or halo evident by light microscopy.[29] On ultrastructural examination, smudge cell inclusions are represented by arrays of hexagonal particles.[33]

Herpes simplex virus is mainly a cause of respiratory infection in the immunocompromised host. Two patterns of infection are recognized: airway spread resulting in necrotizing tracheobronchitis (Fig. 5-17) and blood-borne dissemination producing miliary necrotic parenchymal nodules. DAD and hemorrhage can occur in both forms.[34,35] Characteristic inclusions may be seen in bronchial and alveolar

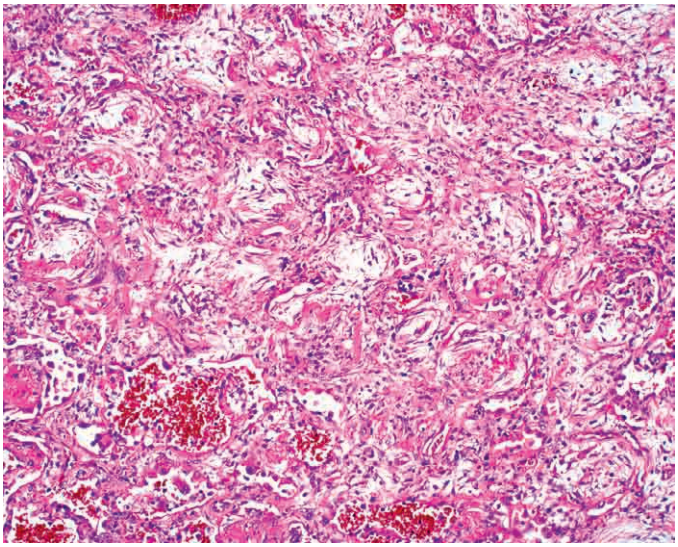

Figure 5-11. Acute respiratory distress syndrome (ARDS): air space organization. Organizing pneumonia–like air space organization can be quite prominent in the late proliferative phase of ARDS.

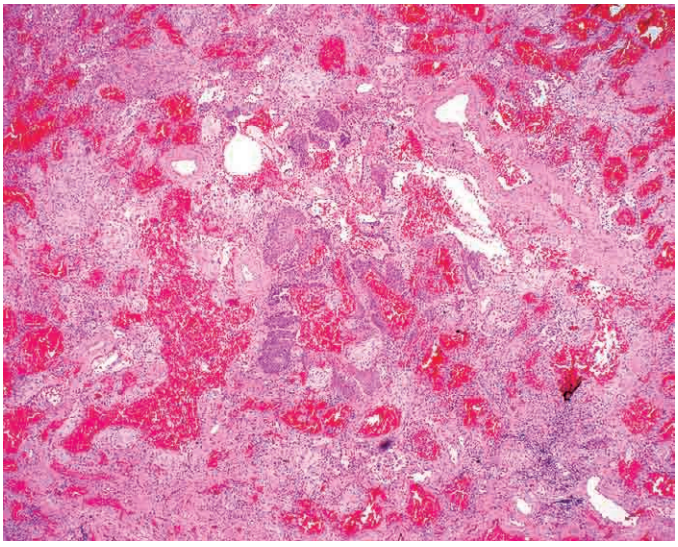

Figure 5-12. Acute respiratory distress syndrome (ARDS): squamous metaplasia. Squamous metaplasia of terminal airways may develop as a subacute proliferative event in ARDS and other forms of diffuse alveolar damage. The nested squamous epithelium often is nodular-appearing at scanning magnification by virtue of patchy terminal airway involvement.

epithelial cells (Fig. 5-18). The more obvious type is an intranuclear eosinophilic inclusion surrounded by clear halo (Cowdry A inclusion), and the other is represented by a basophilic to amphophilic ground-glass nucleus (Cowdry B inclusion). Rounded viral particles with double membranes are seen under the electron microscope.[34,35]

Varicella-zoster virus causes disease predominantly in children and is the agent of chickenpox.[36] Pulmonary complications of chickenpox are rare in children with normal immunity (accounting for less than 1% of the cases). By contrast, however, pneumonia develops in 15% of adults with chickenpox; immunocompetent and immunocompromised persons are equally affected.[32,36] The histopathologic picture in varicella pneumonia (Fig. 5-19) is similar to that in herpes simplex. Although identical intranuclear inclusions are reported to occur,[32,36] these can be considerably more difficult to identify in chickenpox pneumonia.

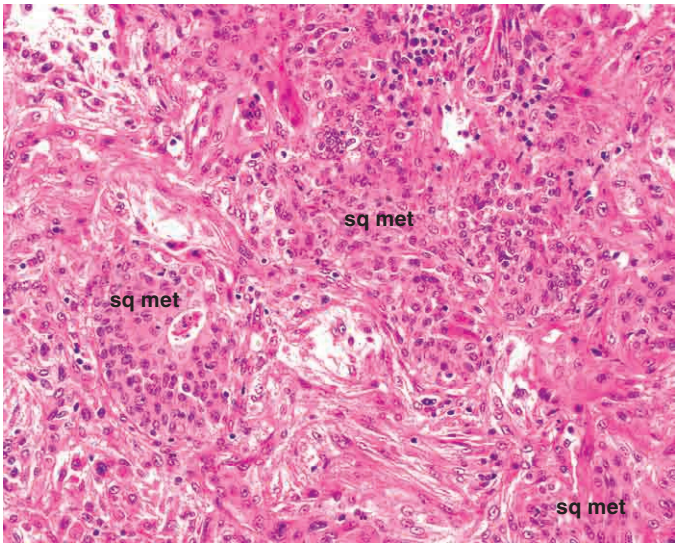

Figure 5-13. Acute respiratory distress syndrome: squamous metaplasia (sq met), high-magnification view. In some instances, squamous metaplasia may be so prominent as to suggest neoplasm.

Box 5-2. Defining Histopathologic Features of Acute Lung Injury

Interstitial (alveolar septal) edema
Fibroblastic proliferation in alveolar septa
Alveolar edema
Alveolar fibrin and cellular debris, with or without hyaline membranes
Reactive type II pneumocytes

Cytomegalovirus is an important cause of symptomatic pneumonia in immunocompromised persons, especially those who have received bone marrow or solid organ transplants, and in patients with human immunodeficiency virus (HIV) infection.[37–39] The histopathologic findings range from little or no inflammatory response to hemorrhagic nodules with necrosis (Fig. 5-20A) and DAD.[37] The diagnostic histopathologic pattern, seen in endothelial cells, macrophages, and epithelial cells, consists of cellular enlargement, a prominent intranuclear inclusion, and an intracytoplasmic basophilic inclusion[37] (see Fig. 5-20B).

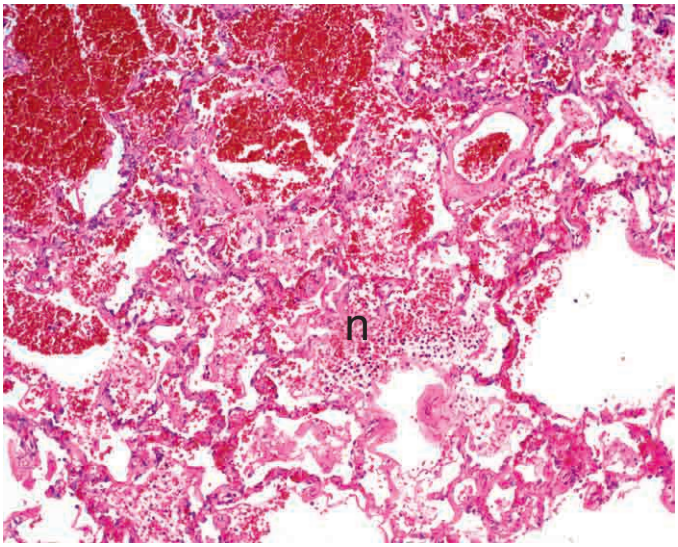

Figure 5-14. Diffuse alveolar damage in influenza pneumonia. Fibrinous and focally neutrophilic diffuse alveolar injury is characteristic. In this case, note the sparse neutrophils present in an air space (n) and abundant blood. No specific viral inclusions are produced by the influenzavirus.

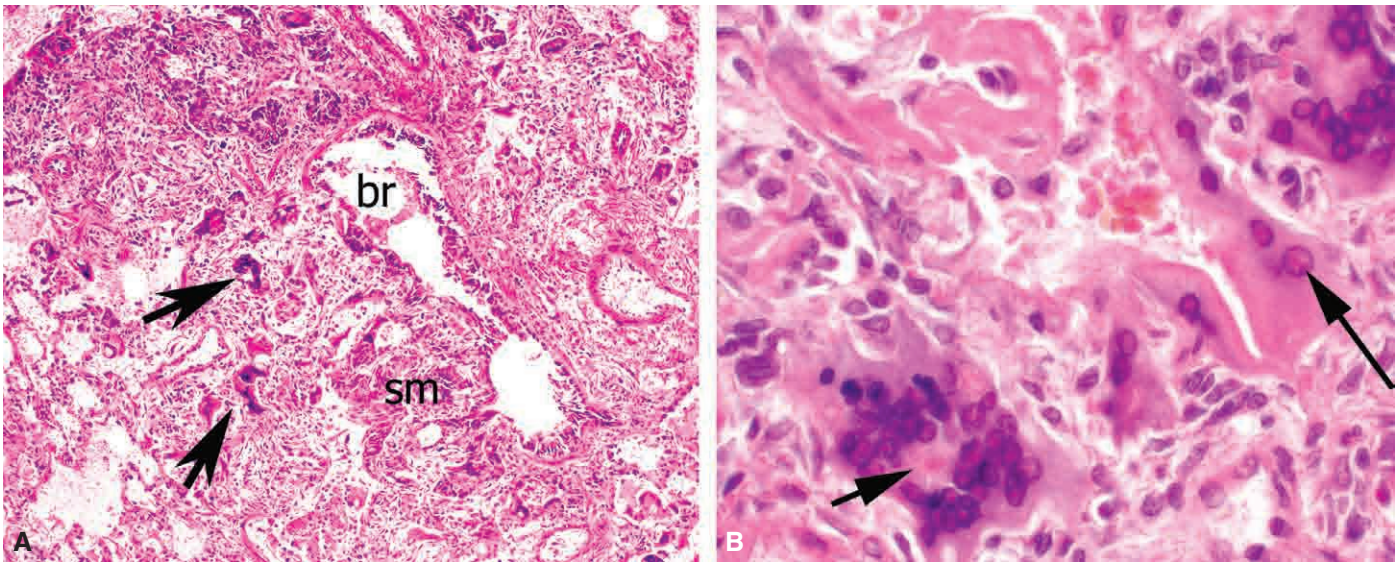

Figure 5-15. Diffuse alveolar damage (DAD) in measles pneumonia. **A,** A terminal airway (br) in a case of acute measles pneumonia with DAD. Squamous metaplasia of the airway also is present (sm). The *arrows* denote multinucleate giant cells, present here in a bronchiolocentric distribution. **B,** The characteristic multinucleate giant cells of measles pneumonia. Note the glassy intranuclear inclusions (*long arrow*) and occasional eosinophilic cytoplasmic inclusions (*short arrow*).

