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Acute Lung Injury

Oi-Yee Cheung, MD, Paolo Graziano, MD, and Maxwell L. Smith, MD

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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 et al. 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 Nowadays this sequence of clinical events is referred to as *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 meta-regression analysis performed by Zamboni and Vincent⁶ of mortality rates from 72 published studies of ARDS identified a decrease of 1.1% per year for the period 1994–2006, 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*.

In 2012 ARDS was redefined according to the Berlin definition. *Acute lung injury*, which formerly encompassed the non-ARDS acute lung injury in the AECC definition, was abolished. ARDS was divided into three categories based on degree of hypoxemia: mild, moderate, and severe with increased mortality, respectively.⁸

The acute lung injury in this chapter refers to the histologic changes seen in acutely injured lung parenchyma and does not intend to represent the clinical entity.

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. Polyps of fibroblastic tissue in the airspace (organizing pneumonia) are part of the histologic spectrum seen in the progression of acute lung injury. However, organizing pneumonia of unknown etiology (cryptogenic organizing pneumonia, previously known as idiopathic bronchiolitis obliterans organizing pneumonia)⁹ typically shows pure organizing pneumonia without other histologic features of acute injury. The clinical syndrome of cryptogenic organizing pneumonia presents subacutely over weeks to months and is discussed with the chronic diffuse diseases (see Chapter 8). DAD and other histologic features of acute lung injury are nonspecific as to etiology and, after being identified, require the pathologist to search the biopsy for further features that may help to identify a specific etiology.

Diffuse Alveolar Damage: The Morphologic Prototype of Acute Lung Injury

The causes of acute lung injury are numerous (Box 6.1). The lung reacts to various types of insults in similar ways, regardless of etiology. The

Box 6.1 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, influenza virus, herpesvirus, CMV, and hantavirus infections; severe acute respiratory syndrome; 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
- Connective tissue disease
 - Systemic lupus erythematosus
 - Rheumatoid arthritis
 - Polymyositis/dermatomyositis
 - Scleroderma
 - Mixed connective disease
- Pulmonary hemorrhage syndrome and vasculitis
- Goodpasture syndrome
- Microscopic polyangiitis
- Polyarteritis nodosa
- Granulomatosis with polyangiitis
- Vasculitis associated with collagen vascular disease
- Ingestants
 - Paraquat
 - Kerosene
 - Denatured rapeseed oil
- Inhalants
 - Oxygen
 - 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, including via radiation-impregnated embolization beads
 - 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
 - Postlymphangiography
 - 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.

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.^{4,10} 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. 6.1)—an early exudative (acute) phase (Fig. 6.2A and B), a subacute proliferative (organizing) phase (Fig. 6.2C), and a late fibrotic phase (Fig. 6.3).^{2,4,5,9,11} The exudative phase is most prominent in the first week of injury. The earliest changes include interstitial and intraalveolar edema with variable amounts of hemorrhage and fibrin deposition (Fig. 6.4). Hyaline membranes (Fig. 6.5), the histologic hallmark of the exudative phase of ARDS, are most prominent at 3 to 7 days after injury (eSlide 6.1). Minimal interstitial mononuclear inflammatory infiltrates (Fig. 6.6) and fibrin thrombi in small pulmonary arteries (Fig. 6.7) also are seen. Type II pneumocyte hyperplasia (Fig. 6.8) 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. 6.9). 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. 6.10). The fibrosis consists of loose aggregates of fibroblasts admixed with scattered inflammatory cells, reminiscent of organizing pneumonia

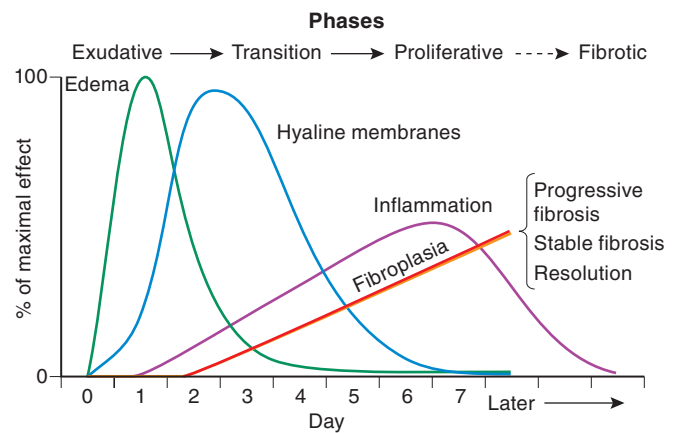


Figure 6.1 Acute respiratory distress syndrome (ARDS) timeline. The phases of ARDS are reproducible and reflect the global mechanisms of wound repair (exudation, proliferation, variable fibrogenesis). The indefinite relationship between proliferation and fibrogenesis is depicted as a *hashed line* in 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.)

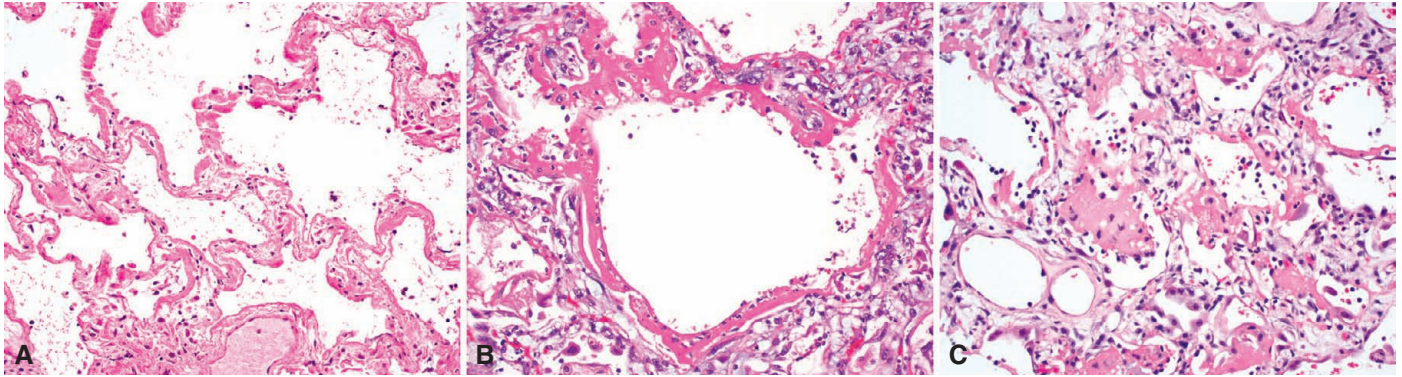


Figure 6.2 Acute respiratory distress syndrome (ARDS): exudative and proliferative phases. The early exudative phase of ARDS, characterized by some edema, cellular debris, and early hyaline membrane formation (A), evolves to include well-defined hyaline membranes (B). Note the increased cellularity in 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 airspace cellularity.

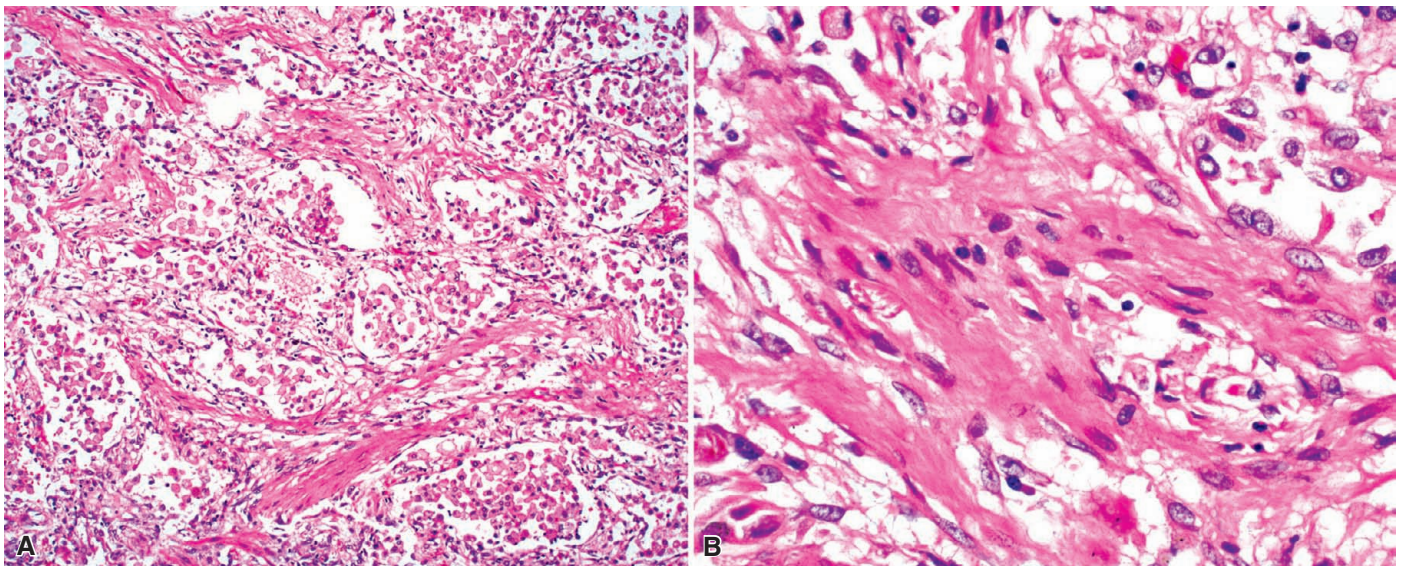


Figure 6.3 Acute respiratory distress syndrome (ARDS): late proliferative and fibrotic stages. The late proliferative phase of ARDS (A) may evolve to fibrosis (B) with cellular fibroblastic proliferation and collagen deposition.

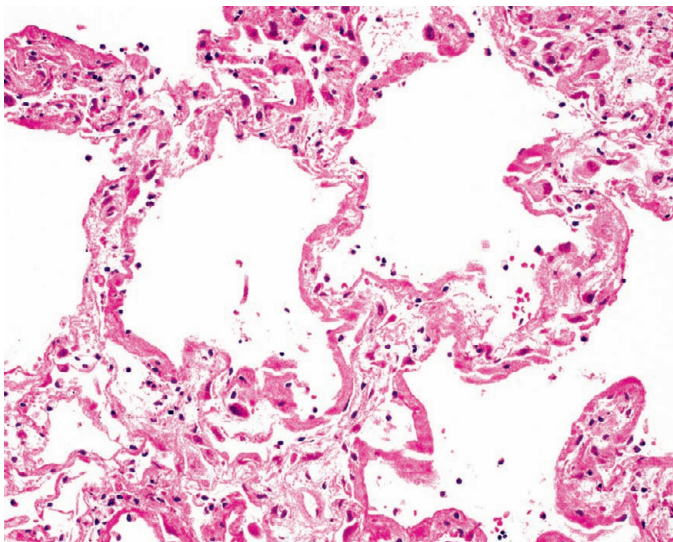


Figure 6.4 Acute respiratory distress syndrome: early exudative phase. Mild interstitial edema with hyaline membranes outlining alveolar spaces is characteristic.

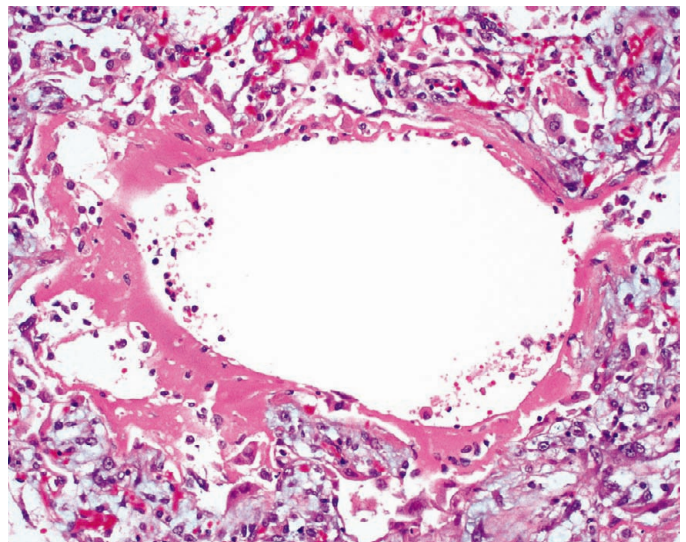


Figure 6.5 Acute respiratory distress syndrome: hyaline membranes. Proteinaceous alveolar exudates accumulate along the periphery of alveoli, closely adherent to alveolar wall-airspace interface.

(Fig. 6.11); collagen deposition is minimal. Reactive type II pneumocytes persist. Immature squamous metaplasia may occur (Fig. 6.12) in and around terminal bronchioles. The degree of cytologic atypia in this squamous epithelium can be so severe as to mimic malignancy (Fig. 6.13). 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 review of outcomes for 109 survivors of ARDS revealed persistent functional disability at 1 year after discharge from intensive care.¹²

By definition, ARDS has a known inciting event. The foregoing description is based on a model of ARDS due to oxygen toxicity,

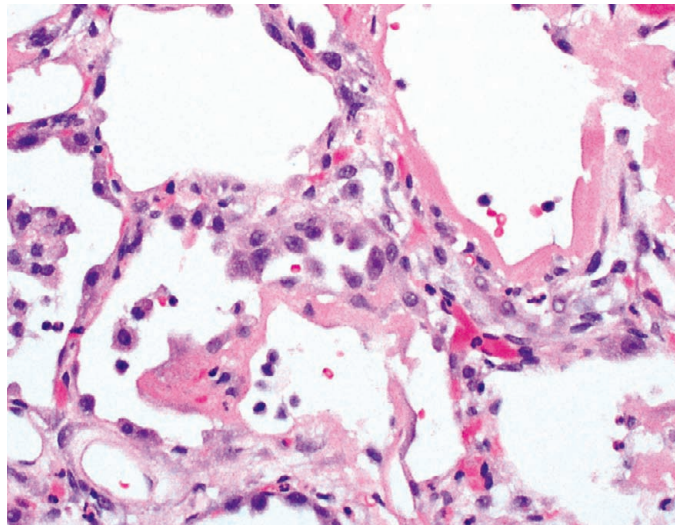


Figure 6.6 Acute respiratory distress syndrome (ARDS): mild interstitial inflammation. In ARDS the inciting event is frequently extrathoracic, and lung injury is therefore superimposed on normal preexisting structure.

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 6.2.

Acute fibrinous and organizing pneumonia (AFOP) is a 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 intraalveolar fibrin balls or aggregates, typically in a patchy distribution. Organizing pneumonia in the form of luminal loose fibroblastic tissue is present surrounding the fibrin (eSlide 6.2). 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.^{13,14}

Specific Causes of Acute Lung Injury Infection

Infection is one of the most common causes of acute lung injury. If the lung injury pattern is accompanied by a significant increase in neutrophils, areas of necrosis, viral cytopathic effect, and/or granulomas, infection should lead the differential diagnosis. 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.

