Chapter 23: Pathology of Restrictive Lung Diseases

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LEARNING OBJECTIVES

The student will be able to define restrictive lung diseases and differentiate their various forms including etiology, pathogenesis if known, and clinical presentation.

The student will be able to describe and recognize gross and microscopic features of acute and chronic restrictive lung diseases.

Restrictive lung diseases are characterized by reduced lung compliance that requires greater pressure to inflate the lungs and, clinically, typically are manifest as dyspnea. Restrictive lung disease can result from external compression of the lung parenchyma; examples include severe scoliosis, chest wall tumors, and expansion of the pleural space by fluid or air (Chaps. 26 and 29). This chapter will focus on restrictive lung diseases in which the restriction is intrinsic to the lung rather than due to external compression. Although many different restrictive lung diseases will be discussed, there are some common themes to restrictive lung disease. Many such diseases show thickening of alveolar septa and alveolar epithelial and endothelial injury that lead to $V_A/Q$ mismatch. With progression of many such diseases, patients develop severe hypoxemia and respiratory failure. These are often complicated with pulmonary hypertension and cor pulmonale (right ventricular dilatation due to lung disease).

ACUTE RESTRICTIVE LUNG DISEASES

The acute respiratory distress syndrome (ARDS) is a clinical syndrome characterized by the acute onset of respiratory distress with hypoxemia, reduced lung compliance, and diffuse pulmonary infiltrates in the absence of primary left heart failure; a less severe form of the syndrome is acute lung injury (ALI) (Chap. 28). Diffuse alveolar damage (DAD) is the morphologic counterpart of ALI/ARDS. Though DAD can complicate many conditions (Table 23.1), more than one-half of cases occur in the settings of sepsis, diffuse pulmonary infections, gastric aspiration, and trauma.

Table 23.1 Conditions associated with development of ALI and ARDS

<table>
<thead>
<tr>
<th>Infection</th>
<th>Inhaled Irritants</th>
<th>Physical Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>Oxygen toxicity</td>
<td>Mechanical trauma, head injury</td>
</tr>
<tr>
<td>Diffuse pulmonary infections</td>
<td></td>
<td>Pulmonary contusion</td>
</tr>
<tr>
<td>Viral pneumonia</td>
<td>Smoke</td>
<td>Near-drowning</td>
</tr>
<tr>
<td>Mycoplasma pneumonia</td>
<td>Irritant gases</td>
<td>Fractures with fat embolism</td>
</tr>
<tr>
<td>Pneumocystis pneumonia</td>
<td>Misc. chemicals</td>
<td>Burns</td>
</tr>
</tbody>
</table>
Miliary tuberculosis  Ionizing radiation

Gastric aspiration  Hematologic Conditions  Hypersensitivity Reactions
Heroin or methadone overdose  Multiple transfusions  Organic solvents
Acetylsalicylic acid  Disseminated intravascular coagulation  Misc. drugs
Barbiturate overdose  Paraquat poisoning
Pancreatitis  Uremia  Cardiopulmonary Bypass


The pathogenesis of DAD begins with endothelial damage or, less frequently, epithelial damage. Within 30 minutes, macrophages secrete canonical proinflammatory cytokines including $\text{TNF-}\alpha$, $\text{IL-1}$, and $\text{IL-8}$, leading to neutrophil chemotaxis and activation (Chap. 10). Activated neutrophils secrete oxidants, proteases, platelet activating factor (PAF), and leukotrienes, the results of which are tissue damage, edema, inactivation of pulmonary surfactant, and the formation of hyaline membranes, the morphologic hallmark of DAD (see below). Later, macrophage secretion of transforming growth factor-beta (TGF-\(\beta\)) and platelet-derived growth factor (PDGF) causes proliferation of fibroblasts with subsequent synthesis of collagen. The pathogenesis of DAD is further discussed in Chap. 28.

Morphologically, lungs with DAD show reduced crepitus and resemble liver in consistency. Early in the course, the lungs are dense and dark red; as collagen deposition occurs, their color changes to gray (Fig. 23.1). Microscopically, DAD shows a spectrum of changes that can be organized into three phases (Fig. 23.2). The earliest of these is the exudative phase, with vascular congestion, interstitial and intra-alveolar edema, alveolar epithelial necrosis, neutrophil margination, dilatation and/or collapse of alveolar ducts, fibrin thrombi, and hyaline membranes. **Hyaline membranes**, the hallmark of DAD, are composed of edema fluid and necrotic epithelial cells. Subsequent to this exudative period is the proliferative phase, in which there is type 2 pneumocyte hyperplasia as well as fibroblast infiltration of the interstitium and the intra-alveolar exudate (ie, the hyaline membranes). Finally, as fibroblasts synthesize collagen, DAD enters the fibrotic phase, with fibrosis of the exudate (also described as organization) and expansion of the interstitium by fibrosis.