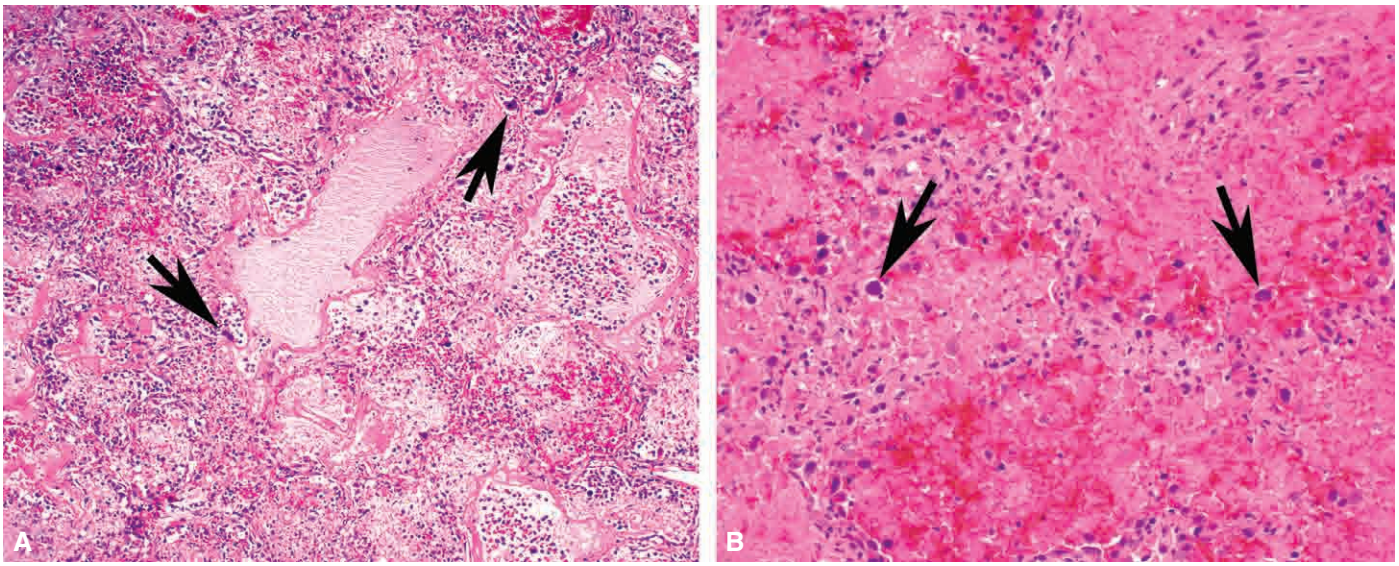

Figure 5-16. Diffuse alveolar damage (DAD) in adenovirus pneumonia. Adenovirus infection produces necrotizing bronchitis/bronchiolitis, and this is especially prominent in the setting of DAD caused by this infection. **A,** The "smudge cells" of adenovirus infection can be seen at scanning magnification (*arrows*). **B,** Smudge cells at higher magnification (*arrows*).

Hantavirus is a rare cause of acute lung injury.[40–42] The infection produces alveolar edema, hyaline membranes, and atypical interstitial mononuclear inflammatory infiltrates[40–42] (Fig. 5-21). Spherical membrane-bound viral particles have been found in the cytoplasm of endothelial cells by electron microscopy.

Fungal Infection

Pneumocystis jiroveci (previously known as *Pneumocystis carinii*) is the most common fungus to cause DAD.[43–45] The histopathology of *Pneumocystis* infection in the setting of profound immunodeficiency is one of frothy intra-alveolar exudates (Fig. 5-22A) (so-called "alveolar casts"), with many organisms[44,45] (see Fig. 5-22B). In the mildly immunocompromised patient, however, this feature is not observed, or the pathologic changes may be subtle. In such cases, several "atypical" manifestations have been described.[43,45,46] DAD is the most dramatic of these atypical presentations (Fig. 5-23A), with the organisms present within hyaline membranes (see Fig. 5-23B) and in isolated intra-alveolar fibrin deposits.[46] The Grocott methenamine silver method (GMS) is routinely used to stain the organisms, which typically are seen in small groups and clusters (see Figs. 5-22B and 5-23B).[43,45,46]

Bacterial Infection

Common bacterial pneumonias rarely cause DAD; however, this lung injury pattern has been described in legionnaires disease, *Mycoplasma* pneumonia, and rickettsial infection.[47–51]

Legionella is a fastidious gram-negative bacillus that causes acute respiratory infection in elderly and immunodeficient individuals.[47,48,51] The histopathologic pattern is that of a pyogenic necrotizing bronchopneumonia (Fig. 5-24A) affecting the respiratory bronchioles, alveolar ducts, and adjacent alveolar spaces. DAD is common.[47,48,51] The rod-shaped organisms (see Fig. 5-24B) can be identified by Dieterle silver stain.[51]

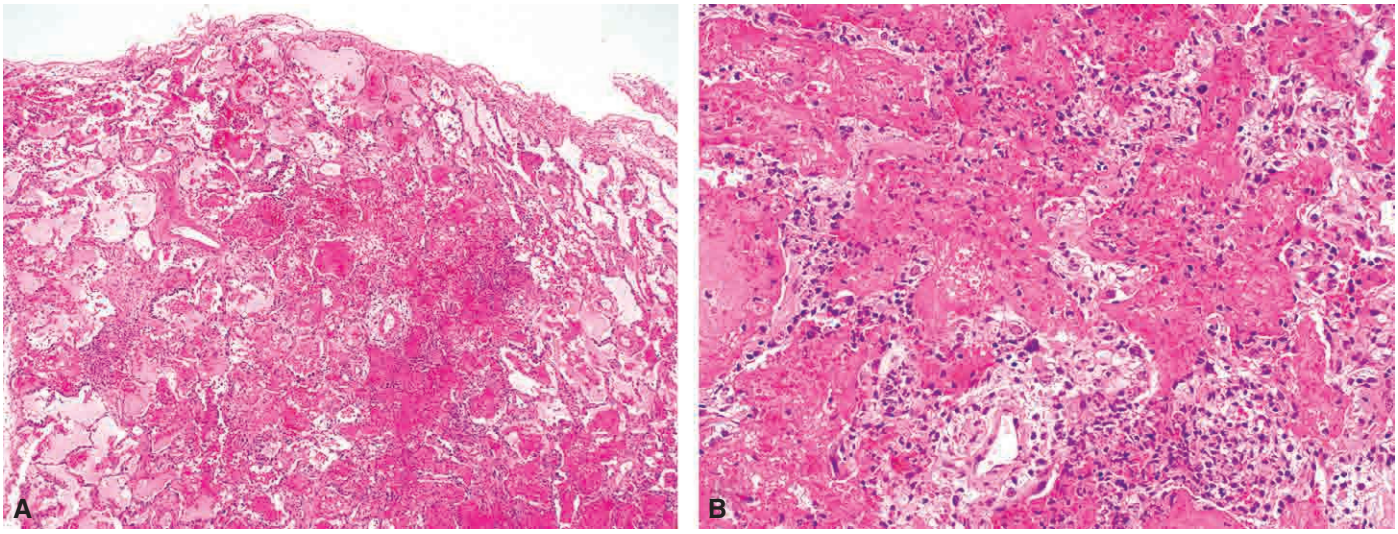

Figure 5-17. Diffuse alveolar damage in herpes simplex pneumonia. Herpesviridae viruses are capable of producing nodular necrotizing pneumonia (see Chapter 6). **A,** The nodular appearance of lung involved by herpes simplex pneumonia is evident, with zonal areas of hemorrhage and necrosis. **B,** A higher-magnification view of the hemorrhagic and necrotizing pneumonia.

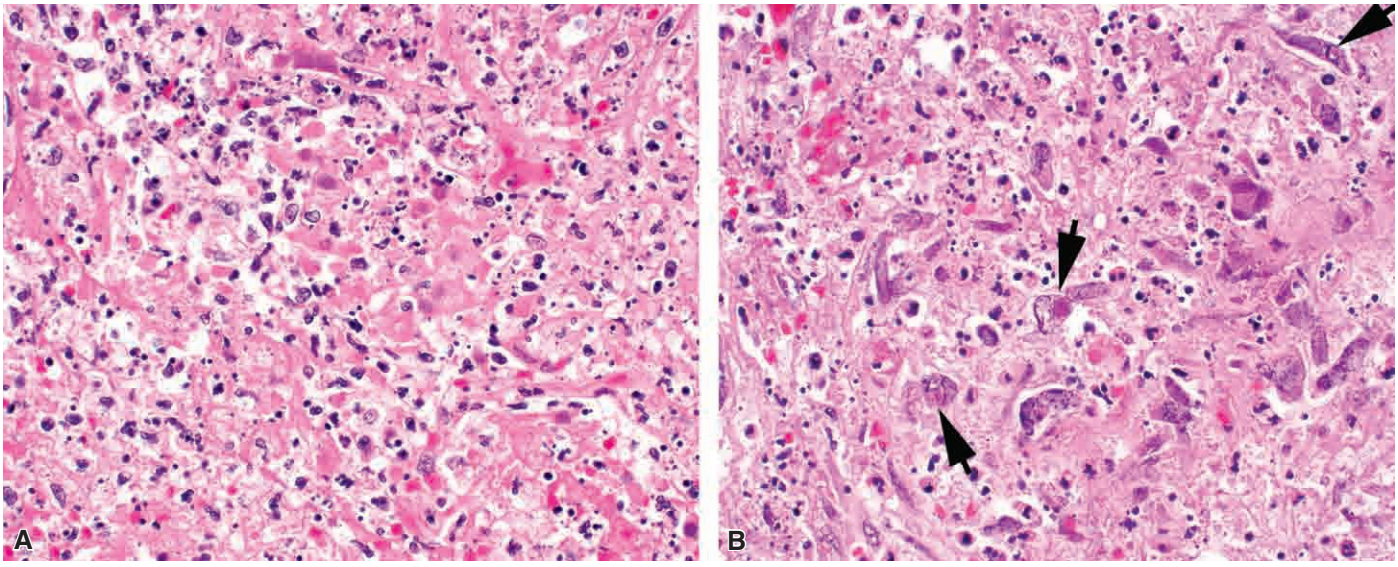

Figure 5-18. Herpes simplex pneumonia: inclusions. **A,** Diffuse alveolar damage associated with herpes simplex pneumonia. **B,** The viral cytopathic effects on bronchial and alveolar epithelium. The classic Cowdry A intranuclear inclusions (*arrows*) usually are easy to find, compared with the basophilic, smudged or ground-glass Cowdry B nuclear inclusions.

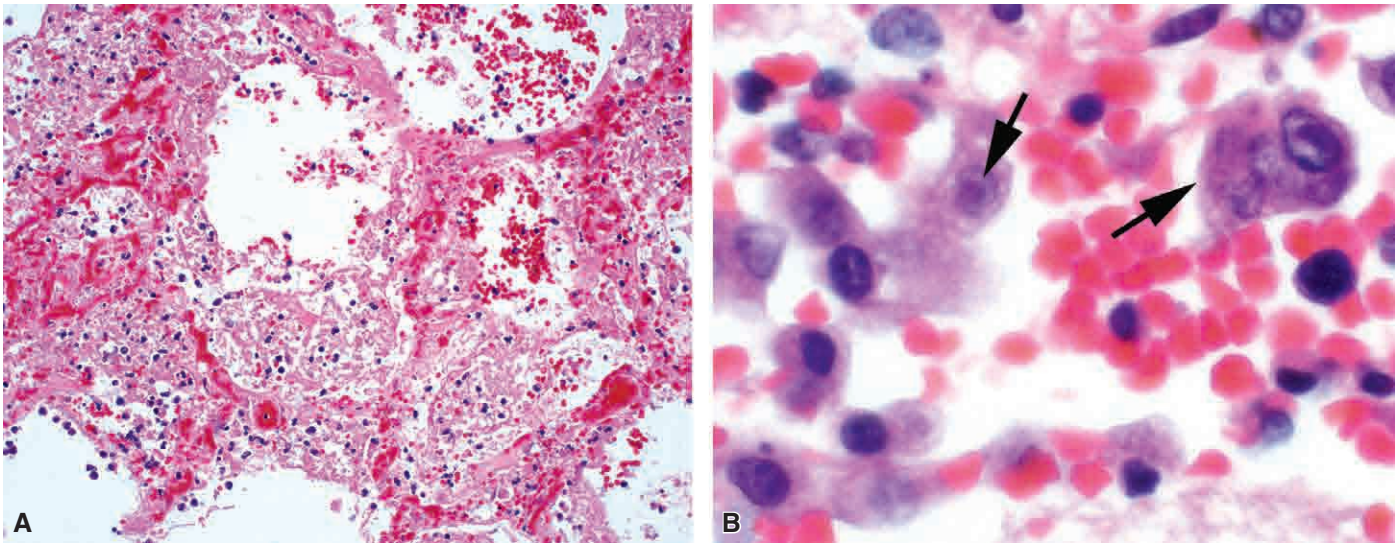

Figure 5-19. Diffuse alveolar damage (DAD) in varicella-zoster. The inclusions are similar to those produced by herpes simplex. **A,** Fibrinous DAD with neutrophils in air spaces in a case of chickenpox pneumonia. **B,** Rare intranuclear eosinophilic inclusions (*arrows*) are identifiable.