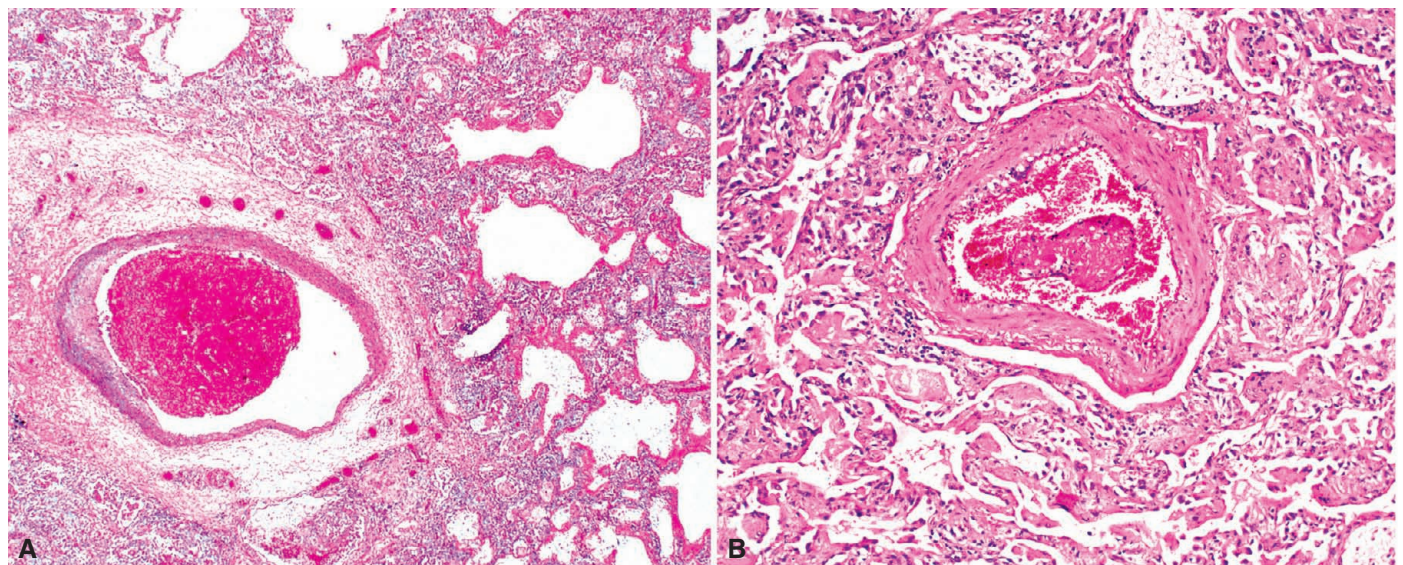


Figure 6.7 Acute respiratory distress syndrome: fibrin thrombi in arteries. Acute lung injury results in local conditions that lead to arterial thrombosis. Thrombi in various stages of organization may be seen (larger pulmonary artery in part A, smaller pulmonary artery in part B).

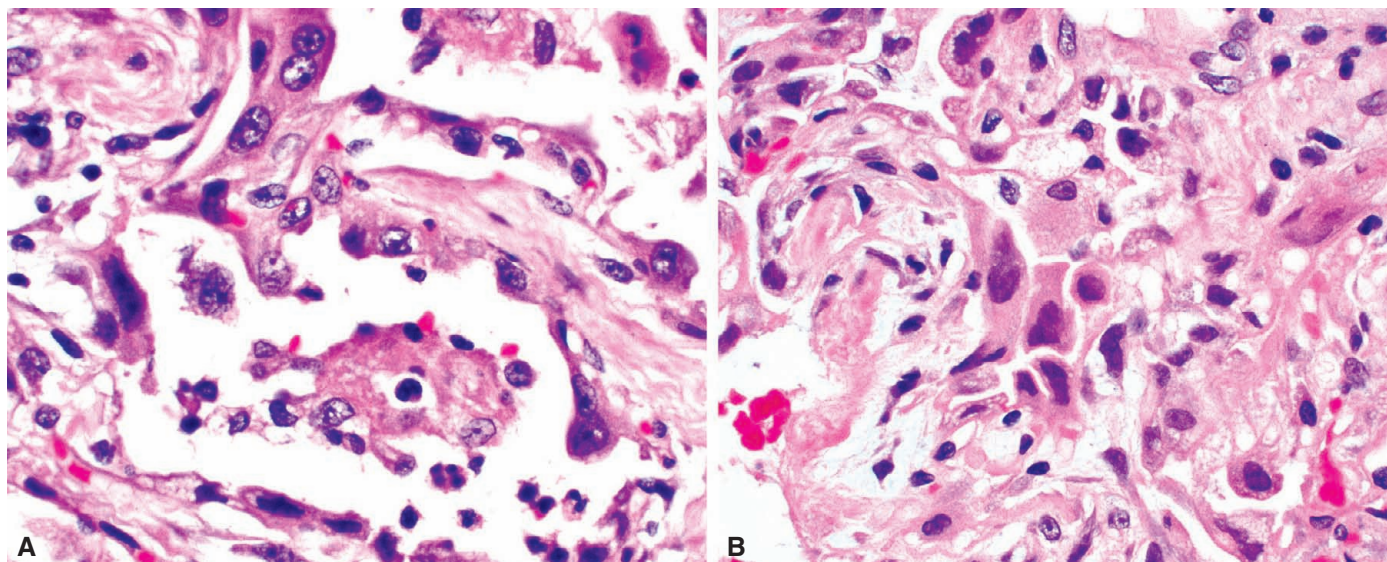


Figure 6.8 Acute respiratory distress syndrome (ARDS): type II cell hyperplasia. Cuboidal type II cells are nearly always prominent in the late exudative phase and throughout the proliferative phase of ARDS. These hyperchromatic and enlarged epithelial cells repopulate the damaged type I cell lining 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.

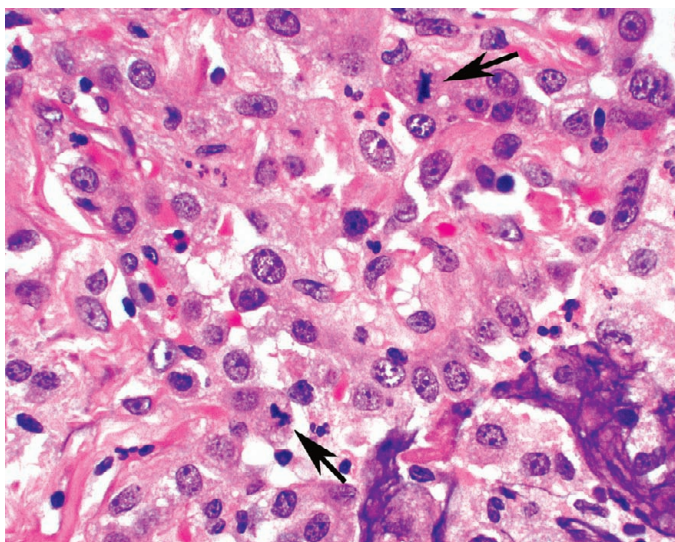


Figure 6.9 Acute respiratory distress syndrome: mitotic figures in type II cells. Mitotic activity can be quite brisk in all forms of acute lung injury (mitotic figures at arrows).

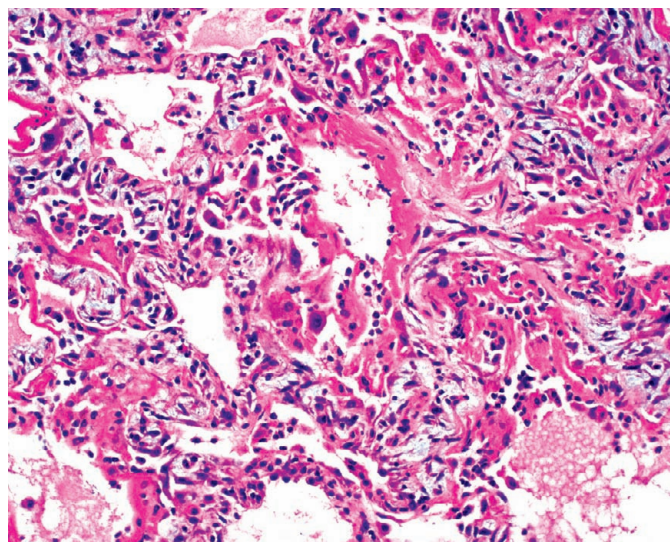


Figure 6.10 Acute respiratory distress syndrome (ARDS): fibroblastic proliferation. Fibroblastic proliferation occurs to a variable degree both in the interstitium and within airspaces in the proliferative and early fibrotic phases of ARDS.

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. 6.14) in fatal cases.^{15,16} Specific viral cytopathic effects are not identifiable by light microscopy. On ultrastructural examination, intranuclear fibrillary inclusions may be seen in epithelial and endothelial cells.¹⁷

The *Coronavirus* responsible for severe acute respiratory syndrome produces the acute lung injury associated with this disorder.^{13,18–20} 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 spikelike 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.

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,

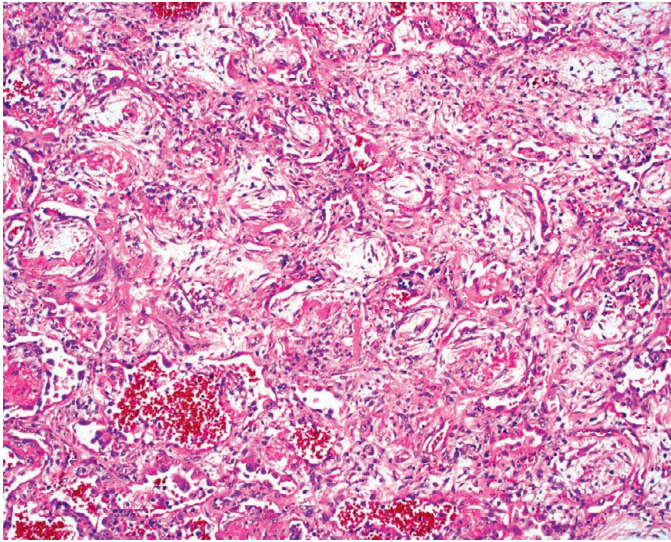


Figure 6.11 Acute respiratory distress syndrome (ARDS): airspace organization. Organizing pneumonia-like airspace organization can be quite prominent in the late proliferative phase of ARDS.

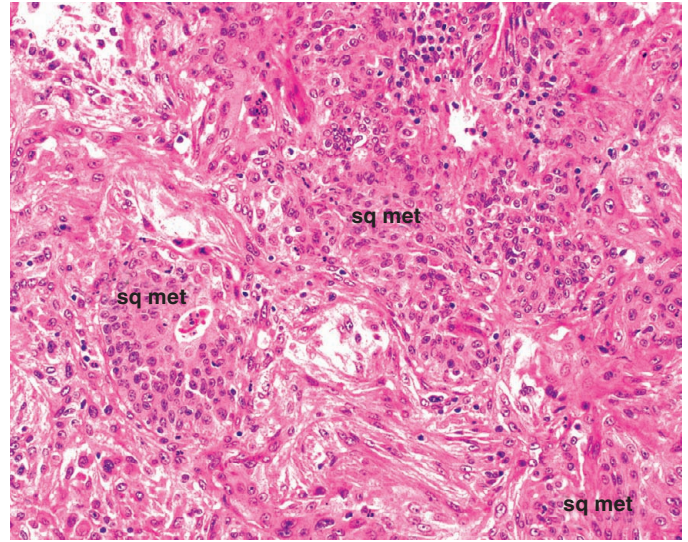


Figure 6.13 Acute respiratory distress syndrome: squamous metaplasia (*sq met*), high-magnification view. In some instances, squamous metaplasia may be so prominent as to suggest neoplasm.

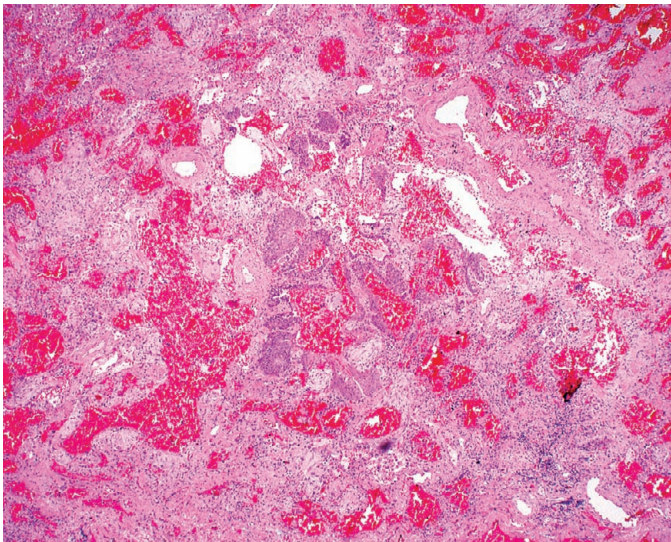


Figure 6.12 Acute respiratory distress syndrome (ARDS): squamous metaplasia. Squamous metaplasia of terminal airways may develop as a subacute proliferative event in ARDS and other forms of diffuse alveolar damage. The nested squamous epithelium often is nodular-appearing at scanning magnification by virtue of patchy terminal airway involvement.

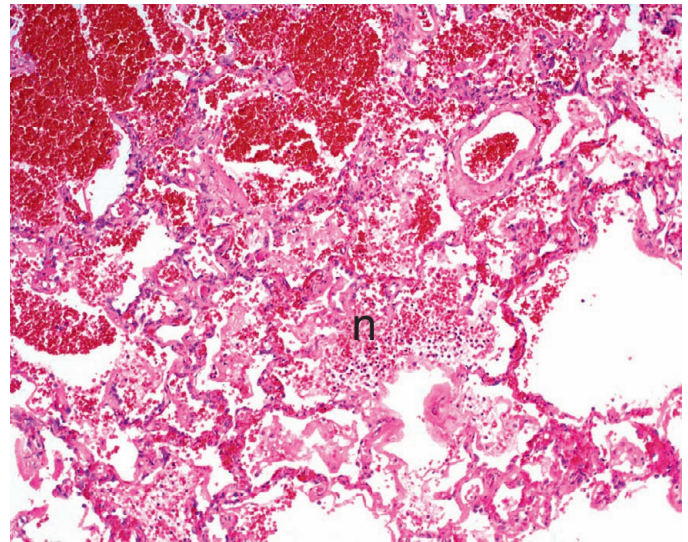


Figure 6.14 Diffuse alveolar damage in influenza pneumonia. Fibrinous and focally neutrophilic diffuse alveolar injury is characteristic. In this case, note the sparse neutrophils present in an airspace (*n*) and abundant blood. No specific viral inclusions are produced by the influenza virus.