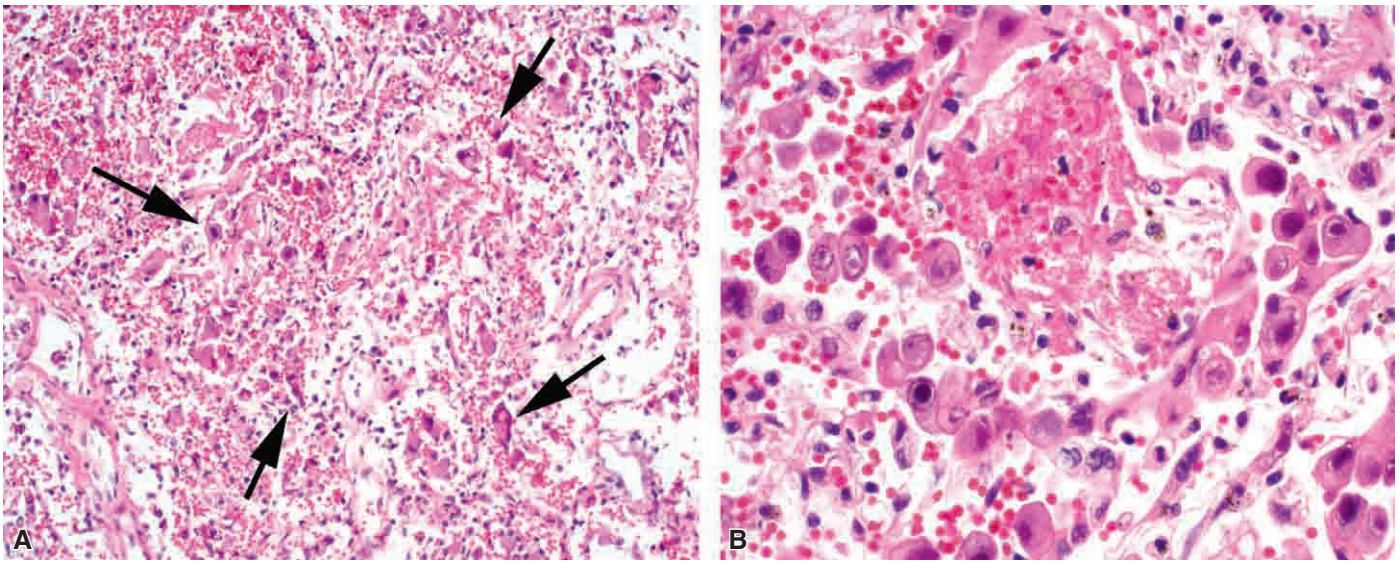

Figure 5-20. Diffuse alveolar damage (DAD) in cytomegalovirus (CMV) pneumonia. DAD from CMV infection can be quite dramatic in the immunocompromised host. **A,** DAD with numerous CMV cells evident at scanning magnification (*arrows*). **B,** CMV-infected cells at higher magnification. Prominent intranuclear inclusions are evident.

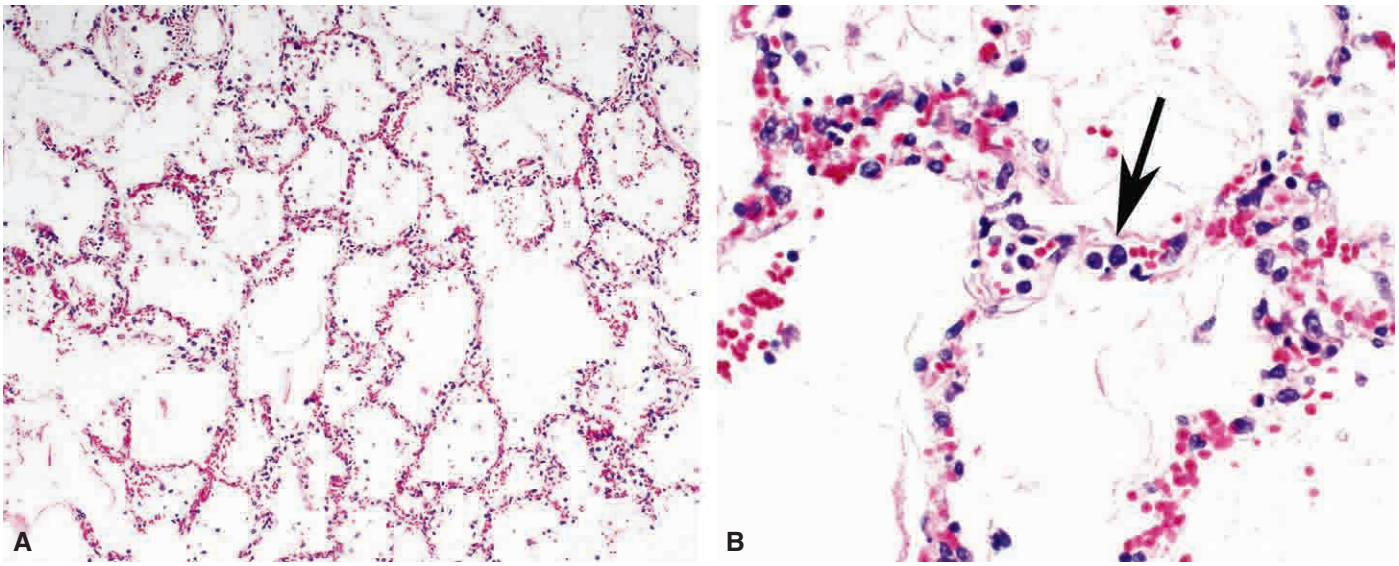

Figure 5-21. Diffuse alveolar damage in hantavirus pneumonia. Hantavirus pneumonia is characterized by alveolar edema, hyaline membranes (**A**), and scattered atypical interstitial mononuclear cells (**B,** *arrow*).

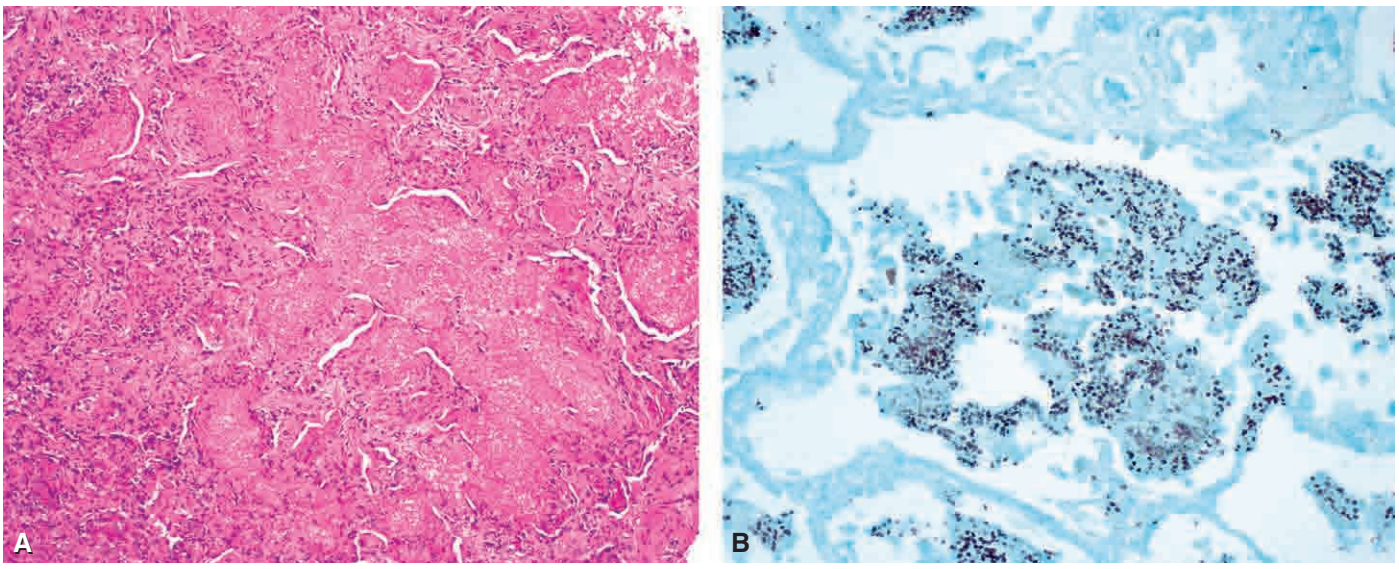

Figure 5-22. Diffuse alveolar damage in *Pneumocystis* pneumonia. **A,** The frothy "alveolar casts" characteristic of *Pneumocystis* pneumonia in the profoundly immunocompromised host (classically, the patient with AIDS or human immunodeficiency virus infection). **B,** Numerous silver-stained organisms are evident within these eosinophilic exudates (methenamine silver stain).

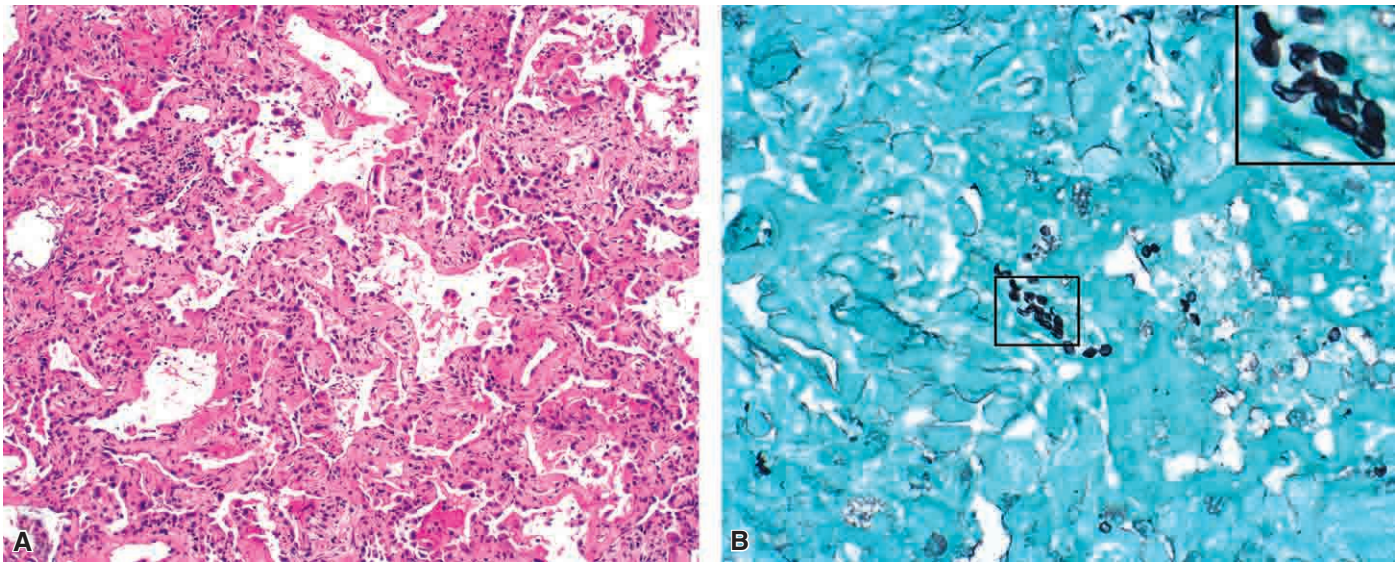

Figure 5-23. Diffuse alveolar damage in *Pneumocystis* pneumonia. **A,** Such diffuse damage also may occur in less severely immunocompromised patients. **B,** In such patients, few organisms may be identifiable by silver stains (methenamine silver stain). A colony of *Pneumocystis* organisms is shown in the *inset*.

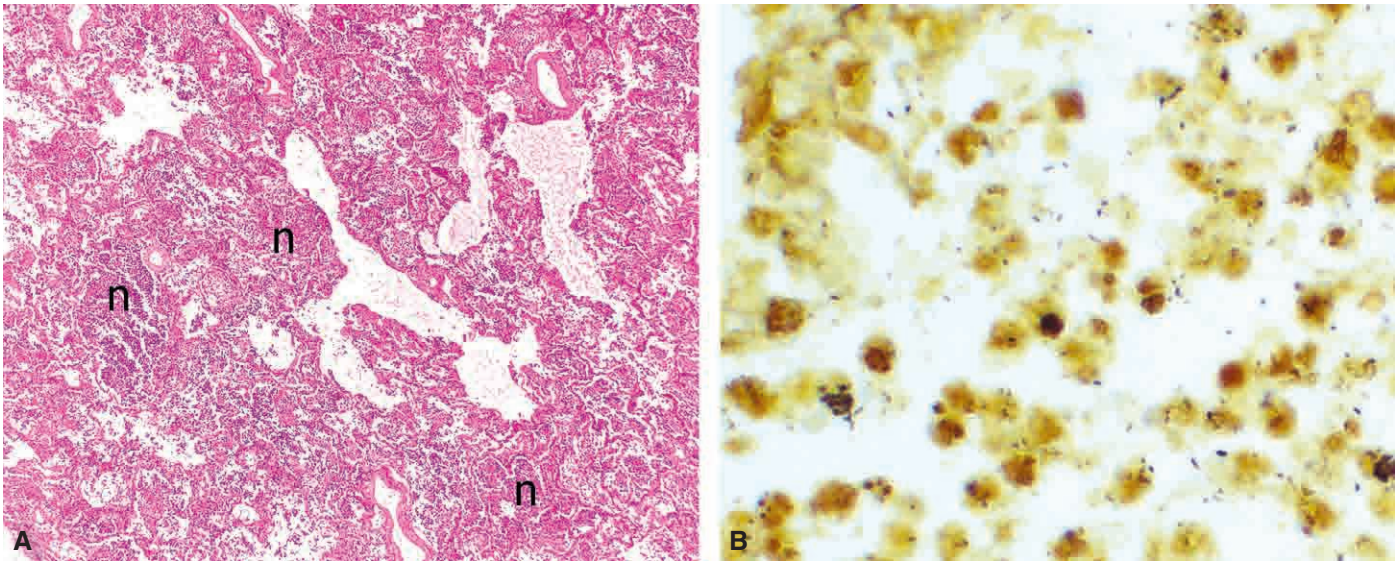

Figure 5-24. Diffuse alveolar damage in *Legionella* pneumonia. **A,** The diffuse alveolar injury caused by *Legionella* infection is prominently neutrophilic (n). **B,** Within these areas, a silver stain shows numerous rod-shaped stained organisms (Dieterle silver method).

Of note, in immunocompromised patients, any type of infection can cause DAD, with *Pneumocystis* pneumonia being the most common.[28] For this reason, it is essential to use special stains (acid-fast bacilli [AFB] stains or GMS or Warthin-Starry silver stain, and so on) on every lung biopsy specimen exhibiting DAD.

Collagen Vascular Diseases

Systemic collagen vascular disorders are a well-known cause of diffuse lung disease.[52–59] In some cases, lung involvement may be the first manifestation of the systemic disease, even without identifiable serologic evidence.[57] Acute lung injury has been reported to occur in the following collagen vascular diseases.

Systemic Lupus Erythematosus

Pulmonary involvement in SLE may manifest as pleural disease, acute or chronic diffuse inflammatory lung disease, airway disease, or vascular disease (vasculitis and thromboembolic lesions). Acute lupus pneumonitis (ALP) is a form of fulminant interstitial disease (Fig. 5-25A) with a high mortality rate.[52] Patients present with severe dyspnea, tachypnea, fever and arterial hypoxemia. ALP represents the first manifestation of SLE in approximately 50% of affected persons.[52,58] The most common histopathologic feature of this acute disease is DAD. Alveolar hemorrhage, with capillaritis and small-vessel vasculitis (see Fig. 5-25B), and pulmonary edema also may be observed.[52,57,60] Immunofluorescence studies demonstrate immune complexes in lung parenchyma, and both immune complexes and tubuloreticular inclusions may be seen on ultrastructural examination.[57,58,60]

Rheumatoid Arthritis

A significant percentage of patients with rheumatoid arthritis have lung disease.[53,54,61–64] Many different morphologic patterns of lung disease in rheumatoid arthritis have been described,[54,57,59] with the rheumatoid nodule being the most specific. Acute lung injury has been reported

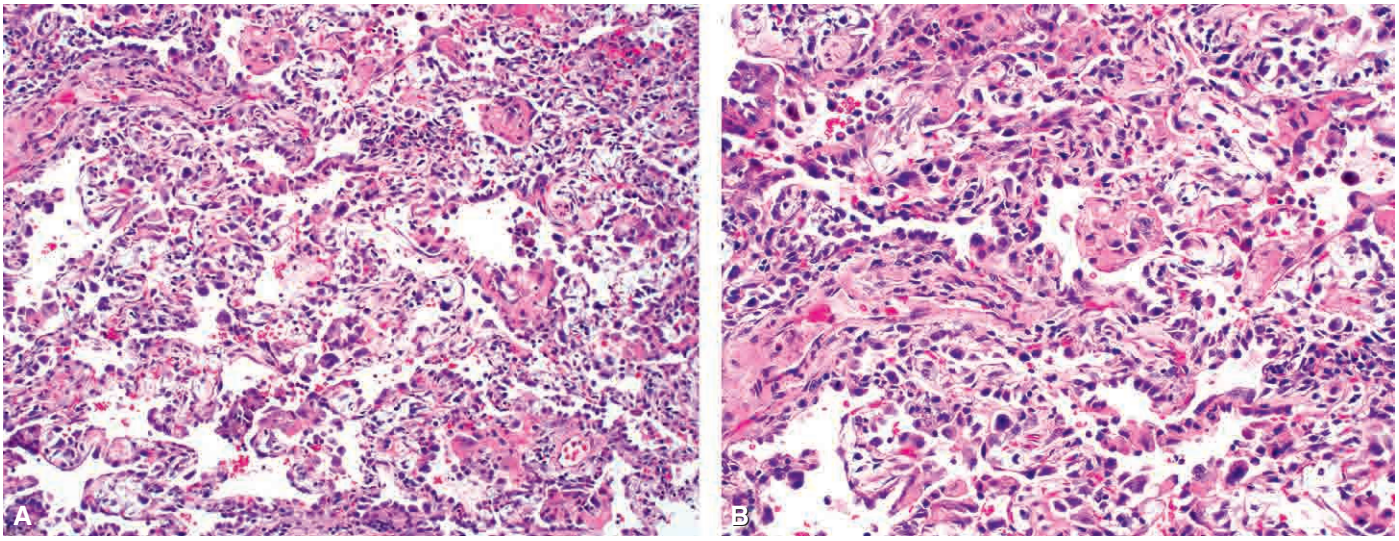

Figure 5-25. Diffuse alveolar damage (DAD) in systemic lupus erythematosus (SLE). The DAD associated with lupus may be quite hemorrhagic and associated with a "pneumonitis." Note the increased mononuclear cells within the alveolar interstitium in both parts **A** and **B**. Sometimes the alveolar hemorrhage of SLE may overlap with diffuse alveolar damage on morphologic grounds.

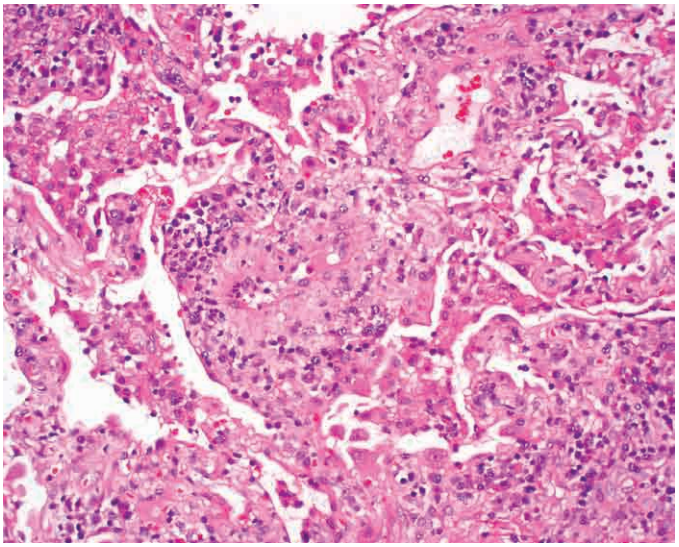

Figure 5-26. Diffuse alveolar damage (DAD) in rheumatoid arthritis. With DAD in rheumatoid arthritis, histopathologic hints of more chronic disease sometimes may be present, with lymphoplasmacellular infiltrates, chronic bronchiolitis, and chronic pleuritis. Here, a perivascular lymphoplasmacellular infiltrate is evident with surrounding air space fibrin and macrophages.

(Fig. 5-26), referred to as acute interstitial pneumonia in some publications[65] and as DAD in others.[54]

Polymyositis/Dermatomyositis

Polymyositis/dermatomyositis, a systemic connective tissue disorder, is well known to be associated with interstitial lung disease.[55,56] Three main clinical presentations are recognized: (1) acute fulminant respiratory distress resembling the so-called Hamman-Rich syndrome, (2) slowly progressive dyspnea, and (3) an asymptomatic form with abnormalities on radiologic and pulmonary function studies.[59] Three major histopathologic patterns have been observed: DAD (Fig. 5-27A), organizing pneumonia (see Fig. 5-27B), and chronic fibrosis (see Fig. 5-27C)—the so-called usual interstitial pneumonia (UIP) pattern.[66] The rapidly progressive clinical presentation is associated with a DAD histopathologic pattern on lung biopsy studies and carries the worst prognosis.[56]

DAD associated with *scleroderma* and *mixed connective disease* also has been described.[57,67]

Many patients with collagen vascular disease receive drug therapy during the course of their illness. A large number of drugs, including cytotoxic agents used for immunosuppression, are known to cause DAD. Also, as a desired result of therapy, patients may be immunosuppressed, making the exclusion of infection a high priority in the case of acute clinical lung disease.

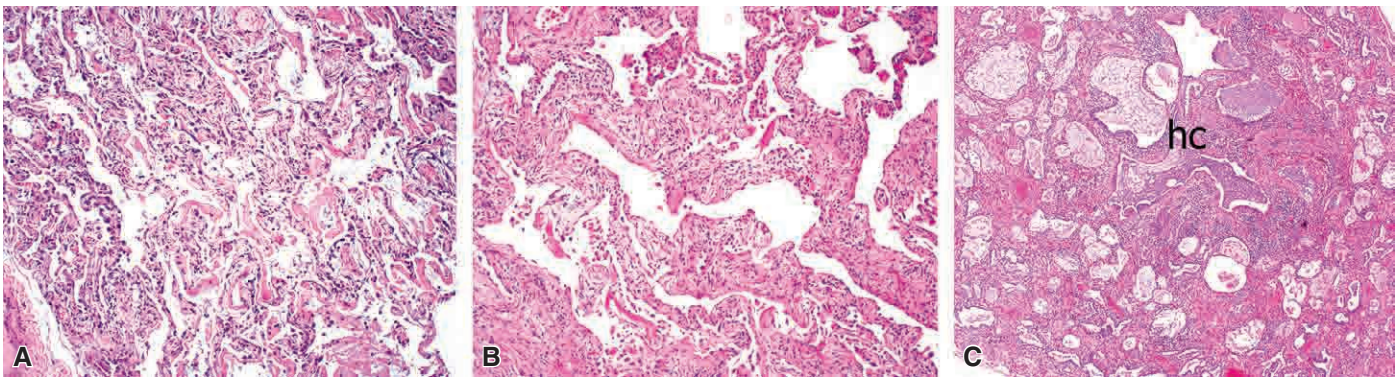

Figure 5-27. Diffuse alveolar damage (DAD) in polymyositis/dermatomyositis. All of the systemic connective tissue diseases can manifest with acute, subacute, and chronic lung disease. Three examples of diffuse lung disease accompanying polymyositis/dermatomyositis are presented: **A,** DAD; **B,** a subacute organizing pneumonia with an interstitial mononuclear infiltrate (nonspecific interstitial pneumonia [NSIP]-like; see Chapter 7); and **C,** a usual interstitial pneumonia (UIP)-like pattern of lung fibrosis with microscopic honeycomb remodeling (hc).