Box 6.2 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

bronchitis and bronchiolitis, and DAD.²⁴ The characteristic histologic feature is the presence of multinucleated giant cells (Fig. 6.15A) with characteristic eosinophilic intranuclear and intracytoplasmic inclusions.^{24–28} These cells are found in the alveolar spaces and within alveolar septa (Fig. 6.15B). 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. 6.16A). 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. 6.16B). 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. 6.17) and

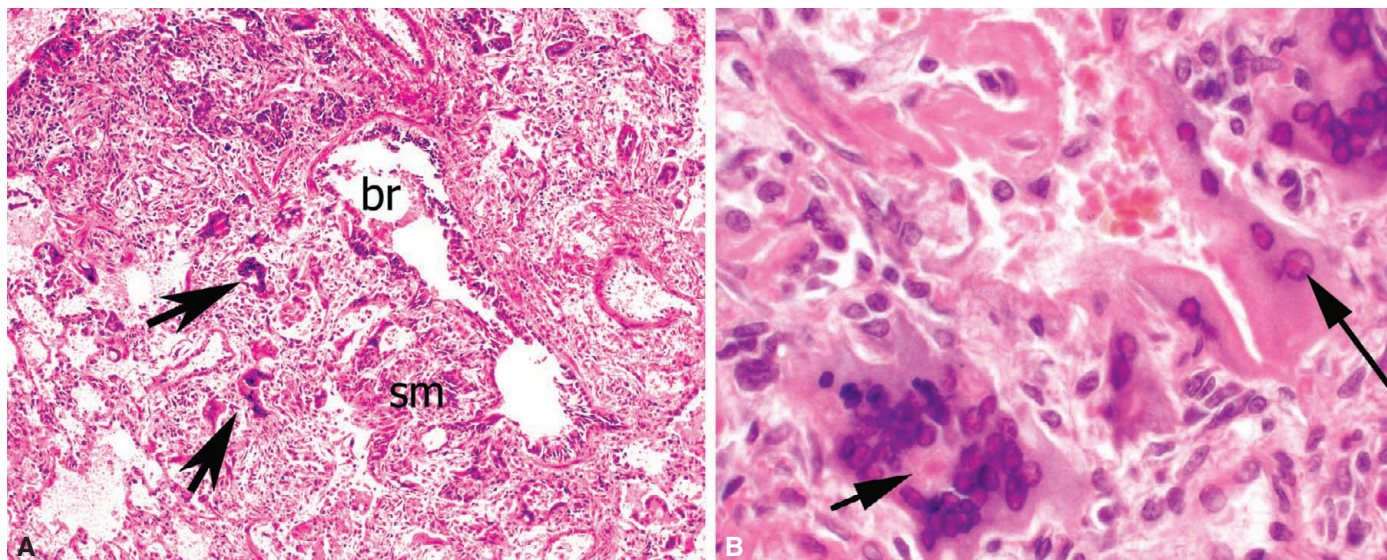


Figure 6.15 Diffuse alveolar damage (DAD) in measles pneumonia. (A) A terminal airway (*br*) in a case of acute measles pneumonia with DAD. Squamous metaplasia of the airway also is present (*sm*). The *arrows* denote multinucleate giant cells, present here in a bronchiolocentric distribution. (B) The characteristic multinucleate giant cells of measles pneumonia. Note the glassy intranuclear inclusions (*long arrow*) and occasional eosinophilic cytoplasmic inclusions (*short arrow*).

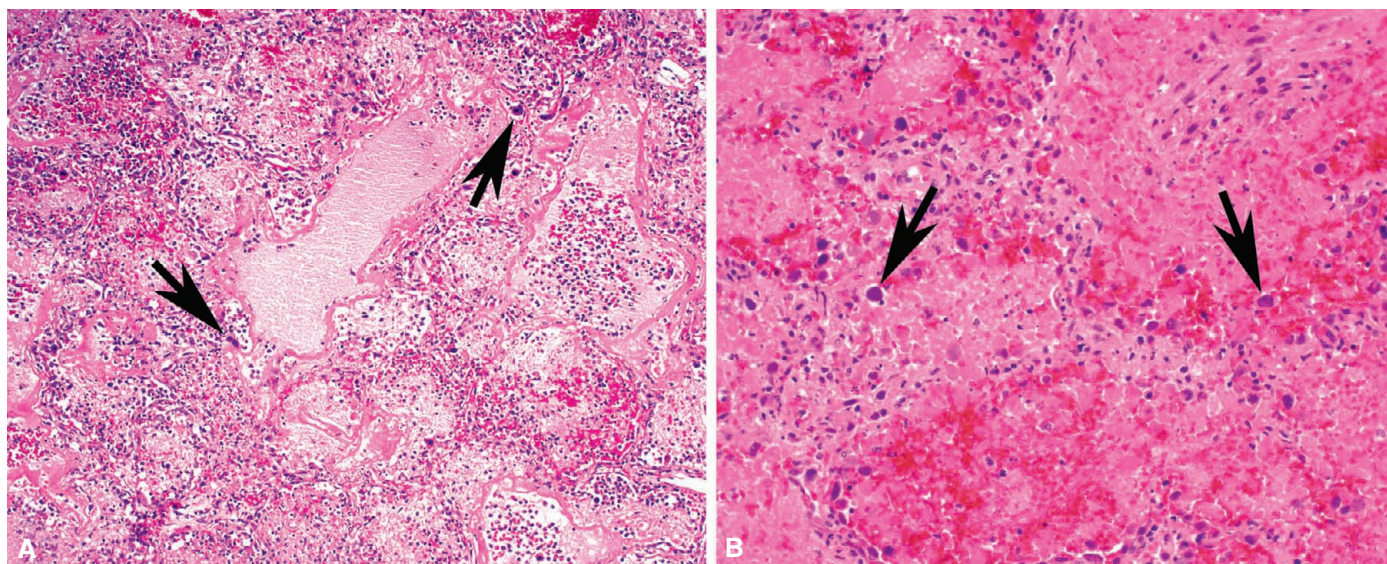


Figure 6.16 Diffuse alveolar damage (DAD) in adenovirus pneumonia. Adenovirus infection produces necrotizing bronchitis/bronchiolitis, and this is especially prominent in the setting of DAD caused by this infection. (A) The “smudge cells” of adenovirus infection can be seen at scanning magnification (*arrows*). (B) Smudge cells at higher magnification (*arrows*).

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 epithelial cells (Fig. 6.18). 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, pneumonia develops in 15% of adults

with chickenpox; immunocompetent and immunocompromised persons are equally affected.^{32,36} The histopathologic picture in varicella pneumonia (Fig. 6.19) 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.

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 infection.^{37–39} The histopathologic findings range from little or no inflammatory response to hemorrhagic nodules with necrosis (Fig. 6.20A) and DAD.³⁷ The diagnostic histopathologic

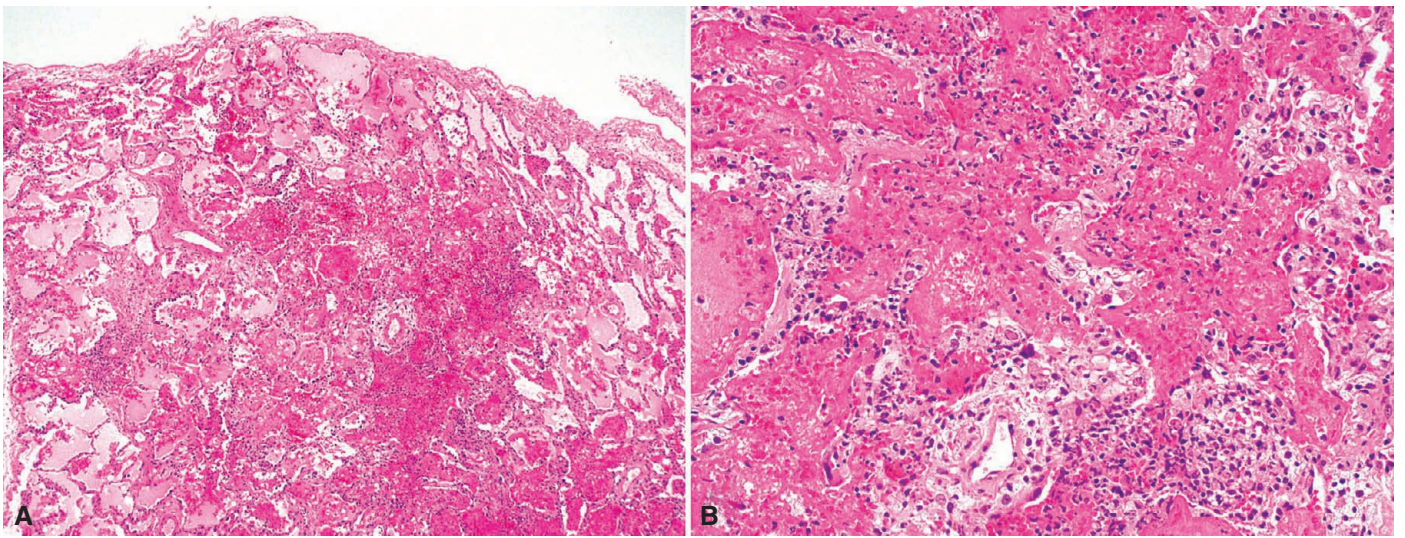


Figure 6.17 Diffuse alveolar damage in herpes simplex pneumonia. Herpesviridae viruses are capable of producing nodular necrotizing pneumonia (see Chapter 7). (A) The nodular appearance of lung involved by herpes simplex pneumonia is evident, with zonal areas of hemorrhage and necrosis. (B) A higher-magnification view of the hemorrhagic and necrotizing pneumonia.

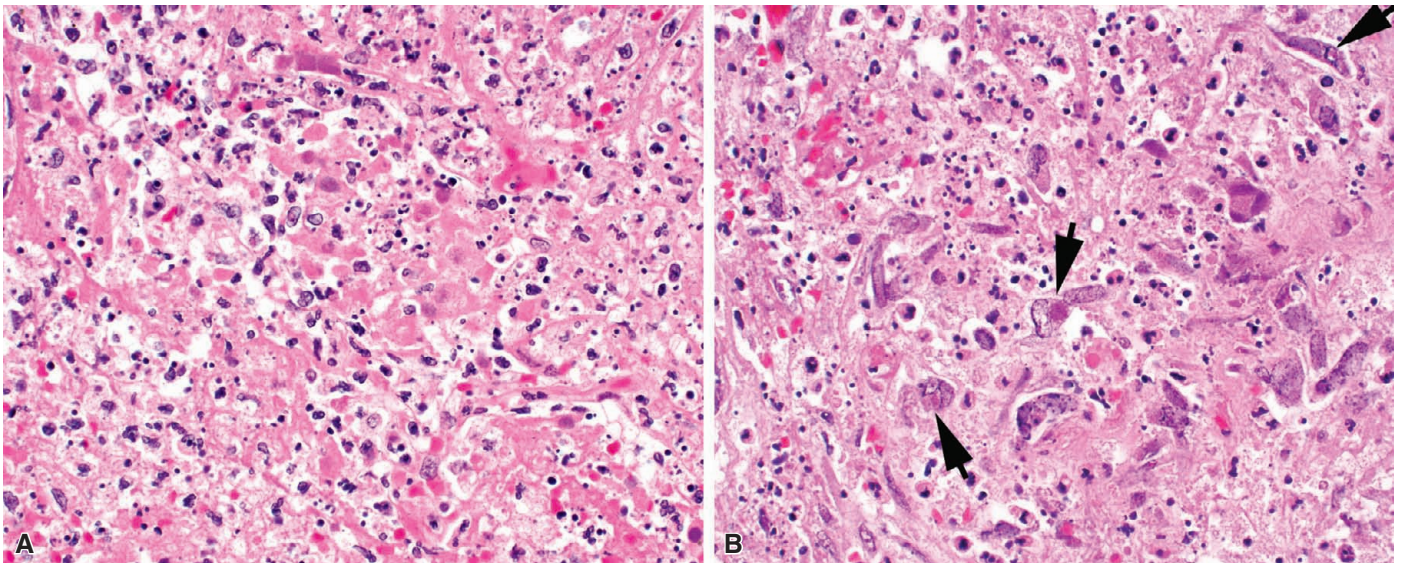


Figure 6.18 Herpes simplex pneumonia: inclusions. (A) Diffuse alveolar damage associated with herpes simplex pneumonia. (B) The viral cytopathic effects on bronchial and alveolar epithelium. The classic Cowdry A intranuclear inclusions (*arrows*) usually are easy to find, compared with the basophilic, smudged, or ground-glass Cowdry B nuclear inclusions.

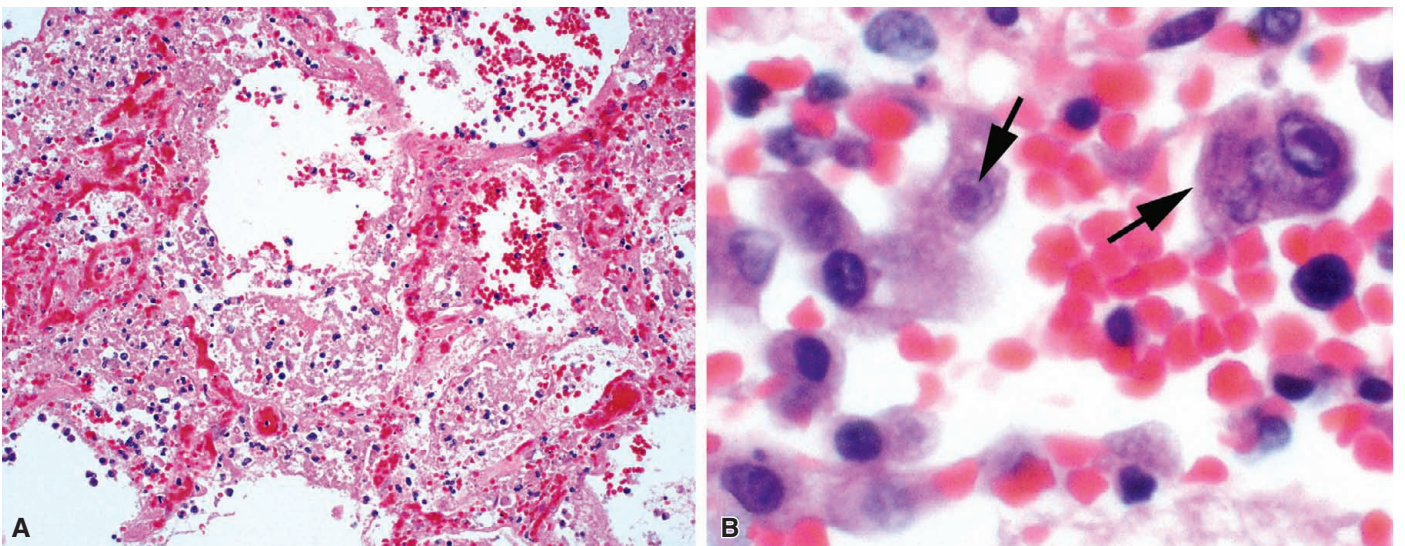


Figure 6.19 Diffuse alveolar damage (DAD) in varicella-zoster. The inclusions are similar to those produced by herpes simplex. (A) Fibrinous DAD with neutrophils in airspaces in a case of chickenpox pneumonia. (B) Rare intranuclear eosinophilic inclusions (*arrows*) are identifiable.

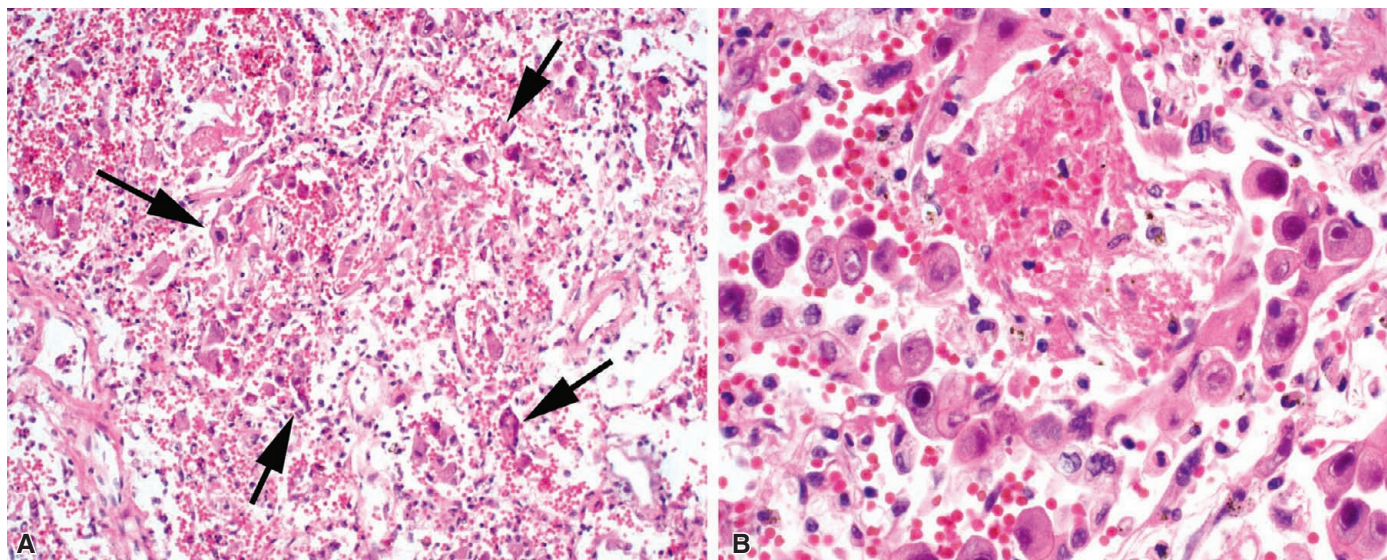


Figure 6.20 Diffuse alveolar damage (DAD) in cytomegalovirus (CMV) pneumonia. DAD from CMV infection can be quite dramatic in the immunocompromised host. (A) DAD with numerous CMV cells evident at scanning magnification (arrows). (B) CMV-infected cells at higher magnification. Prominent intranuclear inclusions are evident.