Drug Effect

Drugs can produce a wide range of pathologic effects with lung manifestations, and the causative agents are numerous.[68–81] The spectrum of drug-induced lung disease runs the entire gamut from DAD to fibrosis. Between these two extremes, subacute clinical manifestations may include organizing pneumonia, chronic interstitial pneumonia, eosinophilic pneumonia, obliterative bronchiolitis, pulmonary hemorrhage, pulmonary edema, pulmonary hypertension, veno-occlusive disease, and granulomatous interstitial pneumonia.[78,82,83]

DAD is a common and dramatic manifestation of pulmonary drug toxicity.[78] Many drugs are known to cause DAD.[82] A few of the more common ones are discussed next. (Drug-related lung disease is also discussed in Chapter 7.)

Chemotherapeutic Agents

DAD frequently is caused by cytotoxic drugs, and the commonly implicated ones include bleomycin (Fig. 5-28), busulfan (Fig. 5-29), and carmustine.[5,78,82] Patients usually present with dyspnea, cough, and diffuse pulmonary infiltrates.[84–88] The histologic pattern most commonly is one of nonspecific acute lung injury with hyaline membranes, but some changes may be present to at least suggest a causative agent. For example, the presence of acute lung injury with associated atypical type II pneumocytes with markedly enlarged pleomorphic nuclei[89] and prominent nucleoli (see Fig. 5-29) is characteristic for busulfan-induced pulmonary toxicity, and on ultrastructural examination, intranuclear tubular structures have been found in type II pneumocytes in association with administration of busulfan and bleomycin.[89–92] In most cases, the possibility that a drug is the cause of DAD can only be inferred from the clinical history. Considerations in the differential diagnosis typically include other treatment-related injury or complication of therapy (e.g., concomitant irradiation or infection). For example, oxygen therapy is a well-recognized cause of DAD (Fig. 5-30) and also may exacerbate bleomycin-induced lung injury.[93] Methotrexate (Fig. 5-31) is

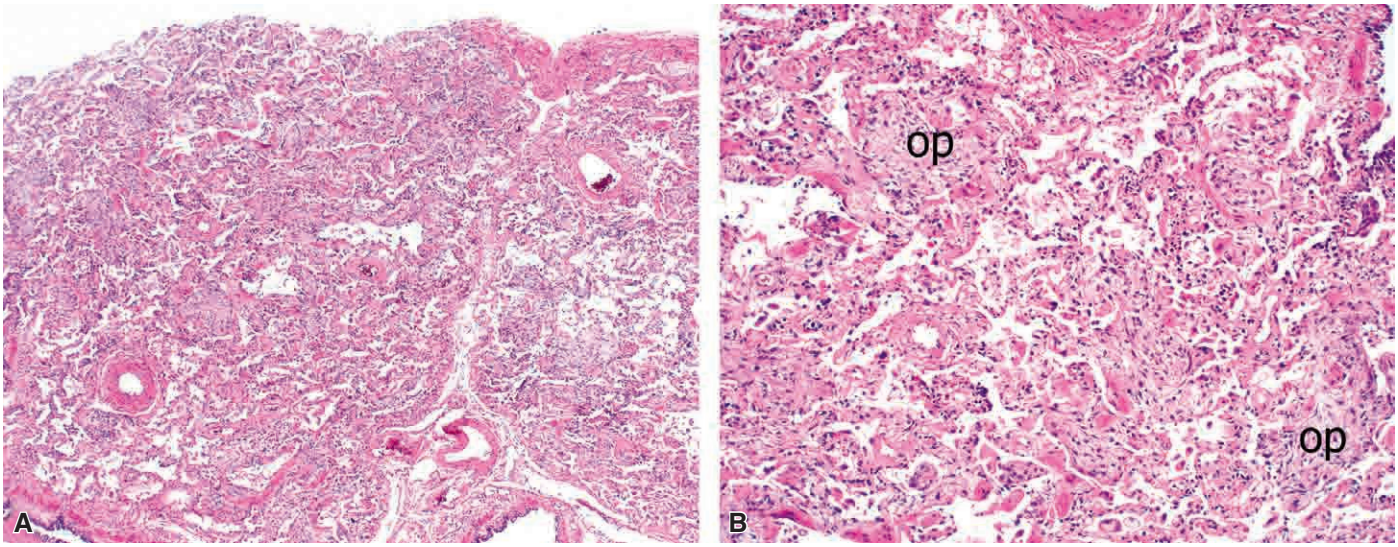

Figure 5-28. Diffuse alveolar damage from bleomycin toxicity. Bleomycin produces a characteristic lung injury in experimental animal models. Such damage has been observed to occur in humans as well (**A**), often typified by the presence of reactive type II cells and organizing pneumonia (op) (**B**).

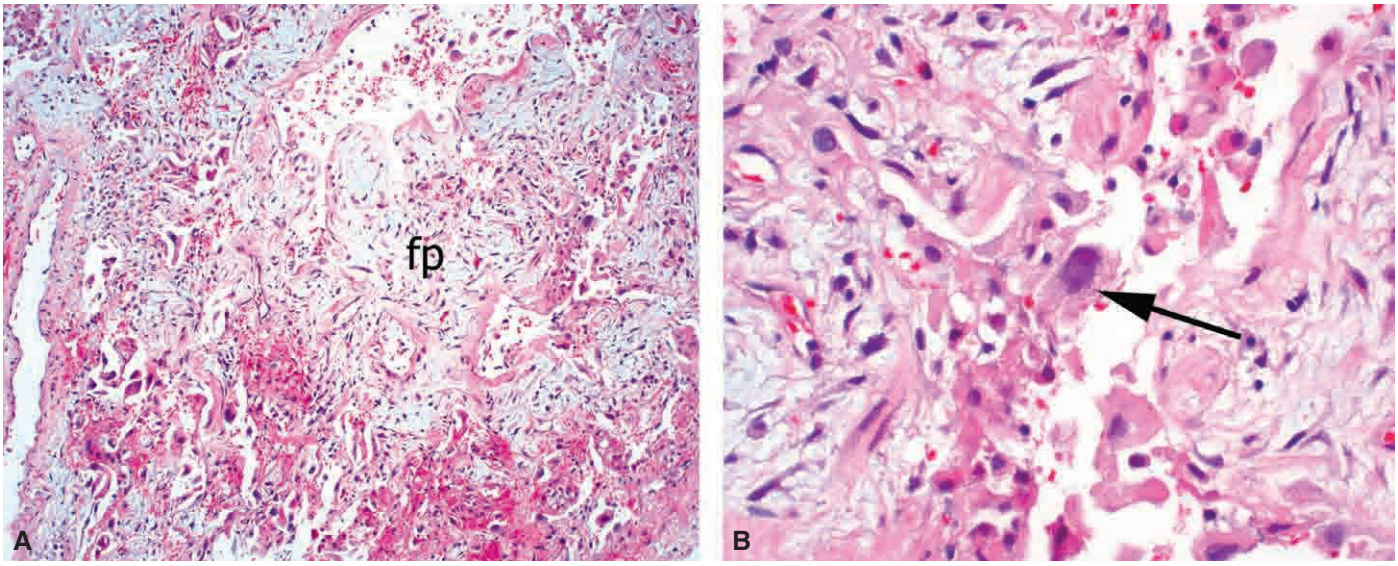

Figure 5-29. Diffuse alveolar damage from busulfan toxicity. Busulfan can produce diffuse injury characterized by the presence of prominently atypical type II cells. **A,** In this case, prominent interstitial organization with edematous fibroblastic proliferation is seen (fp), and hyaline membranes are evident. **B,** Reactive type II cells may appear alarmingly atypical (*arrow*).

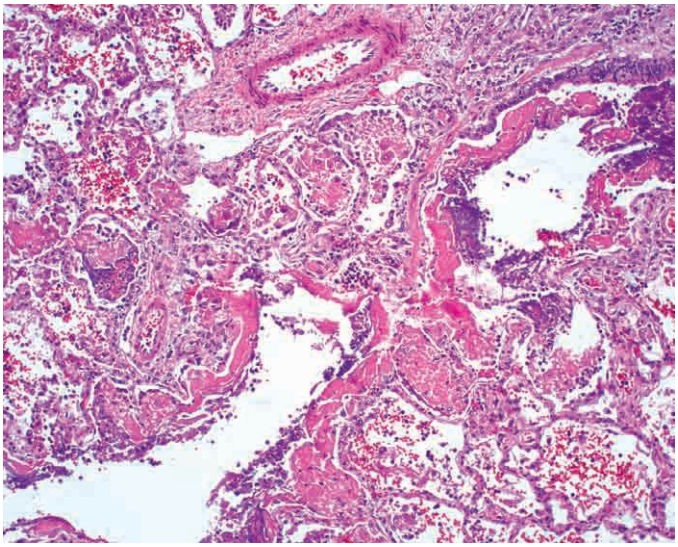

Figure 5-30. Diffuse alveolar damage from oxygen toxicity. Classic oxygen toxicity causes diffuse alveolar injury and necrosis of terminal airway epithelium, as illustrated in this photomicrograph.

another commonly used cytotoxic drug that can cause acute and organizing DAD.[94] Methotrexate also produces other distinctive patterns, such as granulomatous interstitial pneumonia (see Chapter 7) that is seldom seen in association with other commonly used chemotherapeutic agents. To complicate matters further, methotrexate also is used in the treatment of rheumatoid arthritis, a disease known to produce DAD independently as one of its pulmonary manifestations.[57,62]

Amiodarone

Amiodarone is a highly effective antiarrhythmic drug that is increasingly recognized as a cause of pulmonary toxicity.[77,95–99] Because patients taking amiodarone have known cardiac disease, the clinical presentation often is complicated, with several superimposed processes potentially affecting the lungs in various ways. Clinical and radiologic considerations typically include congestive heart failure, pulmonary emboli, and acute lung injury from other causes.[77,99]

Distinctive features may be present on chest CT scans.[77] The lung biopsy commonly shows acute and organizing lung injury (Fig. 5-32A). Other patterns include chronic interstitial pneumonitis with fibrosis and organizing pneumonia.[97] Characteristically, type II pneumocytes and alveolar macrophages show finely vacuolated cytoplasm in response to amiodarone therapy (see Fig. 5-32B), but these changes alone are not evidence of toxicity because they also may be seen in patients taking amiodarone who do not have evidence of lung toxicity.[95–98]

Anti-inflammatory Drugs

Methotrexate and gold, common agents for treatment of rheumatoid arthritis, are frequently implicated in lung toxicity. Methotrexate is discussed earlier in this chapter. Organizing DAD (Fig. 5-33) and chronic interstitial pneumonia are commonly described pulmonary manifestations of so-called gold toxicity.[74,76,100]

Acute Eosinophilic Pneumonia

Acute eosinophilic pneumonia was first described in 1989[101] and is characterized by acute respiratory failure, fever of days' to weeks' duration, diffuse pulmonary infiltrates on radiologic studies, and eosinophilia in bronchoalveolar lavage (BAL) fluid or lung biopsy specimens in the absence of infection, atopy, and asthma.[102] Peripheral eosinophilia frequently is described but is not a consistent finding at initial presentation.[103,104] Acute eosinophilic pneumonia is easily confused with acute interstitial pneumonia because both manifest as acute respiratory distress without an obvious underlying cause.[102] Histologically, the disease is characterized by acute and organizing lung injury showing classic features (Fig. 5-34) of (1) alveolar septal edema, (2) eosinophilic air space macrophages, (3) tissue and air space eosinophils in variable numbers, and (4) marked reactive atypia of alveolar type II cells. Intra-alveolar fibroblastic proliferation (patchy organizing pneumonia) and inflammatory cells are present to a variable degree. Hyaline membranes and organizing intra-alveolar fibrin also may be present (Fig. 5-35). The most significant feature is the presence of interstitial and alveolar eosinophils. Infiltration of small blood vessels by eosinophils also may be seen. It is important to