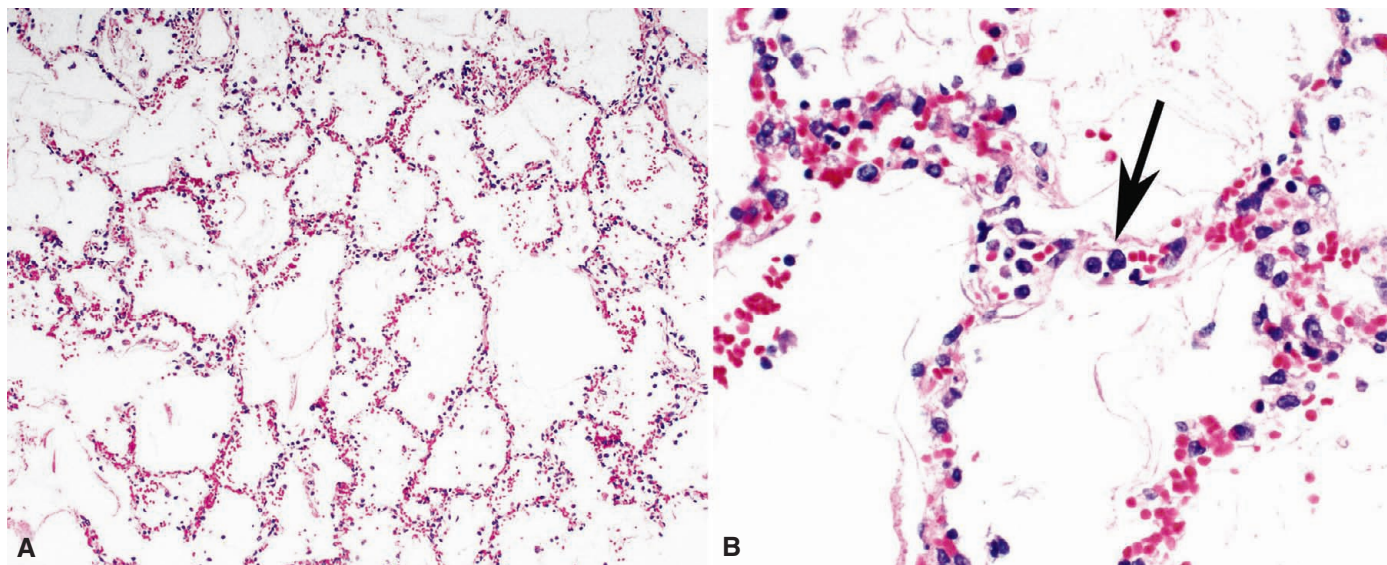


Figure 6.21 Diffuse alveolar damage in hantavirus pneumonia. Hantavirus pneumonia is characterized by alveolar edema, hyaline membranes (A), and scattered atypical interstitial mononuclear cells (B, arrow).

pattern, seen in endothelial cells, macrophages, and epithelial cells, consists of cellular enlargement, a prominent intranuclear inclusion, and an intracytoplasmic basophilic inclusion (Fig. 6.20B).³⁷

Hantavirus is a rare cause of acute lung injury.^{40–42} The infection produces alveolar edema, hyaline membranes, and atypical interstitial mononuclear inflammatory infiltrates (Fig. 6.21).^{40–42} 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 intraalveolar exudates (Fig. 6.22A) (so-called alveolar casts),

with many organisms (see Fig. 6.22B).^{44,45} However, in the mildly immunocompromised patient 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. 6.23A), with the organisms present within hyaline membranes (Fig. 6.23B) and in isolated intraalveolar fibrin deposits.⁴⁶ The Grocott methenamine silver (GMS) method is routinely used to stain the organisms, which typically are seen in small groups and clusters (Figs. 6.22B and 6.23B).^{43,45,46}

Bacterial Infection

Common bacterial pneumonias rarely cause DAD; however, this lung injury pattern has been described in legionnaires’ disease, *Mycoplasma pneumoniae*, and rickettsial infection.^{47–51}

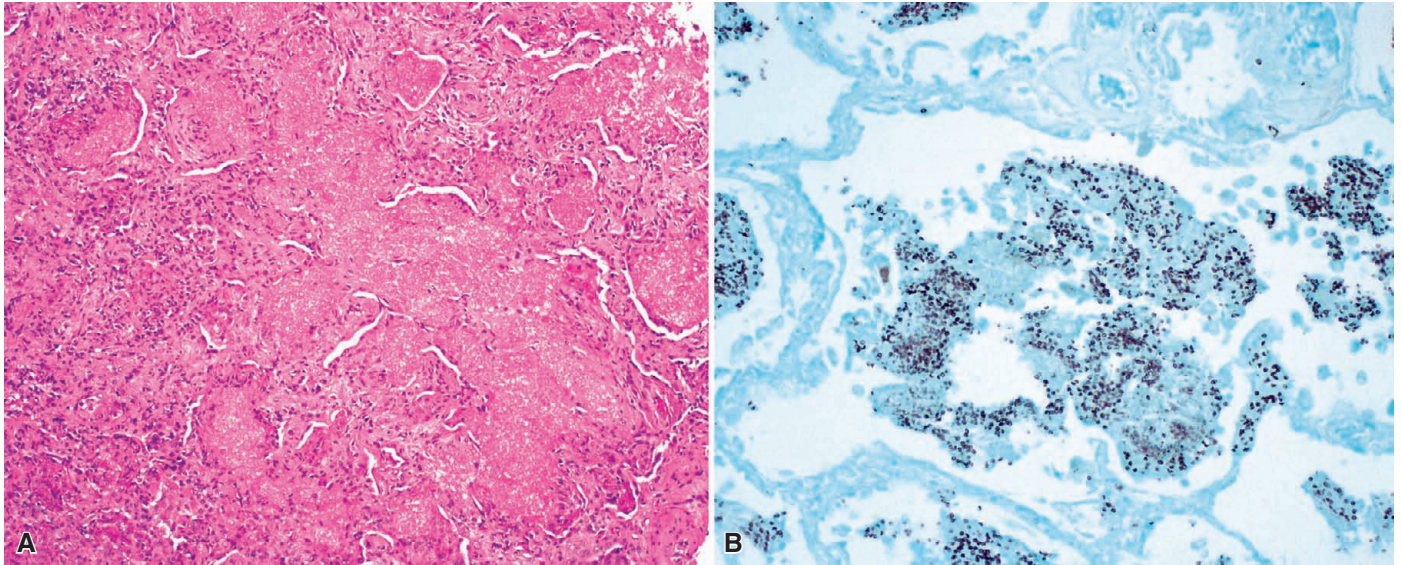


Figure 6.22 Diffuse alveolar damage in pneumocystis pneumonia. (A) The frothy “alveolar casts” characteristic of pneumocystis pneumonia in the profoundly immunocompromised host (classically, the patient with acquired immunodeficiency syndrome or human immunodeficiency virus infection). (B) Numerous silver-stained organisms are evident within these eosinophilic exudates (methenamine silver stain).

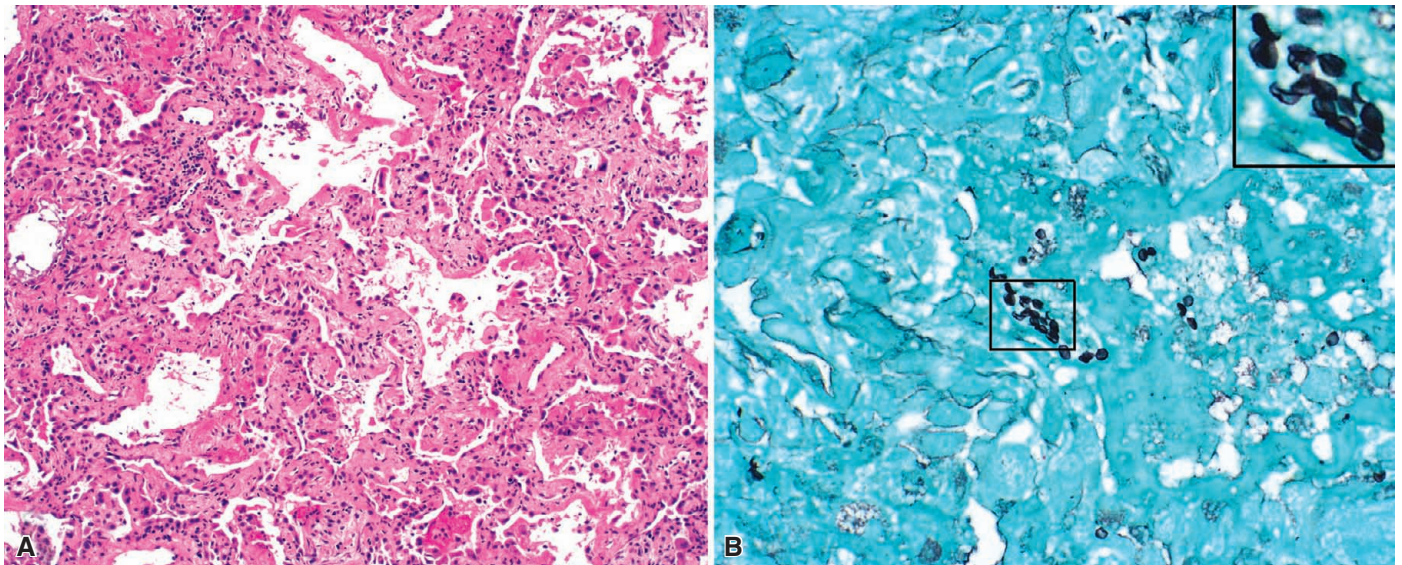


Figure 6.23 Diffuse alveolar damage in pneumocystis pneumonia. (A) Such diffuse damage also may occur in less severely immunocompromised patients. (B) In such patients, few organisms may be identifiable by silver stains (methenamine silver stain). A colony of *Pneumocystis* organisms is shown in the inset.

Legionella is a fastidious gram-negative bacillus that causes acute respiratory infection in older adults and immunodeficient individuals.^{47,48,51} The histopathologic pattern is that of a pyogenic necrotizing bronchopneumonia (Fig. 6.24A) affecting the respiratory bronchioles, alveolar ducts, and adjacent alveolar spaces. DAD is common.^{47,48,51} The rod-shaped organisms (Fig. 6.24B) can be identified by Dieterle silver stain.⁵¹

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, etc.) on every lung biopsy specimen exhibiting DAD.

Connective Tissue Disease

Systemic connective tissue 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 Histologic clues that suggest the acute lung injury is secondary to connective tissue disease include associated bronchiolitis (especially if it is follicular bronchiolitis), pleuritis, capillaritis, hemorrhage, and

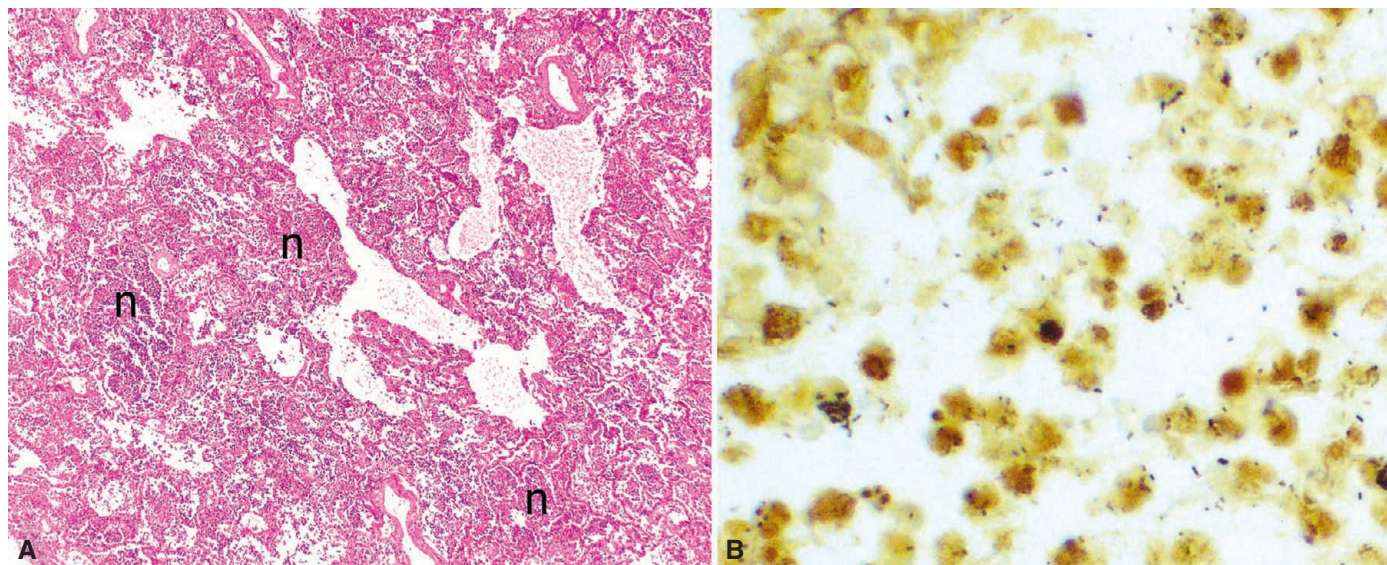


Figure 6.24 Diffuse alveolar damage in *Legionella* pneumonia. (A) The diffuse alveolar injury caused by *Legionella* infection is prominently neutrophilic (n). (B) Within these areas, a silver stain shows numerous rod-shaped stained organisms (Dieterle silver method).