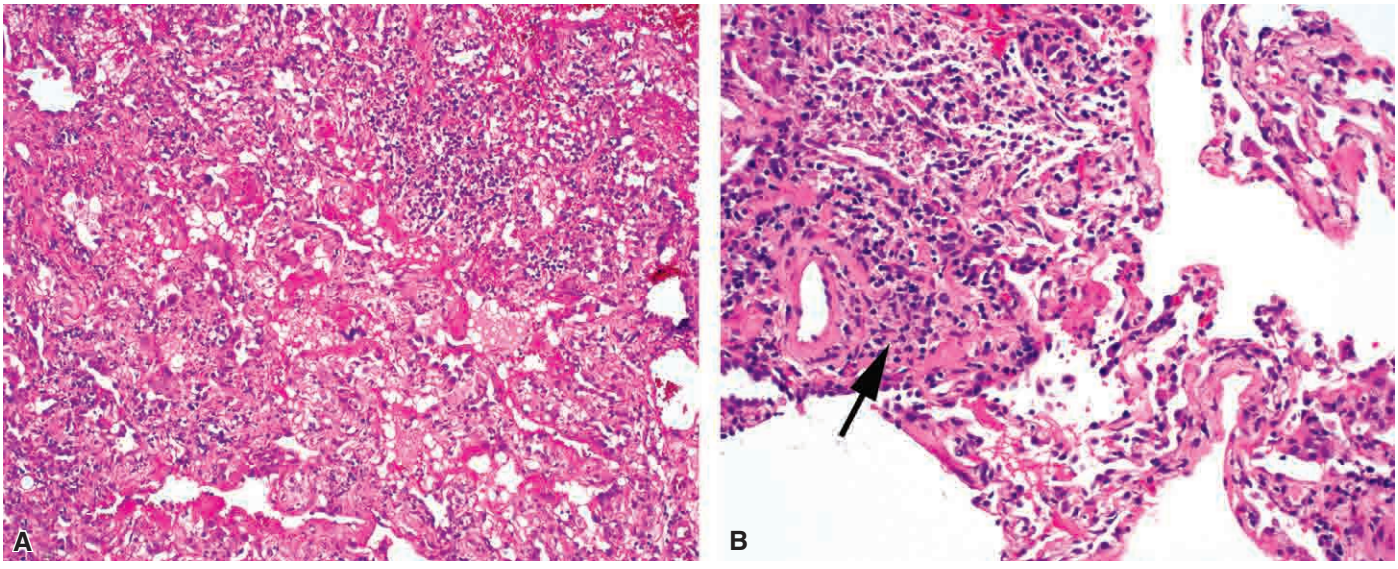

Figure 5-31. Diffuse alveolar damage (DAD) from methotrexate toxicity. **A** and **B,** Methotrexate produces small, poorly formed granulomas in subacute and chronic manifestations of lung toxicity. Early aggregations of macrophages may be seen resembling poorly formed granulomas in cases in which DAD is the manifestation of injury, but these are not required for the diagnosis (*arrow*).

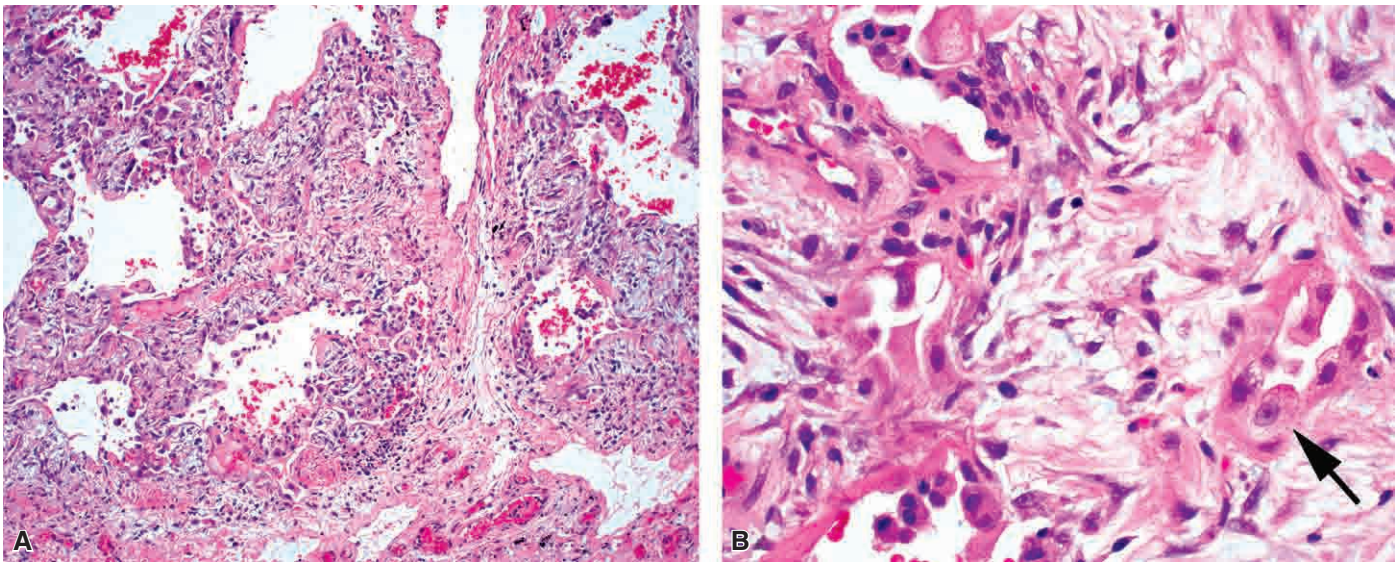

Figure 5-32. Diffuse alveolar damage from amiodarone toxicity. Amiodarone can produce acute, subacute, and chronic lung toxicity. **A,** Scanning magnification of amiodarone-induced diffuse alveolar injury. **B,** The finely vacuolated macrophages in type II cells are clearly evident (*arrow*).

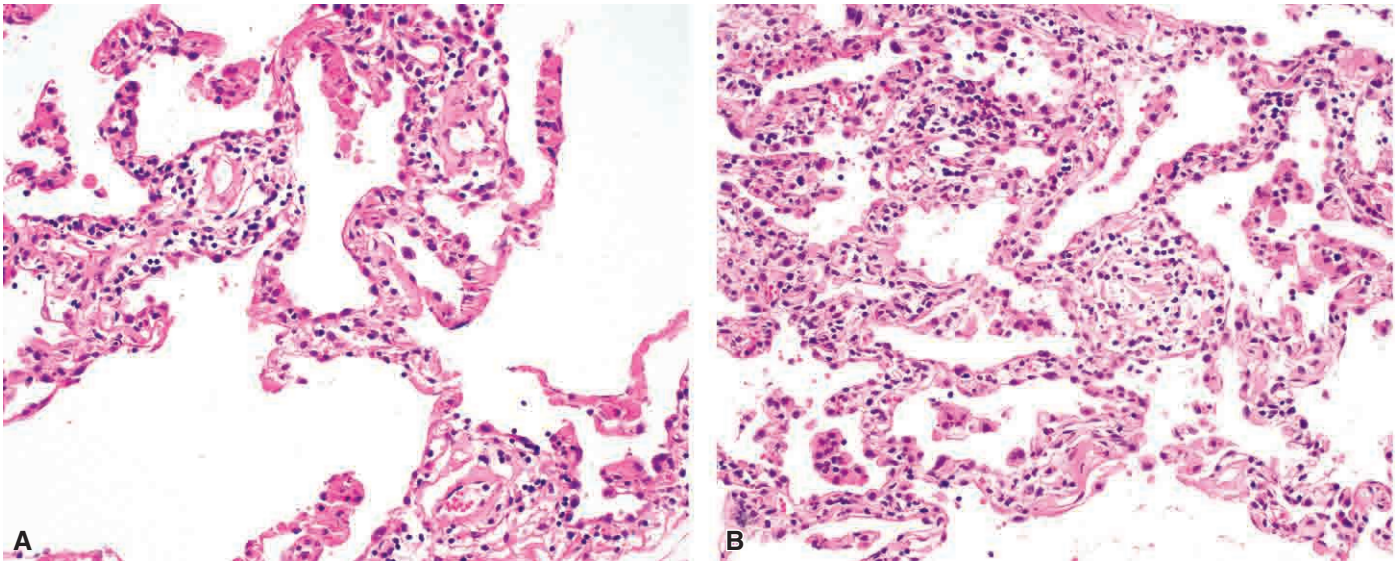

Figure 5-33. Diffuse alveolar damage from gold therapy toxicity. **A,** Gold therapy for rheumatoid arthritis may produce diffuse alveolar injury with hyaline membranes. **B,** A chronic or subacute cellular inflammatory process also has been described.

distinguish acute eosinophilic pneumonia from other causes of DAD, because patients typically benefit from systemic corticosteroid treatment, with prompt recovery. Before initiation of immunosuppressive therapy, however, infection should be rigorously excluded by culture and special stains, because parasitic and fungal infections also can manifest as tissue eosinophilia.

Acute Interstitial Pneumonia

Acute interstitial pneumonia, also commonly referred to as Hamman-Rich syndrome, is a fulminant lung disease of unknown etiology occurring in previously healthy patients.[105–107] Patients usually report a prodromal illness simulating viral infection of the upper respiratory tract, followed by rapidly progressive respiratory failure. The mortality rate is high, with death occurring weeks or months after the acute onset.[105,107] The classic histopathologic pattern is that of acute and organizing DAD,[105,107] with septal edema and hyaline membranes in the early phase and septal fibroblastic proliferation with reactive type II pneumocytes prominent in the organizing phase. In practice, a combination of acute and organizing changes (Fig. 5-36) often are seen in the lung at the time of biopsy.[108] A variable degree of air space organization, mononuclear inflammatory infiltrates, thrombi in small pulmonary arteries, and reparative peribronchiolar squamous metaplasia also are seen in most cases.

Because acute interstitial pneumonia is idiopathic, other specific causes of acute lung injury must be excluded before making this diagnosis. Considerations in the differential diagnosis include infection, collagen vascular disease, acute exacerbation of idiopathic pulmonary fibrosis (IPF), drug effect, and other causes of DAD.[108] Most cases of DAD are not acute interstitial pneumonia, and detailed clinical information, radiologic findings (localized versus diffuse disease), serologic data, and microbiologic results will often point to or rule out a specific etiologic condition. Use of special stains

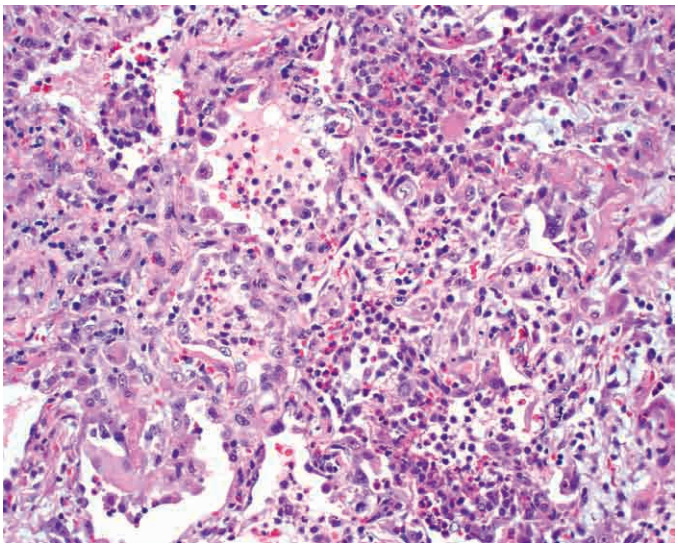

Figure 5-34. Acute eosinophilic pneumonia. The histopathologic changes seen in eosinophilic pneumonia are well known to most pathologists. Reactive type II cell hyperplasia in combination with the pesence of air space fibrin, eosinophilic air space macrophages, and scattered eosinophils yields a characteristic picture.