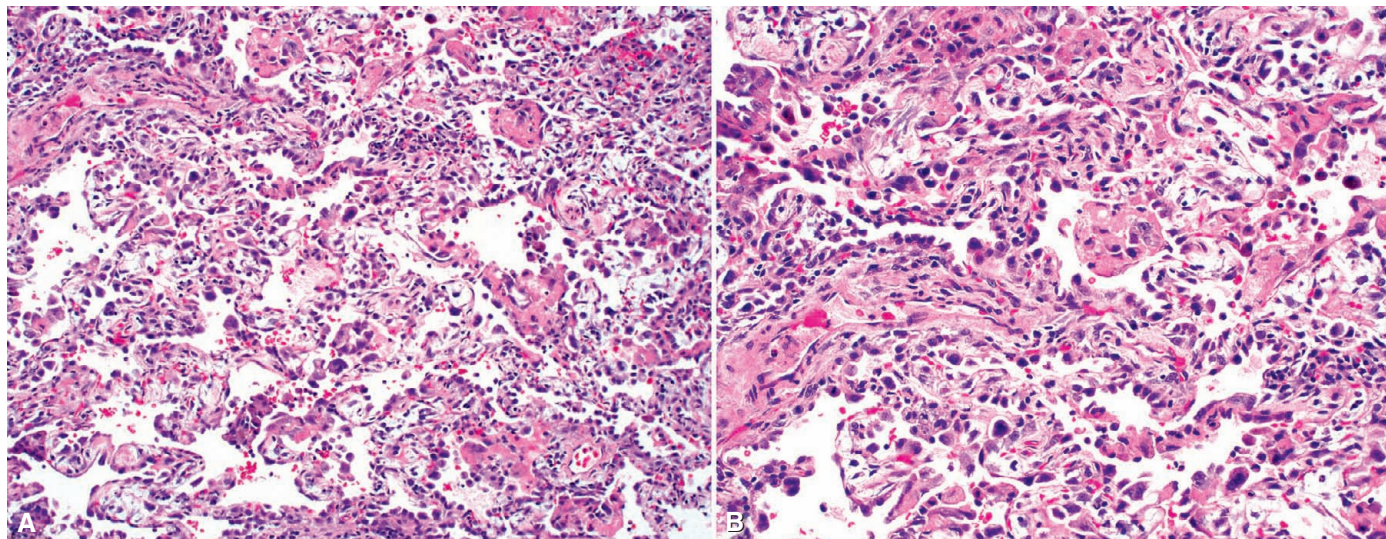


Figure 6.25 Diffuse alveolar damage (DAD) in systemic lupus erythematosus (SLE). The DAD associated with lupus may be quite hemorrhagic and associated with a “pneumonitis.” Note the increased mononuclear cells within the alveolar interstitium in both parts (A and B). Sometimes the alveolar hemorrhage of SLE may overlap with diffuse alveolar damage on morphologic grounds.

a cellular lymphoplasmacytic infiltrate. Acute lung injury has been reported to occur in the following connective tissue diseases.

Systemic Lupus Erythematosus

Pulmonary involvement in systemic lupus erythematosus (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. 6.25A) 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 (eSlide 6.3). Alveolar hemorrhage, with capillaritis

and small vessel vasculitis (Fig. 6.25B), 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 (Fig. 6.26), referred to as acute interstitial pneumonia in some publications⁶⁵ 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. 6.27A), organizing pneumonia (Fig. 6.27B), and chronic fibrosis (Fig. 6.27C)—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 connective tissue 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. In addition, 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.

Drug Effect

Drugs can produce a wide range of pathologic 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, venoocclusive 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 8.) As a generalization, marked cytologic atypia and numerous foamy macrophages in the airspaces are histologic harbingers of possible drug reaction.

Chemotherapeutic Agents

DAD frequently is caused by cytotoxic drugs, and the commonly implicated ones include bleomycin (Fig. 6.28), busulfan (Fig. 6.29), 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 nuclei⁸⁹ and prominent nucleoli (see Fig. 6.29) 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. 6.30) and also may exacerbate bleomycin-induced lung injury.⁹³ Methotrexate (Fig. 6.31) is 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 8) that is seldom

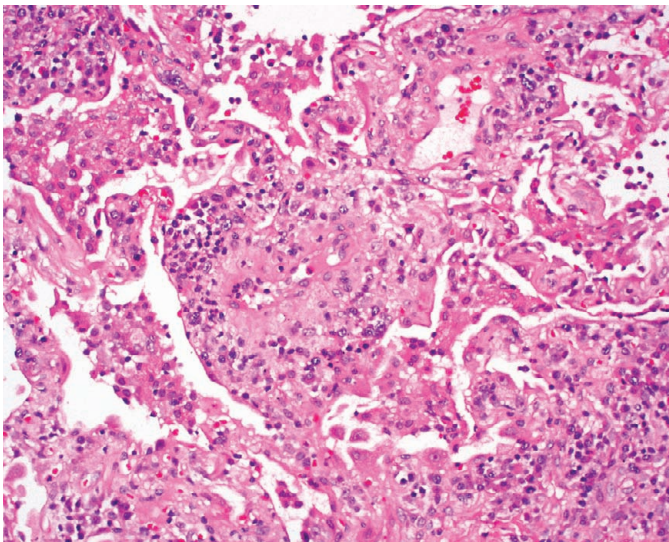


Figure 6.26 Diffuse alveolar damage (DAD) in rheumatoid arthritis. With DAD in rheumatoid arthritis, histopathologic hints of more chronic disease sometimes may be present, with lymphoplasmacellular infiltrates, chronic bronchiolitis, and chronic pleuritis. Here, a perivascular lymphoplasmacellular infiltrate is evident with surrounding airspace fibrin and macrophages.

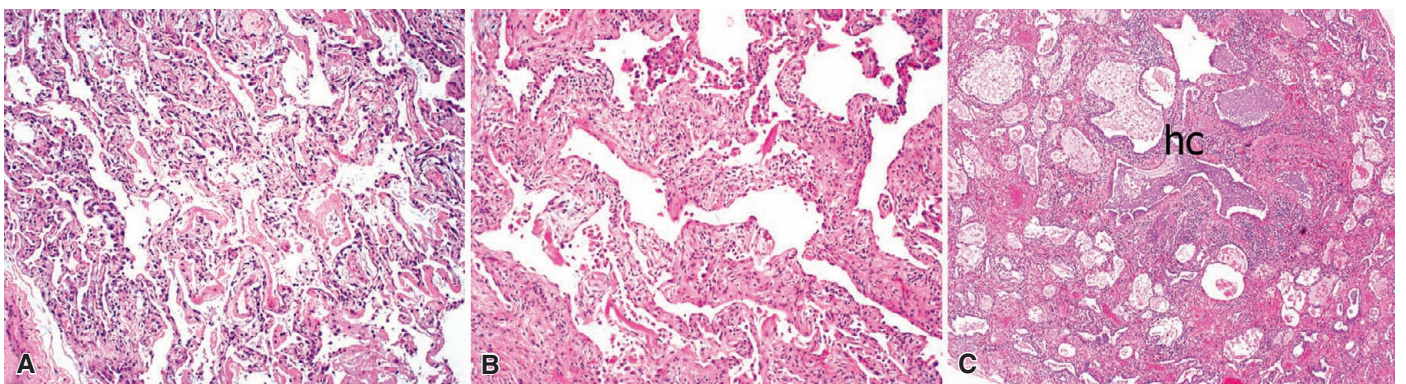


Figure 6.27 Diffuse alveolar damage (DAD) in polymyositis/dermatomyositis. All of the systemic connective tissue diseases can manifest with acute, subacute, and chronic lung disease. Three examples of diffuse lung disease accompanying polymyositis/dermatomyositis are presented: (A) DAD; (B) a subacute organizing pneumonia with an interstitial mononuclear infiltrate (nonspecific interstitial pneumonia–like pattern) (see Chapter 8); and (C) a usual interstitial pneumonia–like pattern of lung fibrosis with microscopic honeycomb remodeling (*hc*).

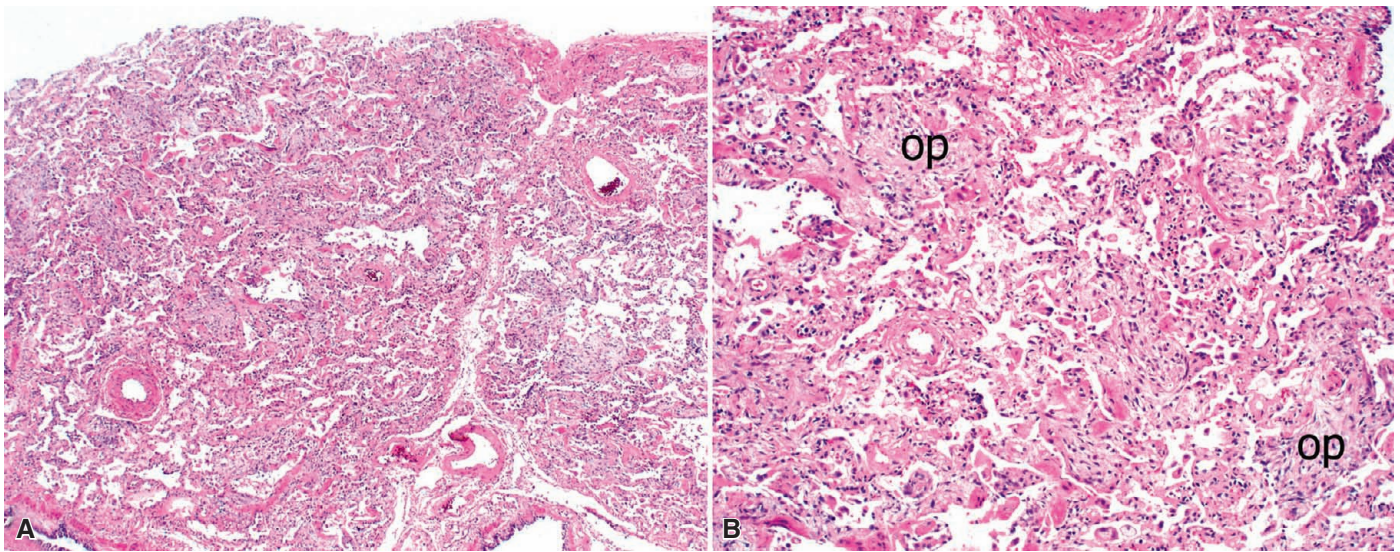


Figure 6.28 Diffuse alveolar damage from bleomycin toxicity. Bleomycin produces a characteristic lung injury in experimental animal models. Such damage has been observed to also occur in humans (A) often typified by the presence of reactive type II cells and organizing pneumonia (*op*) (B).

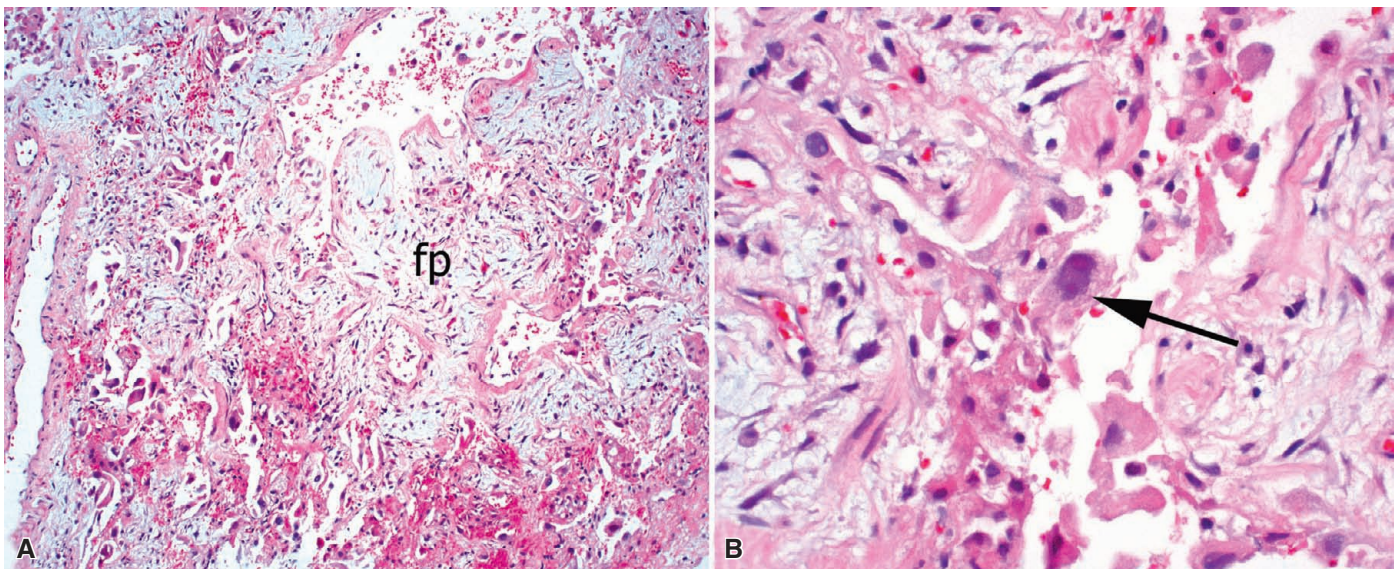


Figure 6.29 Diffuse alveolar damage from busulfan toxicity. Busulfan can produce diffuse injury characterized by the presence of prominently atypical type II cells. (A) In this case, prominent interstitial organization with edematous fibroblastic proliferation is seen (*fp*), and hyaline membranes are evident. (B) Reactive type II cells may appear alarmingly atypical (*arrow*).

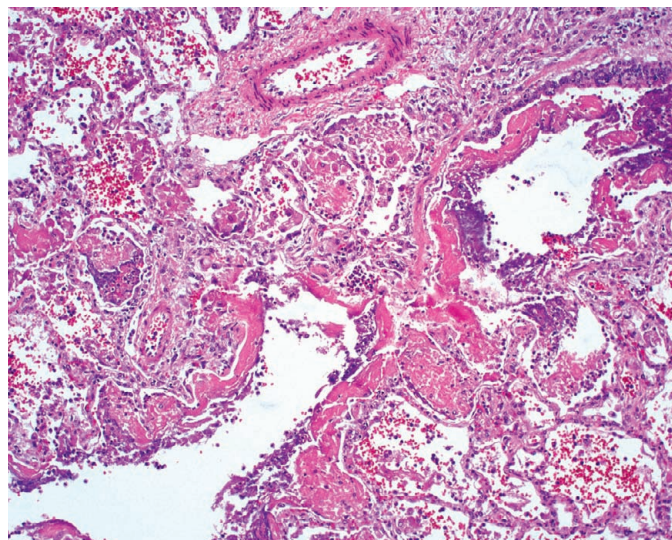


Figure 6.30 Diffuse alveolar damage from oxygen toxicity. Classic oxygen toxicity causes diffuse alveolar injury and necrosis of terminal airway epithelium, as illustrated in this photomicrograph.

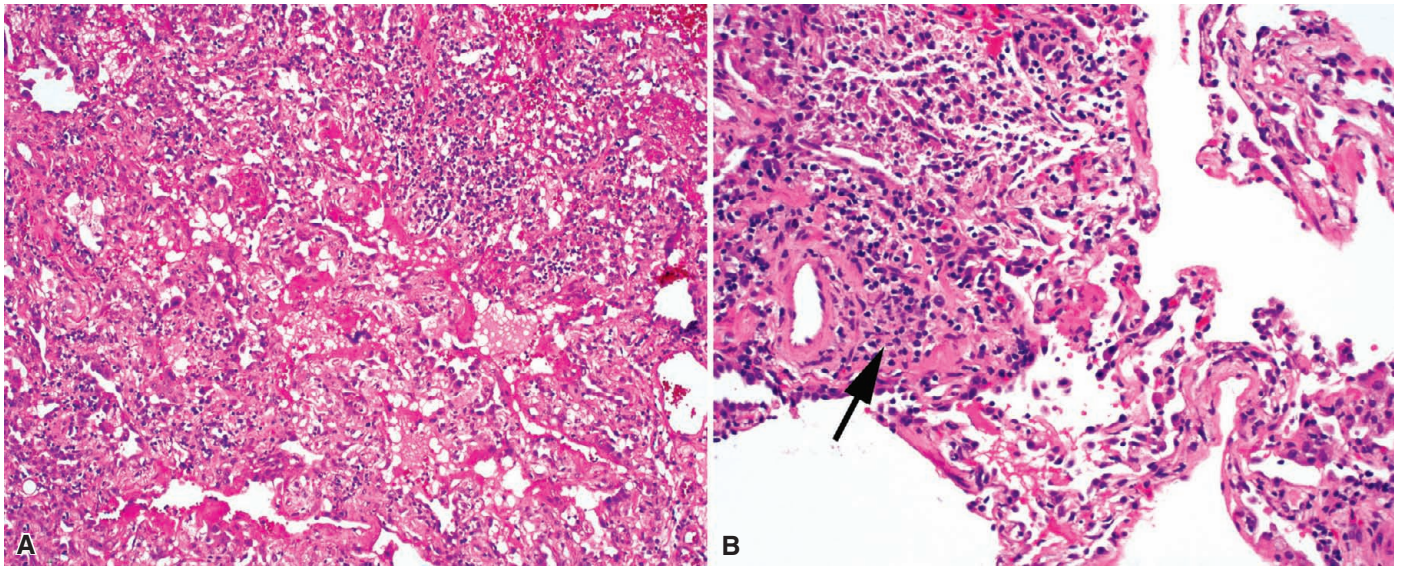


Figure 6.31 Diffuse alveolar damage (DAD) from methotrexate toxicity. (A and B), Methotrexate produces small, poorly formed granulomas in subacute and chronic manifestations of lung toxicity. Early aggregations of macrophages may be seen resembling poorly formed granulomas in cases in which DAD is the manifestation of injury, but these are not required for the diagnosis (*arrow*).

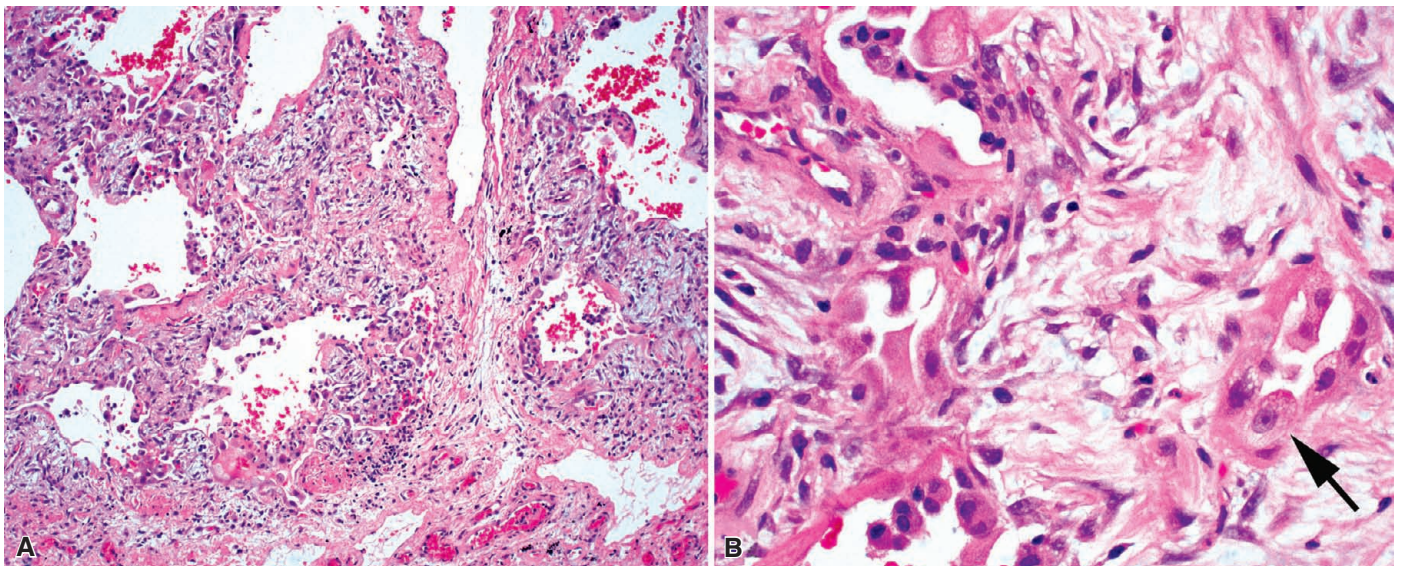


Figure 6.32 Diffuse alveolar damage from amiodarone toxicity. Amiodarone can produce acute, subacute, and chronic lung toxicity. (A) Scanning magnification of amiodarone-induced diffuse alveolar injury. (B) The finely vacuolated macrophages in type II cells are clearly evident (*arrow*).

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}

Epidermal growth factor receptor tyrosine kinase inhibitors have been reported to be associated with DAD.^{95,96} The increasing use of targeted therapy drugs in cancer patients warrants a notice of this category as a potential cause.

Amiodarone

Amiodarone is a highly effective antiarrhythmic drug that is increasingly recognized as a cause of pulmonary toxicity.^{77,97–101} 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.^{77,101}

Distinctive features may be present on chest computed tomography scans.⁷⁷ The lung biopsy commonly shows acute and organizing lung injury (Fig. 6.32A and eSlide 6.4). Other patterns include chronic interstitial pneumonitis with fibrosis and organizing pneumonia.⁹⁹ Characteristically, type II pneumocytes and alveolar macrophages show finely vacuolated cytoplasm in response to amiodarone therapy (see Fig. 6.32B), 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.^{97–100}

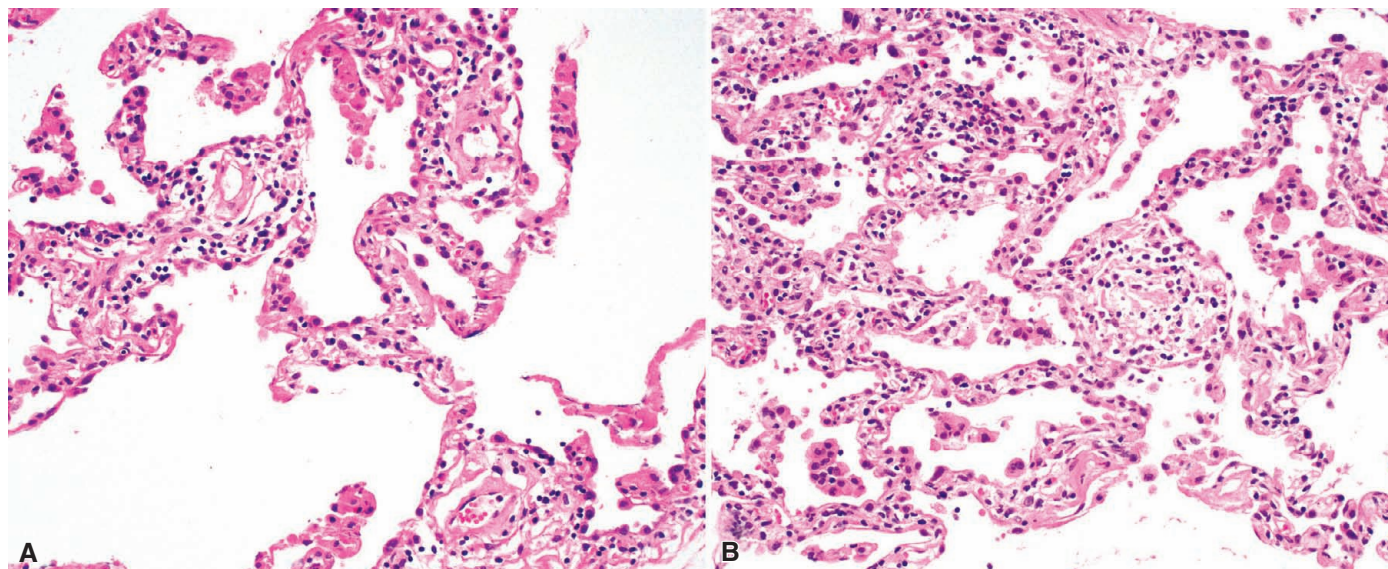


Figure 6.33 Diffuse alveolar damage from gold therapy toxicity. (A) Gold therapy for rheumatoid arthritis may produce diffuse alveolar injury with hyaline membranes. (B) A chronic or subacute cellular inflammatory process also has been described.

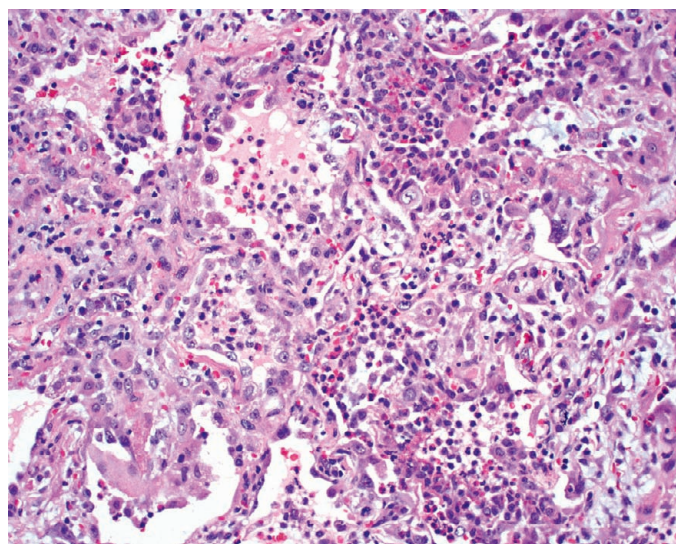


Figure 6.34 Acute eosinophilic pneumonia. The histopathologic changes seen in eosinophilic pneumonia are well known to most pathologists. Reactive type II cell hyperplasia in combination with the presence of airspace fibrin, eosinophilic airspace macrophages, and scattered eosinophils yields a characteristic picture.

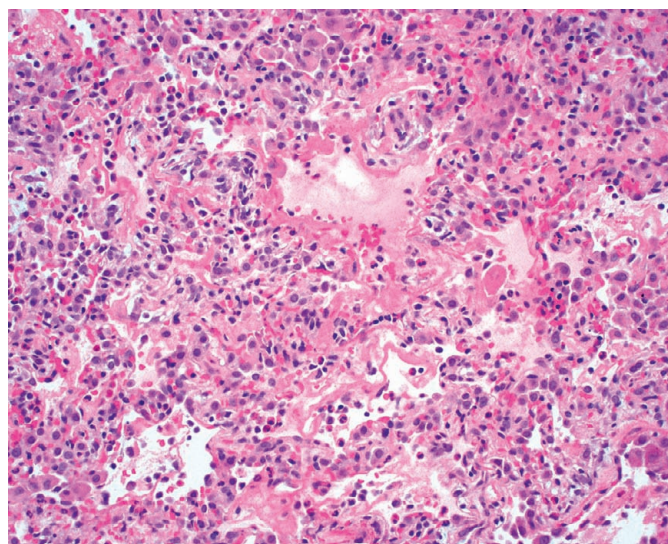


Figure 6.35 Diffuse alveolar damage (DAD) with acute eosinophilic pneumonia: hyaline membranes. Organization of hyaline membranes may occur in the acute lung injury of eosinophilic pneumonia. An awareness of this association is important so that eosinophilic pneumonia is not overlooked as a potential cause of DAD with hyaline membranes.

Antiinflammatory 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. 6.33) and chronic interstitial pneumonia are commonly described pulmonary manifestations of so-called gold toxicity.^{74,76,102}

Acute Eosinophilic Pneumonia

Acute eosinophilic pneumonia was first described in 1989¹⁰³ and is characterized by acute respiratory failure, fever of days' to weeks' duration, diffuse pulmonary infiltrates on radiologic studies, and eosinophilia in bronchoalveolar lavage fluid or lung biopsy specimens in the absence of infection, atopy, and asthma.¹⁰⁴ Peripheral eosinophilia frequently is

described but is not a consistent finding at initial presentation.^{103,105} Acute eosinophilic pneumonia is easily confused with acute interstitial pneumonia because both manifest as acute respiratory distress without an obvious underlying cause.¹⁰⁴ Histologically, the disease is characterized by acute and organizing lung injury showing classic features (Fig. 6.34) of (1) alveolar septal edema, (2) eosinophilic airspace macrophages, (3) tissue and airspace eosinophils in variable numbers, and (4) marked reactive atypia of alveolar type II cells (eSlide 6.5). Intraalveolar fibroblastic proliferation (patchy organizing pneumonia) and inflammatory cells are present to a variable degree. Hyaline membranes and organizing intraalveolar fibrin also may be present (Fig. 6.35). 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 distinguish acute eosinophilic pneumonia from other causes of DAD because patients typically benefit from systemic corticosteroid treatment, with prompt recovery. However, before initiation of immunosuppressive therapy, infection should be rigorously excluded by culture and special stains because parasitic and fungal infections also can manifest as tissue eosinophilia. Treatment with steroids prior to the biopsy can make the number of eosinophils less impressive.

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.¹⁰⁷⁻¹⁰⁹ Acute interstitial pneumonia is one of the major idiopathic interstitial pneumonias included in the most recent classification scheme for diffuse interstitial pneumonia.¹¹⁰ 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.^{107,109} The classic histopathologic pattern is that of acute and organizing DAD,^{107,109} 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. 6.36) often is seen in the lung at the time of biopsy.¹¹¹ A variable degree of airspace 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, connective tissue disease, acute exacerbation of idiopathic pulmonary fibrosis (IPF), drug effect, and other causes of DAD.¹¹¹ Most cases of DAD are not acute interstitial pneumonia, and detailed clinical information, radiologic findings (localized vs. diffuse disease), serologic data, and microbiologic results will often point to or rule out a specific etiologic condition. Use

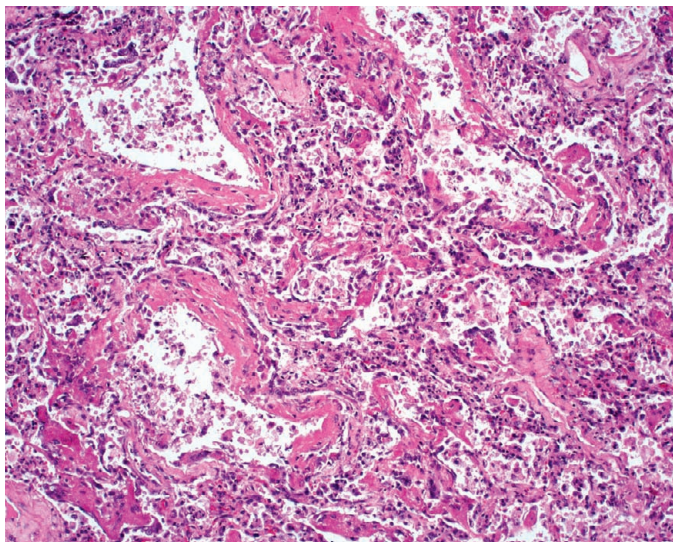


Figure 6.36 Acute interstitial pneumonia (AIP). Idiopathic AIP may take the form of every possible morphologic manifestation of acute respiratory distress syndrome, depending on the timing of biopsy relative to the onset of symptoms. Here, a classic pattern of diffuse alveolar damage (DAD) with hyaline 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.

of special stains 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,¹¹² in addition to the characteristic alveolar hemorrhage and hemosiderin-laden macrophages. In some patients, DAD may be the dominant histopathologic pattern.¹¹³ In a study by Lombard et al. in patients with Goodpasture syndrome, all showed acute lung injury ranging in distribution from focal to diffuse lung involvement.¹¹³ Histopathologic examination demonstrated typical acute and organizing DAD, with widened and edematous alveolar septa, fibroblastic proliferation, reactive type II pneumocytes, and, rarely, even hyaline membranes (Figs. 6.37 and 6.38). Alveolar hemorrhage, either focal or diffuse, was present in all cases. Capillaritis, an important finding indicating true alveolar hemorrhage,¹¹² 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.¹¹⁴ Alveolar hemorrhage with arteritis, capillaritis (Fig. 6.38), and venulitis may be seen in some cases.¹¹⁴

Polyarteritis nodosa and vasculitis associated with systemic connective tissue disease (notably SLE and rheumatoid arthritis) can also show acute lung injury with alveolar hemorrhage as the dominant histopathologic finding.^{57,115}

Cryoglobulinemia is a rare cause of acute lung injury and alveolar hemorrhage.¹¹⁶⁻¹¹⁸

Radiation Pneumonitis

Radiation can produce both acute and chronic damage to the lung, manifesting as acute radiation pneumonitis and chronic progressive fibrosis, respectively.¹¹⁹ 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.^{5,79,120,121} Acute radiation pneumonitis manifests 1 to 2 months after radiation therapy.^{5,121} With traditional external beam radiation the pneumonitis is typically confined to the radiation field. However, more diffuse radiation pneumonitis can be seen following yttrium 90-impregnated microsphere chemoembolization for nonoperable hepatic tumors.¹²² Clinical findings include dyspnea, cough, pleuritic pain, fever, and chest infiltrates. The lung biopsy specimen shows acute and organizing DAD.^{119,121} Markedly atypical type II pneumocytes with enlarged hyperchromatic nuclei and vacuolated cytoplasm constitute a hallmark of the disease (Fig. 6.39A), 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 (Fig. 6.39B), with or without transmural fibrinoid necrosis, is common.^{79,123-125}

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 later). 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.