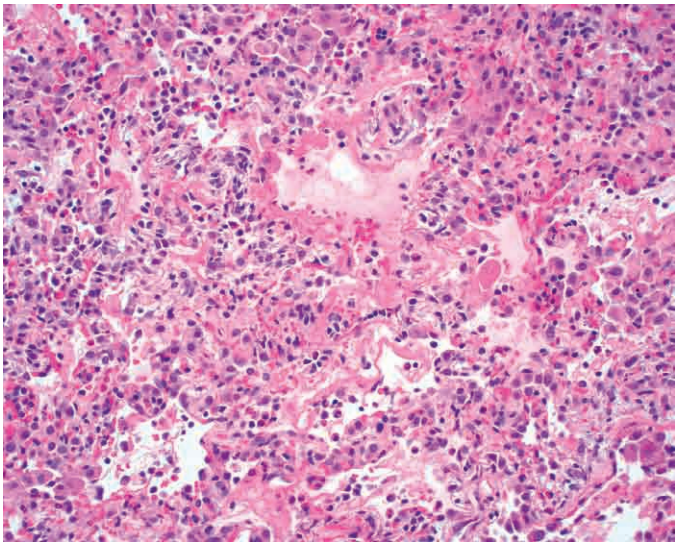

Figure 5-35. Diffuse alveolar damage (DAD) with acute eosinophilic pneumonia: hyaline membranes. Organization of hyaline membranes may occur in the acute lung injury of eosinophilic pneumonia. An awareness of this association is important, so that eosinophilic pneumonia is not overlooked as a potential cause of DAD with hyaline membranes.

applied to tissue sections or cytologic preparations (e.g., AFB, GMS or Warthin-Starry silver stain) also is essential to rule out infectious organisms in this setting.

Immunologically Mediated Pulmonary Hemorrhage and Vasculitis

So-called "pulmonary hemorrhage syndromes" may feature the histopathologic changes of acute lung injury,[109] in addition to the characteristic alveolar hemorrhage and hemosiderin-laden macrophages. In some patients, DAD may be the dominant histopathologic pattern.[110] In the study by Lombard and colleagues in patients with Goodpasture syndrome, all showed acute lung injury ranging in distribution from focal to diffuse lung involvement.[110] Histopathologic

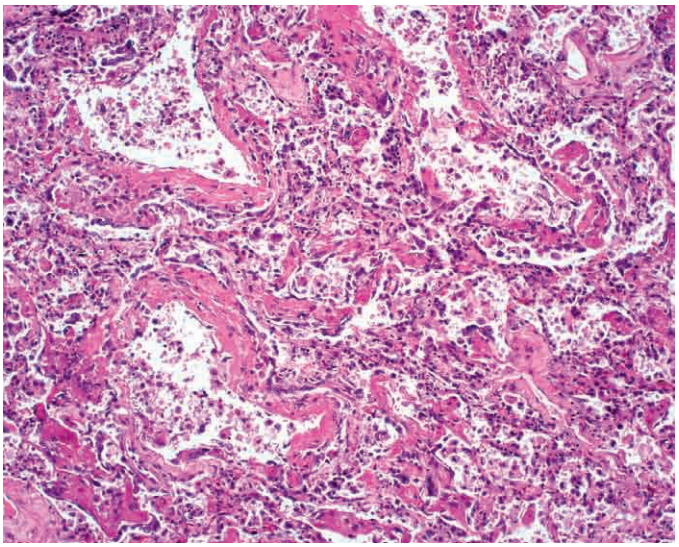

Figure 5-36. Acute interstitial pneumonia (AIP). Idiopathic AIP may take the form of every possible morphologic manifestation of acute respiratory distress syndrome, depending on the timing of biopsy relative to the onset of symptoms. Here, a classic pattern of diffuse alveolar damage (DAD) with hyaline membranes of variable cellularity is seen (midproliferative phase). Interstitial fibroblastic proliferation may be more or less prominent from case to case and should not serve as a qualifying morphologic finding for the diagnosis. AIP is nothing more than DAD of unknown causation.

examination demonstrated typical acute and organizing DAD, with widened and edematous alveolar septa, fibroblastic proliferation, reactive type II pneumocytes, and, rarely, even hyaline membranes (Fig. 5-37). Alveolar hemorrhage, either focal or diffuse, was present in all cases. Capillaritis, an important finding indicating true alveolar hemorrhage,[109] also was seen, as evidenced by marked septal neutrophilic infiltration. Capillaritis was absent in one case for which DAD was the dominant histopathologic pattern.

Microscopic polyangiitis can manifest as an acute interstitial pneumonia both clinically and histopathologically. Affected patients have vasculitis as the known cause of acute lung injury.[111] Alveolar hemorrhage with arteritis, capillaritis and venulitis may be seen in some cases.[111]

Polyarteritis nodosa and vasculitis associated with systemic connective tissue disease (notably systemic lupus erythematosus and rheumatoid arthritis) can also show acute lung injury with alveolar hemorrhage as the dominant histopathologic finding.[57,112]

Radiation Pneumonitis

Radiation can produce both acute and chronic damage to the lung, manifesting as acute radiation pneumonitis and chronic progressive fibrosis, respectively.[113] The effect is dependent on radiation dosage, total time of irradiation, and tissue volume irradiated. Concomitant chemotherapy and infections, which in themselves are causes of DAD, may potentiate the effect of radiation injury.[5,79,114,115] Acute radiation pneumonitis manifests 1 to 2 months after radiation therapy.[5,115] Clinical findings include dyspnea, cough, pleuritic pain, fever, and chest infiltrates. The lung biopsy specimen shows acute and organizing DAD.[113,115] Markedly atypical type II pneumocytes with enlarged hyperchromatic nuclei and vacuolated cytoplasm constitute a hallmark of the disease (Fig. 5-38A), and increased numbers of alveolar macrophages are seen. Foamy cells are present in the intima and media of pulmonary blood vessels in some cases, and thrombosis (see Fig. 5-38B), with or without transmural fibrinoid necrosis, is common.[79,116–118]

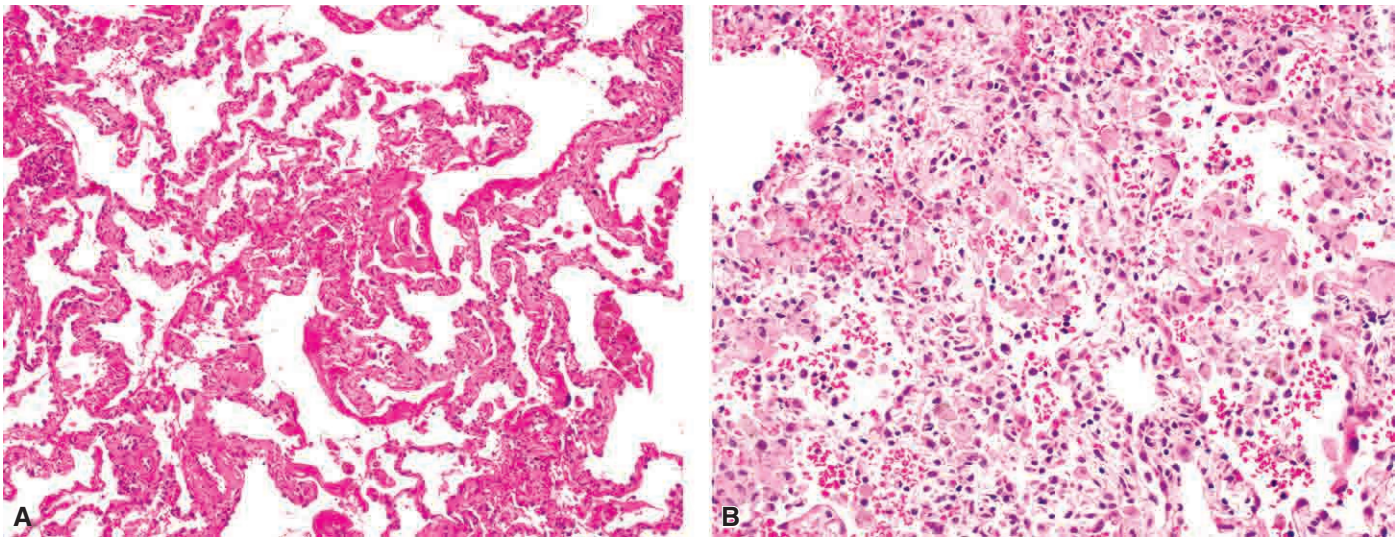

Figure 5-37. Diffuse alveolar damage (DAD) in Goodpasture syndrome. **A,** Goodpasture syndrome characteristically produces alveolar hemorrhage, but acute lung injury with hyaline membranes also can occur. **B,** In another example of DAD in Goodpasture syndrome, greater interstitial fibroblast proliferation is evident, along with more numerous air space macrophages.

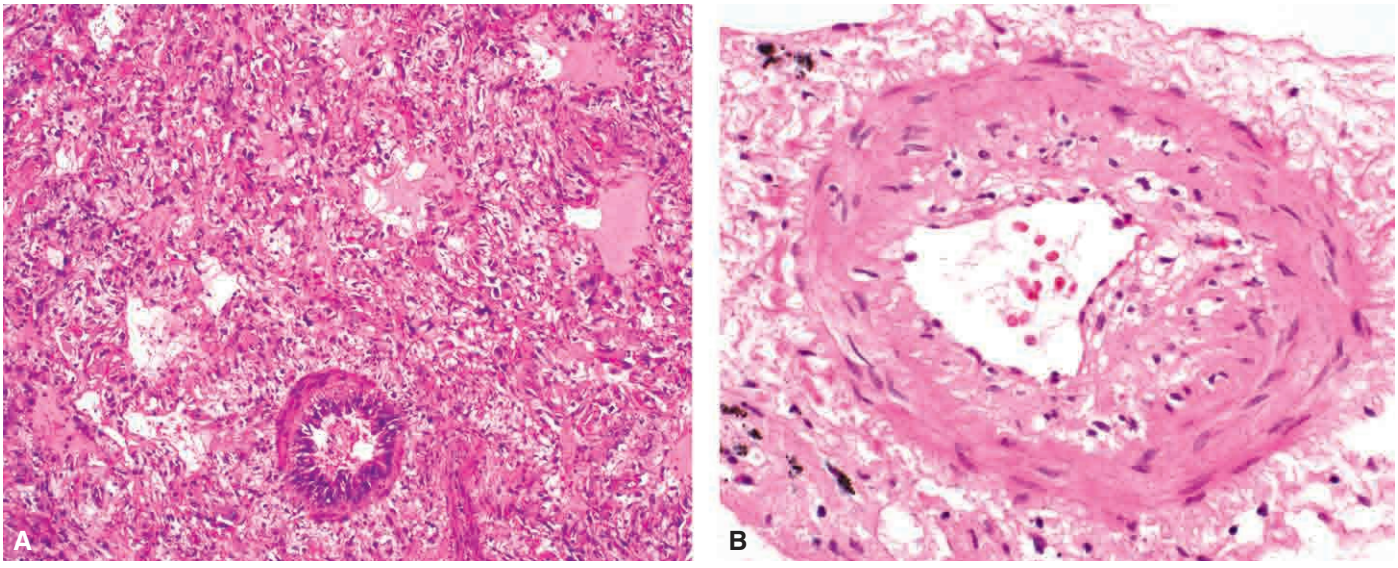

Figure 5-38. Diffuse alveolar damage (DAD) from radiation injury. **A,** Radiation injury to the lung can produce DAD with striking reactive type II cell hyperplasia. **B,** Foamy macrophages are present in the wall of a pulmonary artery involved in radiation pneumonitis.

Disease Presenting as Classic Acute Respiratory Distress Syndrome

By definition, ARDS must be associated with an identifiable inciting event. The histopathologic pattern is that of classic DAD. The histopathologic changes should be consistent with those expected for the time interval from the onset of clinical disease (see further on). In many cases, the ARDS may be caused by a combination of factors, each potentiating the other.[4] For the purposes of illustration, a few thoroughly studied causes are discussed next.