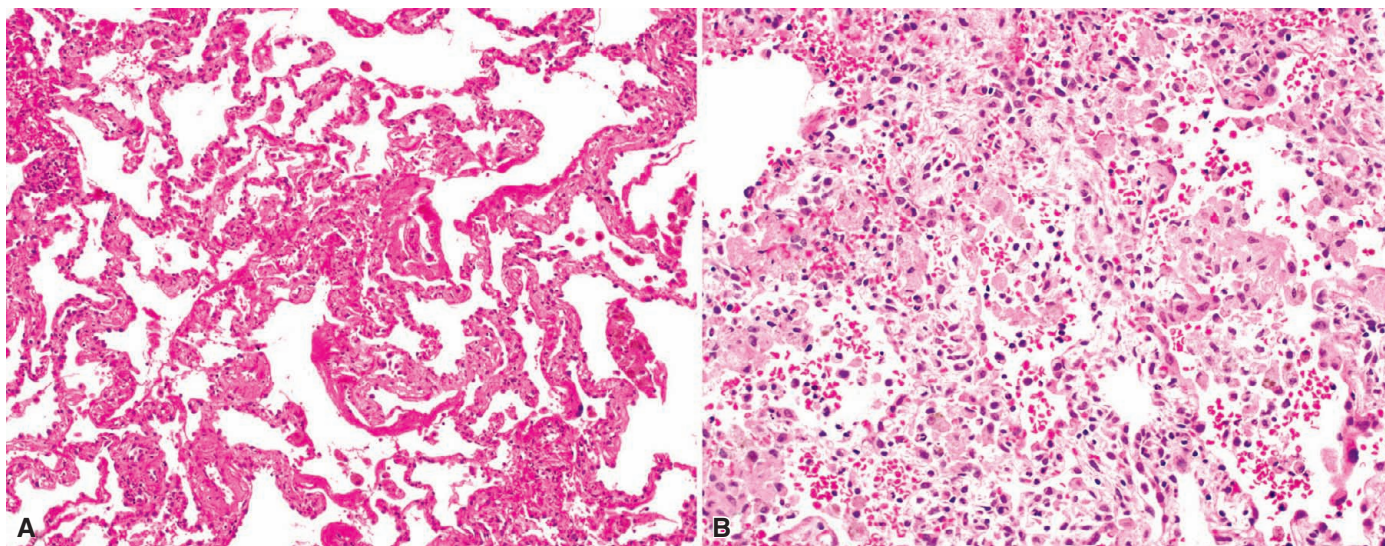


Figure 6.37 Diffuse alveolar damage (DAD) in Goodpasture syndrome. (A) Goodpasture syndrome characteristically produces alveolar hemorrhage, but acute lung injury with hyaline membranes also can occur. (B) In another example of DAD in Goodpasture syndrome, greater interstitial fibroblast proliferation is evident, along with more numerous airspace macrophages.

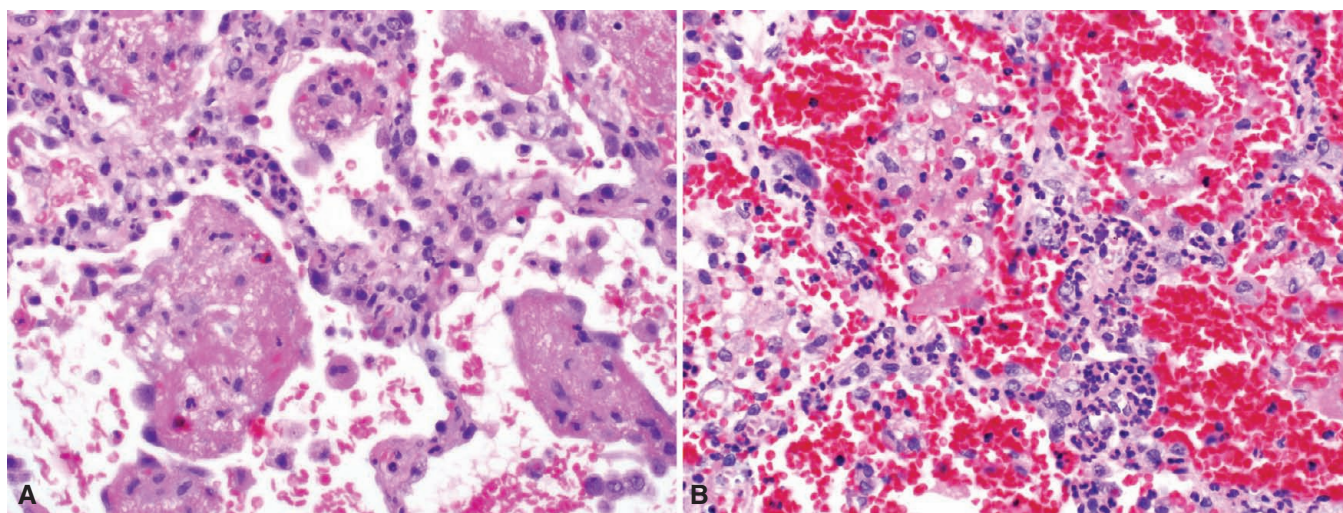


Figure 6.38 Acute lung injury in the setting of pulmonary vasculitis. (A) Acute lung injury with interstitial edema, airspace fibrin, and fresh red blood cells in a patient who presented with acute hemoptysis and renal failure and was found to have a positive anti-glomerular basement membrane autoantibody. (B) Marked capillaritis associated with airspace edema and fresh hemorrhage in a patient who was found to have a perinuclear antineutrophil cytoplasmic antibody–associated vasculitis most consistent with microscopic polyangiitis.

Oxygen Toxicity and Inhalants

Oxygen is a well-known cause of ARDS and a useful model for all types of DAD.^{4,126,127} 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.¹²⁸ In 1967 Nash et al. described the sequential histopathologic changes of this injury,¹²⁶ later reemphasized by Pratt.¹²⁷ In neonates receiving oxygen for hyaline membrane disease, bronchopulmonary dysplasia was reported to occur.¹²⁹ As might be expected, the features of hyaline membrane disease in

neonates and oxygen-induced DAD in adults are indistinguishable (see Fig. 6.30). 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, posttraumatic pulmonary insufficiency, and progressive pulmonary consolidation.² It

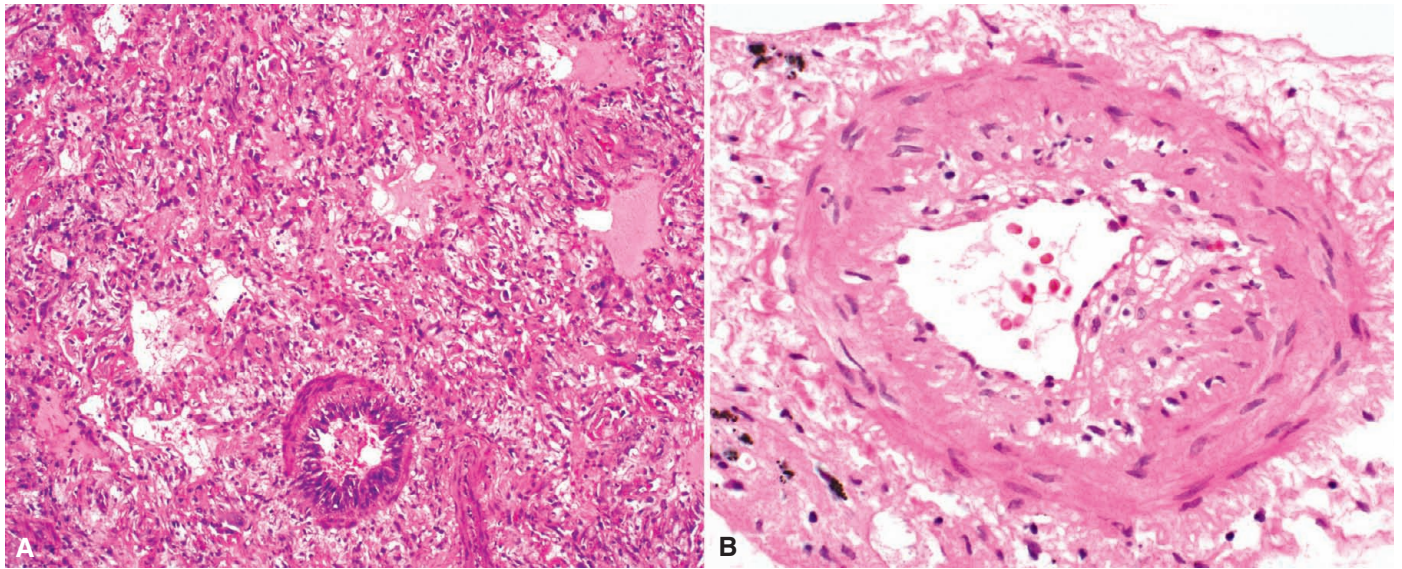


Figure 6.39 Diffuse alveolar damage (DAD) from radiation injury. (A) Radiation injury to the lung can produce DAD with striking reactive type II cell hyperplasia. (B) Foamy macrophages are present in the wall of a pulmonary artery involved in radiation pneumonitis.

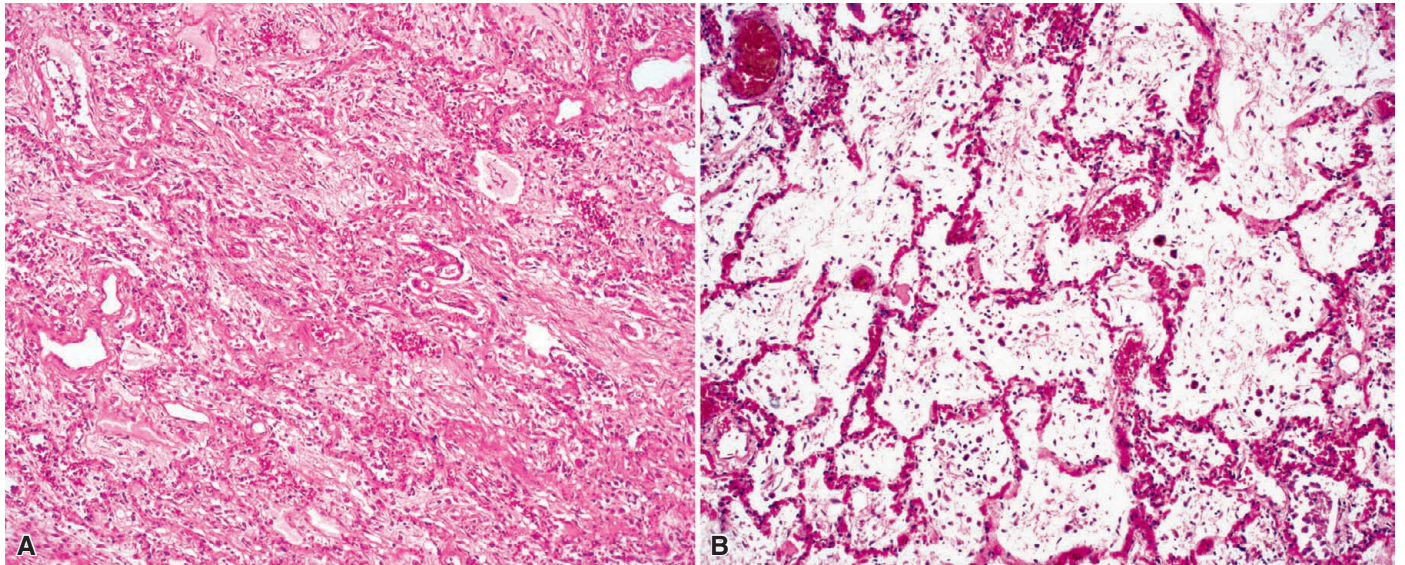


Figure 6.40 Diffuse alveolar damage from paraquat poisoning. Paraquat produces a dramatic and characteristic pattern of lung injury with prominent airspace fibroplasia (A) and eventual fibrosis with collagen deposition in a loose pattern (B).

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. After ARDS begins, the mortality rate is high.^{1,2,130}

Ingested Toxins

Paraquat is a potent herbicide that causes the release of hydrogen peroxide and superoxide free radicals, resulting in damage to cell membranes.¹³¹⁻¹³³ 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. 6.40). 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

Pathologist Approach to the Differential Diagnosis of Acute Lung Injury

The histologic spectrum encountered in acute lung injury is broad. Very early cases may look nearly normal with only mild interstitial and alveolar edema. Other more advanced cases are clearly abnormal with fibrin, inflammation, and organization. The basic elements of the acute injury pattern include interstitial edema, alveolar edema, fibrin, hyaline membranes, reactive pneumocytes, and organization (see Box 6.2). Acute lung injury is a pathologic pattern and by itself is a nonspecific finding. From a practical perspective, after an acute lung injury pattern is

identified, careful search for the following additional features often help to narrow the list of possible causes (summarized in Table 6.1).

Presence of hyaline membranes. The most commonly encountered potential etiologic disorders include infection, connective tissue disease, drug toxicity, and an idiopathic form of diffuse alveolar damage (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.^{121,134} 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.^{44,46,51}

Presence of eosinophils. Acute and organizing DAD with prominent interstitial and alveolar eosinophils is characteristic of acute eosinophilic pneumonia.¹⁰⁴ However, if the patient has been treated with 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.¹¹² Care must be taken not to interpret the pigmented macrophages seen in the lungs of cigarette smokers as evidence of hemorrhage.¹³⁵ The hemosiderin in macrophages related to true hemorrhage in the lung (from any cause) is globular, often slightly refractile, and golden-brown in color.^{57,112–114}

Presence of atypical cells. Viral infections often produce cytopathic effects, including intracellular inclusions (see Chapter 7). 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.^{33,37,38,136,137} 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.^{79,124,125}

Presence of foamy cells. Alveolar lining cells with vacuolated cytoplasm accompanied by intraalveolar foamy macrophages are characteristic features seen in patients taking amiodarone, and amiodarone toxicity may lead to acute lung injury changes.^{97–99,101} In some cases of radiation pneumonitis, foam cells are seen in the intima and media of blood vessels.^{79,125}

Presence of foreign material. Foreign material in the spaces in the form of vegetable matter or other food elements is indicative of aspiration. Massive aspiration events may cause DAD. Other foreign material, such as radiation impregnated beads may also be encountered.