Oxygen Toxicity and Inhalants

Oxygen is a well-known cause of ARDS and a useful model for all types of DAD.[4,119,120] Oxygen toxicity also is important in that it is widely used in the care of patients, often in the setting of other injuries that can potentially cause ARDS, such as sepsis, shock, and trauma. Exposure to high concentrations of oxygen for prolonged periods can lead to characteristic pulmonary damage. In 1958, Pratt first noted pulmonary changes due to high concentrations of inspired oxygen.[121] In 1967, Nash and colleagues described the sequential histopathologic changes of this injury,[119] later reemphasized by Pratt.[120] In neonates receiving oxygen for hyaline membrane disease, bronchopulmonary dysplasia was reported to occur. [122] As might be expected, the features of hyaline membrane disease in neonates and oxygen-induced DAD in adults are indistinguishable (see Fig. 5-30). Other inhalants such as chlorine gas, mercury vapor, carbon dioxide in high concentrations, and nitrogen mustard all have been reported to cause ARDS.[2,4,5]

Shock and Trauma

Massive extrapulmonary trauma and shock first became recognized as causes of unexplained respiratory failure during the wars of the second half of the 20th century. A variety of names were assigned to this wartime condition, including shock lung, congestive atelectasis, traumatic wet lung, Da Nang lung, respiratory insufficiency syndrome, post-traumatic pulmonary insufficiency, and

progressive pulmonary consolidation.[2] It became clear that shock of any cause (e.g., hypovolemia due to hemorrhage, cardiogenic shock, sepsis), could cause ARDS, and that in most cases, a number of factors come into play. In the typical presentation, dyspnea of rapid onset is accompanied by development of diffuse chest infiltrates several hours to days after an episode of shock. Once ARDS begins, the mortality rate is high.[1,2,123]

Ingested Toxins

Paraquat is a potent herbicide that causes the release of hydrogen peroxide and superoxide free radicals, resulting in damage to cell membranes.[124–126] Oropharyngitis is the initial sign of poisoning, followed by impaired renal and liver function. Approximately 5 days later, ARDS develops. The histopathologic pattern in most cases is one of organizing DAD (Fig. 5-39). The diagnosis is confirmed by tissue analysis for paraquat, which can be performed even on autopsy specimens. Other ingested toxins (e.g., kerosene, rapeseed oil) also have been reported to cause ARDS.[5]

Additional Features in the Differential Diagnosis of Acute Lung Injury

Acute lung injury is a pathologic pattern and by itself is a nonspecific finding. The following additional features often help narrow the list of possible causes (summarized in Table 5-1).

Presence of hyaline membranes. The most commonly encountered potential etiologic disorders include infection, collagen vascular disease, drug toxicity, and an idiopathic form (i.e., acute interstitial pneumonia).[2,5]

Presence of neutrophils. The presence of neutrophils in lung alveolar spaces should always raise the possibility of infection.[115,127] For example, legionnaires disease characteristically is associated with acute bronchopneumonia with DAD.[51]

Presence of frothy exudates. The presence of frothy exudates in alveolar spaces is a classic feature of *Pneumocystis* pneumonia. However, this feature is not always present. In some cases, especially in mildly immunocompromised patients, DAD may be the only finding.[46]

Presence of necrosis. Among the infectious causes of DAD, viral infection figures prominently. Influenzavirus, herpes simplex virus, varicella-zoster virus, and adenovirus infections are well known to produce DAD,[29,31,34–36] and all of these viral infections typically are accompanied by necrosis. *Legionella* and *Pneumocystis* infections also can produce acute lung injury with necrosis.[46,51,128]

Presence of eosinophils. Acute and organizing DAD with prominent interstitial and alveolar eosinophils is characteristic of acute eosinophilic pneumonia.[102] However, if the patient has been treated with

Table 5-1. Key Histopathologic Findings in Acute Lung Injury, with Possible Causes

Finding	Possible Causes
Hyaline membranes	Infection, collagen vascular disease, drug toxicity, oxygen and inhalant toxicity, idiopathic (acute interstitial pneumonia); acute exacerbation of idiopathic pulmonary fibrosis (characteristic associated findings: background fibrosis and microscopic honeycombing)
Neutrophils and fibrinous exudates	Infection (viral, fungal, bacterial), alveolar hemorrhage
Diffuse alveolar hemorrhage (with or without capillaritis and small-vessel vasculitis)	Collagen vascular diseases (SLE, RA, MCTD, polymyositis/dermatomyositis, scleroderma), Goodpasture syndrome, microscopic polyangiitis, Wegener granulomatosis (organizing pneumonia—capillaritis variant)
Organizing pneumonia (alveolar organization)	Resolving infection, drug toxicity, collagen vascular diseases, idiopathic (cryptogenic organizing pneumonia); acute exacerbation of idiopathic pulmonary fibrosis
Fibrin and organization	Infection, drug toxicity, idiopathic (acute fibrinous and organizing pneumonitis), collagen vascular diseases; acute exacerbation of idiopathic pulmonary fibrosis
Alveolar eosinophils with fibrin	Infection, collagen vascular disease, drug toxicity; idiopathic acute eosinophilic pneumonia
Necrosis	Infection and infarction
Atypical cells	Infection (especially viral), radiation pneumonitis, chemotherapy-related changes (and effects of other drugs)
Foamy alveolar cells	Amiodarone and other drug toxicity, radiation pneumonitis

MCTD, mixed connective tissue disease; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

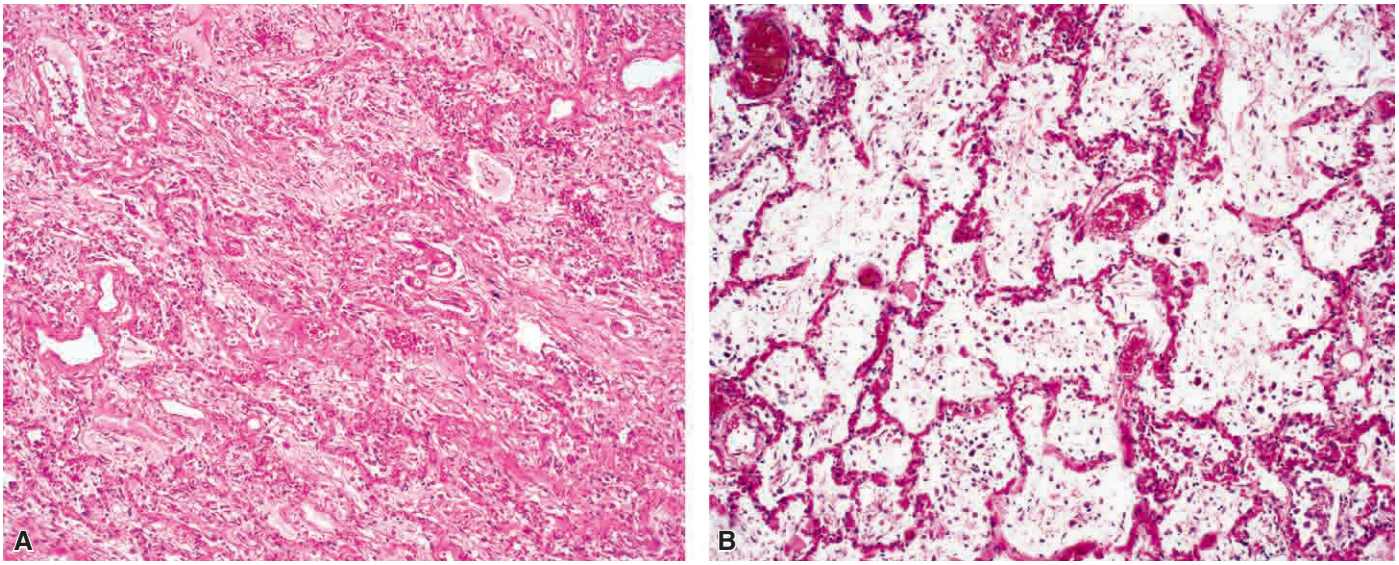

Figure 5-39. Diffuse alveolar damage from paraquat poisoning. Paraquat produces a dramatic and characteristic pattern of lung injury with prominent air space fibroplasia (**A**) and eventual fibrosis with collagen deposition in a loose pattern (**B**).

steroid before biopsy, very few eosinophils may remain, and the diagnosis may be difficult or impossible.

Presence of siderophages and capillaritis. Hemosiderin-laden macrophages with or without capillaritis in the setting of acute lung injury should raise consideration of immunologically mediated pulmonary hemorrhage.[109] Care must be taken not to interpret the pigmented macrophages seen in the lungs of cigarette smokers as evidence of hemorrhage.[129] The hemosiderin in macrophages related to true hemorrhage in the lung (from any cause) is globular, often slightly refractile, and golden-brown in color.[57,109–111]

Presence of atypical cells. Viral infections often produce cytopathic effects, including intracellular inclusions (see Chapter 6). Examples of intracellular inclusions are the Cowdry A and B inclusions seen in herpesvirus infection, cytomegaly with intranuclear and intracytoplasmic inclusions of cytomegalovirus, the multinucleated giant cells of measles virus and respiratory syncytial virus, and the smudged cells of adenovirus infection.[33,37,38,130,131] Chemotherapeutic drugs such as busulfan and bleomycin often are associated with markedly atypical type II pneumocytes, which may have enlarged pleomorphic nuclei and prominent nucleoli.[90,91] Markedly atypical type II pneumocytes that may be suggestive of a viropathic effect also are seen in radiation pneumonitis.[79,117,118]

Presence of foamy cells. Alveolar lining cells with vacuolated cytoplasm accompanied by intra-alveolar foamy macrophages are characteristic features seen in patients taking amiodarone, and amiodarone toxicity may lead to acute lung injury changes.[95–97,99] In some cases of radiation pneumonitis, foam cells are seen in the intima and media of blood vessels.[79,118]

Presence of advanced interstitial fibrosis. Clinical idiopathic pulmonary fibrosis is associated with the changes of UIP on pathologic examination (see Chapter 7), with advanced lung remodeling. Of interest, idiopathic pulmonary fibrosis undergoes episodic exacerbation, and on occasion such exacerbation may be overwhelming, with resultant DAD.[132] It is prudent to examine lung biopsy sections for the presence of dense fibrosis with structural remodeling (microscopic honeycombing) in cases of DAD, to identify the rare case of idiopathic pulmonary fibrosis that manifests for the first time as an acute episode of "exacerbation."

Clinicopathologic Correlation

Because the morphologic manifestations of acute diffuse lung disease may be relatively stereotypical, clinicopathologic correlation is often helpful in arriving at a specific diagnosis. A summary of the more important history and laboratory data pertinent to this correlation is presented in Box 5-3.

Box 5-3. Essential Information for Determining the Underlying Cause of Acute Lung Injury

- Immune status
- Acuity of onset
- Radiologic distribution and character of abnormalities
- History of inciting event (e.g., shock)
- History of lung disease (e.g., "usual interstitial pneumonia" with current acute exacerbation)
- History of systemic disease (e.g., connective tissue disease, heart disease)
- History of medication use or drug abuse
- History of other recent treatment (e.g., radiotherapy for malignancy)
- Results of serologic studies: erythrocyte sedimentation rate determination, assays for autoimmune antibodies (e.g., ANA, RF, ANCA, Scl-70, Jo-1)
- Results of microbiology studies

ANA, antinuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; RF, rheumatoid factor.

One of the first questions to be addressed is whether or not a known inciting event was identified clinically (i.e., Is this ARDS?). Next, the results of any sampling procedures to identify infection should be checked, along with application of special stains to the tissue sections, to exclude infection. Finally, data regarding related disease, such as infection, autoimmune disease, underlying lung disease, are needed. For example, if the patient is immunosuppressed, infection should always be the leading consideration in the differential diagnosis. Another point to keep in mind is that patients with certain diseases may be taking medications with the potential to cause DAD (e.g., amiodarone for cardiac arrhythmia). Moreover, laboratory studies may reveal antibodies related to connective tissue disease (e.g., antineutrophil antibody [ANA], rheumatoid factor [RF], Jo-1, Scl-70, anti-fibrillarin, anti-Mpp10, SS-A, SS-B).

Regarding the pathologist's role and responsibility in biopsy cases of acute lung injury, use of special stains for organisms (at a minimum, methenamine silver and acid-fast stains) is indicated. Additional stains (auramine-rhodamine, Dieterle or Warthin-Starry silver stain, immunohistochemical stains for specific organisms, or molecular probes) may be used, especially in patients known to be immunocompromised from any cause.

Self-assessment questions related to this chapter can be found online on the Expert Consult site for this title.

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