Presence of advanced interstitial fibrosis. Clinical IPF is associated with the changes of UIP on pathologic examination (see Chapter 8), with advanced lung remodeling. Of interest, IPF undergoes episodic exacerbation, and on occasion such exacerbation may be overwhelming, with resultant DAD.¹³⁸ 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 IPF that manifests for the first time as an acute episode of exacerbation.

Table 6.1 Key Histopathologic Findings in Acute Lung Injury, With Possible Causes

Finding	Possible Causes
Hyaline membranes	Infection, connective tissue 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)	Connective tissue diseases (SLE, RA, MCTD, polymyositis/dermatomyositis, scleroderma), Goodpasture syndrome, microscopic polyangiitis, granulomatosis with polyangiitis (organizing pneumonia—capillaritis variant)
Organizing pneumonia (alveolar organization)	Resolving infection, drug toxicity, connective tissue diseases, idiopathic (cryptogenic organizing pneumonia); acute exacerbation of idiopathic pulmonary fibrosis
Fibrin and organization	Infection, drug toxicity, idiopathic (acute fibrinous and organizing pneumonitis), connective tissue diseases; acute exacerbation of idiopathic pulmonary fibrosis
Alveolar eosinophils with fibrin	Infection, connective tissue 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
Foreign material	Aspiration, yttrium 90 microspheres

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

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 6.3.

Box 6.3 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, antineutrophil 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, rheumatoid factor, Jo-1, Scl-70, antifibrillar, 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. The pathology in immunocompromised patients may not show necrosis, neutrophils, or granulomas, all features favoring an infectious etiology.

Self-assessment questions and cases related to this chapter can be found online at ExpertConsult.com.

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Multiple Choice Questions

- Which of the following steps is/are appropriate in the processing of lung biopsies from pediatric patients?
 - Touch imprints of the tissue for histochemical evaluation
 - Fixation of a portion of the specimen in glutaraldehyde
 - Submission of tissue from the operating room for cultures
 - Freezing of a portion of the specimen in cryomatrix
 - All of the above

ANSWER: E

- Which of the following is NOT in the macroscopic differential diagnosis of cystic lung lesions in children?
 - Adenomatoid malformation
 - Intralobar sequestration
 - Congenital lobar overinflation
 - Lymphangioliomyomatosis
 - Pneumatocele

ANSWER: D

- Pulmonary sequestration is characterized by:
 - Communication with second-order bronchial lumina
 - Solely systemic vascular supply
 - Exclusive extralobar localization
 - Densely apposed, atelectatic airspaces
 - Multifocal aggregates of eosinophils

ANSWER: B

- Extralobar pulmonary sequestrations may occasionally contain which ONE of the following heterotopic tissues?
 - Bone
 - Glial nodules
 - Hepatoid anlage
 - Striated muscle
 - Enteric-type epithelium

ANSWER: D

- Congenital malformations of the pulmonary airways:
 - Are most often seen in stillborns or newborns
 - Represent malformations of each bronchopulmonary segment
 - May be difficult to subclassify in fetal lungs
 - Must be distinguished from pleuropulmonary blastoma
 - All of the above

ANSWER: E

- Which ONE of the following tissues may have implications for future lung pathology, if it is present in a congenital malformation of the pulmonary airways?
 - Striated muscle
 - Cartilage
 - Mucinous epithelium
 - Embryonic-type mesenchymal tissue
 - Lymphoid aggregates

ANSWER: C

- Pulmonary interstitial emphysema in children:
 - May be caused by alveolar rupture
 - Can show a bronchovascular distribution
 - Is associated with mechanical ventilation
 - Shows microcysts mantled by giant cells
 - All of the above

ANSWER: E

- Peripheral cysts in hypoplastic lung tissue have been associated with:
 - Cri du chat syndrome
 - Holoprosencephaly
 - Beckwith-Wiedemann syndrome
 - Down syndrome
 - Cornelia de Lange syndrome

ANSWER: D

- Congenital lobar overinflation:
 - May result from bronchomalacia
 - Is often linked with pleuropulmonary blastoma
 - Is synonymous with congenital malformation of the pulmonary airways, type 0
 - Is idiopathic in 75% of cases
 - Occurs almost exclusively in the lower lobes

ANSWER: A

- Acinar pulmonary dysplasia:
 - Features cystic change and enlargement of all lobes
 - Accounts for one of the most common surgical specimens in pediatric lung pathology
 - Demonstrates a lack of alveolarization microscopically
 - Usually becomes manifest clinically at approximately 2 years of age
 - All of the above

ANSWER: C

- Pulmonary hyperplasia:
 - Refers to an increased number of alveoli relative to the corresponding conducting airways
 - Shows radial alveolar counts of 20 to 30
 - Is usually associated with proximal airway atresia
 - Is part of the Beckwith-Wiedemann syndrome
 - Characteristically is a consequence of hyaline membrane disease

ANSWER: C

- Alveolar capillary dysplasia:
 - Is asymptomatic unless pneumonia develops
 - Produces isolated pulmonary venous hypertension
 - Is an alternate diagnostic term for bronchopulmonary dysplasia
 - May be associated with extrapulmonary malformations
 - Is thought to be caused by prolonged mechanical ventilation of infants

ANSWER: D

13. Congenital pulmonary lymphangiectasis:
- A. Manifests itself with recurrent chylothorax in children
 - B. Occurs in all compartments of the lungs except the broncho-vascular bundles
 - C. Is a “nuisance” condition with no significant mortality
 - D. Can be imitated morphologically by chronic heart failure
 - E. None of the above

ANSWER: D

14. Pulmonary arteriovenous malformation:
- A. Is always lethal before 5 years of age
 - B. May produce sudden death in children
 - C. Is, by definition, a panlobar and multifocal process
 - D. May be part of the Osler-Weber-Rendu syndrome
 - E. All of the above

ANSWER: D

15. Which ONE of the following statements concerning hyaline membrane disease of the newborn is FALSE?
- A. It is caused by overproduction of structurally abnormal surfactant
 - B. It ultimately results from shear stress on alveolar walls
 - C. Aggressive mechanical ventilation exacerbates the disorder
 - D. It can be complicated by infection with alveolar neutrophilia
 - E. It has a morphologic image similar to that of adult respiratory distress syndrome

ANSWER: A

16. Bronchopulmonary dysplasia:
- A. Is caused by partial deletion of chromosome 6q
 - B. Produces macroscopic pleural pseudofissures
 - C. Manifests with marked cytologic atypia of bronchial epithelial cells
 - D. Shows uniform hypoaeration of the most distal airspaces
 - E. Results in radial alveolar counts in the range of 40 to 50

ANSWER: B

17. Chronic pneumonitis of infancy:
- A. Is associated with in utero infection by cytomegalovirus
 - B. Shows a virtual absence of type II pneumocytes
 - C. Demonstrates conspicuous remodeling of airspaces
 - D. Has a good prognosis and can be managed conservatively
 - E. All of the above

ANSWER: C

18. Obliterative bronchiolitis in children can be associated with all of the following EXCEPT:
- A. Adenovirus
 - B. Influenza
 - C. Stevens-Johnson syndrome
 - D. Paragonimiasis
 - E. Graft-versus-host disease

ANSWER: D

19. Which ONE of the following storage disorders does NOT usually involve the lung parenchyma?
- A. Niemann-Pick disease
 - B. Gaucher disease
 - C. Glycogen storage disease
 - D. Mucopolipidosis
 - E. Ceroid lipofuscinosis

ANSWER: E

20. Which of the following is/are potential cause(s) of recurrent intrapulmonary hemorrhage in children?
- A. Capillaritis
 - B. Coagulopathies
 - C. Milk aspiration syndrome
 - D. Venooclusive disease
 - E. All of the above

ANSWER: E

Case 1

Diffuse alveolar damage with hyaline membranes (eSlide 6.1)

- a. History—A 49-year-old male without significant past medical history presented to the emergency room with acute shortness of breath and cough. A week prior he participated in a half marathon without difficulty. He was taking no medications and had no exposures. His oxygen saturation was 82% on room air. He progressed to respiratory failure after being admitted to the intensive care unit. A surgical lung biopsy was performed.
- b. Pathologic findings—From scanning magnification the biopsy shows preserved lung parenchyma without significant scarring. However, there is a diffuse process that gives the biopsy a “pink” appearance from low power. At higher power, the histologic features of diffuse alveolar damage (DAD) are recognized including alveolar wall edema, reactive type-II pneumocytes, and hyaline membranes. A few foci of organization are also present. A significant inflammatory cell infiltrate is not recognized. There is no pleuritis, hemosiderosis, granulomas, or necrosis.
- c. Diagnosis—Diffuse alveolar damage.
- d. Discussion—Features of acute lung injury are readily apparent, and the numerous hyaline membranes support a diagnosis of diffuse alveolar hemorrhage. The biopsy is negative for numerous eosinophils, foamy macrophages, alveolar hemorrhage, foreign material, neutrophils, necrosis, and granulomas. Therefore the histology does not suggest a particular etiology on this case. Acid-fast and fungal stains were negative. Extensive serologic screening studies were negative, and cultures are negative to date. Because the additional work-up is negative, this case is best categorized as acute respiratory distress syndrome.

Case 2

Acute and fibrinous organizing pneumonia (eSlide 6.2)

- a. History—A 55-year-old female presented with acute onset dyspnea. Her past medical history was significant for rheumatoid arthritis for which she had recently begun methotrexate. Imaging studies show bilateral ground-glass infiltrates in upper and lower lobes. A surgical lung biopsy was performed.
- b. Pathologic findings—From scanning magnification, the lung architecture appears preserved without significant fibrosis. At higher power there is an extensive airspace filling process. Many airspaces are filled with fibrin and scattered inflammatory cells. In other areas there is light pink material suggestive of edema. Finally, some early fibroblastic polyps of organization are present. The interstitium shows

edema and a mixed lymphoplasmacytic infiltrate. No hemorrhage, necrosis, or hyaline membranes are present.

- c. Diagnosis—Acute fibrinous and organizing pneumonia (AFOP).
- d. Discussion—AFOP presents in the same fashion as diffuse alveolar damage (DAD) and the differential diagnosis for AFOP and DAD is the same, including drug reaction, toxin exposure, connective tissue disease, infection, and as an idiopathic reaction. They both represent forms of acute lung injury. In this case the degree of lymphoplasmacytic inflammation in the interstitium raises the possibility of a background connective tissue disease. Additional history revealed she had recently cut her methotrexate dose in half to save money. She had also recently experienced inflammatory flares in her joints. All of these factors support a diagnosis of AFOP related to rheumatoid arthritis. A definitive etiology for AFOP is identified in a minority of patients.

Case 3

Acute lupus pneumonitis (eSlide 6.3)

- a. History—A 34-year-old African-American female presented with the emergency room with cough and shortness of breath. Upon further questioning, she reported some blood-tinged sputum. The patient was febrile, and chest imaging studies showed bilateral ground-glass infiltrates without lobar distribution. Serologic studies revealed an elevated erythrocyte sedimentation rate and C-reactive protein and positive antinuclear antibodies and anti-double-stranded DNA antibodies. A surgical lung biopsy was performed.
- b. Pathologic findings—The biopsy shows preserved lung architecture with a diffuse abnormality from scanning magnification. There is extensive alveolar wall edema with numerous foci of hyaline membranes. Patchy organization is present, along with a relatively diffuse lymphoplasmacytic interstitial infiltrate.
- c. Diagnosis—Acute lupus pneumonitis.
- d. Discussion—Based on the histologic features alone, this biopsy is diagnostic of diffuse alveolar damage. However, the clinical history is required to arrive at a more specific diagnosis of acute lupus pneumonitis. The biopsy does show a mild increase in lymphoplasmacytic interstitial inflammation that would be unusual for most cases of idiopathic acute respiratory distress syndrome.

Case 4

Amiodarone-induced diffuse alveolar damage (eSlide 6.4)

- a. History—A 71-year-old male presented to the emergency room with acute shortness of breath first noted the evening prior. His past history was significant for a deceased donor renal transplant 10 days prior to presentation for end-stage renal disease secondary to diabetes. He also had a history of hypertension and atrial fibrillation. Imaging studies showed bilateral ground-glass opacities in the upper and lower lobes.
- b. Pathologic findings—From scanning magnification there is preserved architecture without significant fibrosis. There is diffuse alveolar wall thickening, mostly by edema. Overlying pneumocytes show reactive epithelial changes. Numerous hyaline membranes and focal fibrin in airspaces are present. Some airspaces are filled with numerous macrophages showing finely vacuolated cytoplasm. Some

pneumocytes show similar cytoplasmic vacuolization. There is no necrosis, neutrophils, or hemorrhage.

- c. Diagnosis—Diffuse alveolar damage (DAD) with foamy macrophages. A drug reaction leads the differential diagnosis.
- d. Discussion—Based on the presence of the patchy but marked cytoplasmic vacuolization in the macrophages and pneumocytes, a drug reaction is the most likely etiology for the DAD pattern. In particular, amiodarone is a commonly used drug that causes this cytoplasmic vacuolization, even in the absence of associated lung injury. This was communicated to the clinical services who identified the patient was indeed taking amiodarone, even on the day of transplant. Amiodarone-induced lung injury is associated with prolonged use of the drug and with an inciting event (such as a major operation). This patient had been on amiodarone for several years. Following clinicopathologic correlation, this case is best diagnosed as amiodarone-induced DAD. The patient was treated with pulse high-dose steroids and eventually had a full recovery.

Case 5

Acute eosinophilic pneumonia (eSlide 6.5)

- a. History—A previously healthy 29-year-old female presented to the emergency room with acute-onset shortness of breath and cough. She was initially evaluated and admitted to the medicine floor for presumed pneumonia. However, she quickly deteriorated and was transferred to the medical intensive care unit and required intubation. Imaging studies showed bilateral ground-glass opacities without lobar distribution. Additional history obtained from the patient's roommate revealed the patient was recently treated with sulfamethoxazole and trimethoprim for a urinary tract infection.
- b. Pathologic findings—The overall architecture of the lung appears intact, but there is a diffuse acute lung injury pattern including alveolar wall edema, airspace fibrin, organization, and scattered hyaline membranes. Pneumocytes show marked reactive atypia. There are numerous eosinophils in the airspaces, embedded within the fibrin, and within the interstitium. Numerous airspace macrophages are also present. No necrosis or granulomas are identified.
- c. Diagnosis—Acute eosinophilic pneumonia.
- d. There are four key histologic features in acute eosinophilic pneumonia, all of which are satisfied in this case.
 - i. Alveolar septal edema
 - ii. Eosinophilic airspace macrophages
 - iii. Tissue and airspace eosinophils
 - iv. Reactive atypia of type-II pneumocytes

There is a differential diagnosis for the acute eosinophilic pneumonia pattern of injury including drug reaction, infection, connective tissue disease, smoking related, and idiopathic. Rigorous exclusion of infection is imperative and requires both infectious stains on the tissue blocks and culture studies. Recognition of this injury pattern is of particular importance as these patients typically respond dramatically to high-dose steroids and have a better prognosis than that of diffuse alveolar damage. In this patient the exposure to a sulfa drug in the days prior to presentation was the likely etiology. She was treated with steroids, dramatically improved, and was discharged in 4 days.