**FIGURE 23.1**

In diffuse alveolar damage (DAD), lungs are initially dense and dark red (a). As collagen deposition occurs, their color becomes gray (b). From Travis et al. Atlas of Nontumor Pathology: Volume 2: Non-Neoplastic Disorders of the Lower Respiratory Tract, American Registry of Pathology; 2002.
Clinically, ARDS begins with dyspnea and tachypnea; early in its course, a chest radiograph may be normal. Subsequently, the patient develops cyanosis, hypoxemia, and respiratory failure, at which point a chest
radiograph typically shows diffuse bilateral infiltrates. As hypoxemia becomes unresponsive to oxygen therapy, respiratory acidosis often develops. Of note, oxygen therapy can worsen the alveolar epithelial damage. ARDS can be complicated by secondary infection of the hyaline membranes and/or by death, the latter occurring in approximately 40% of cases in the United States.

**Acute interstitial pneumonia** is a rapidly progressive acute restrictive lung disease with a presentation similar to ARDS but without a known underlying etiology; an alternate name is **idiopathic ALI-DAD**. Morphologically, it closely resembles DAD and may be indistinguishable from DAD. Mortality rates in various studies have ranged from 33% to 74%. Survivors often experience complete or near complete recovery.

**CHRONIC RESTRICTIVE LUNG DISEASES**

The chronic restrictive lung diseases are also called **diffuse interstitial lung diseases**, because changes in the interstitium dominate the morphologic appearance, and **diffuse infiltrative diseases**, because chest radiographs show diffuse infiltrates. Chronic restrictive lung diseases are a heterogeneous group of disorders without uniform classification, without uniform terminology, and often without known etiology or pathogenesis. Nevertheless, they share many clinical and morphological features and, at end-stage, they may be indistinguishable from each other. Clinically, patients with chronic restrictive lung diseases have dyspnea, tachypnea, end-inspiratory crackles, and eventual cyanosis (Chap. 24). Later, these patients often develop secondary pulmonary hypertension (Chap. 26) and right heart failure with cor pulmonale. Pathogenetically, many of the chronic restrictive lung diseases begin with **alveolitis**, leading to distortion of alveolar structure and release of mediators that incite cell injury and induce fibrosis. Morphologically, many of the chronic restrictive lung diseases, particularly in later stages, are characterized by **interstitial fibrosis**. The end-stage of many of the chronic restrictive lung diseases is the classic **honeycomb lung**.

**Idiopathic pulmonary fibrosis** (IPF) is a poorly understood, idiopathic, nongranulomatous chronic restrictive lung disease that morphologically is characterized by diffuse interstitial fibrosis. Although many alternate names for the disease exist, **cryptogenic fibrosing alveolitis** is the one most frequently encountered. The pathogenesis of IPF is poorly understood but appears to involve repeated cycles of alveolitis (due to an unidentified agent) that are followed by wound healing with fibroblast proliferation. Grossly, lungs with well-developed IPF have a pleural surface with a **cobblestone** appearance due to wound contraction in interlobular septa. The cut surface of IPF lungs shows rubbery-to-firm, white patches in subpleural regions and in the interlobular septa (Fig. 23.3).

**FIGURE 23.3**

Usual interstitial pneumonia in idiopathic pulmonary fibrosis. Pale regions represent fibrosis with cystic change (honeycomb pattern) and are concentrated in the lower lobe and in the subpleural zone of the upper lobe (left of image). The darker parenchyma represents portions of lung with little or no fibrosis. From Travis et al. Atlas of Nontumor Pathology: Volume 2: Non-Neoplastic Disorders of the Lower Respiratory Tract, American Registry of Pathology; 2002.
Histologically, the morphology of IPF is described as **usual interstitial pneumonia (UIP)** *(Fig. 23.4)*. Although required for a diagnosis of IPF, UIP is not specific and can be seen in other diseases (eg, collagen vascular diseases, asbestosis; see below). UIP is characterized by regional and temporal heterogeneity where different lung foci show different stages of disease. In addition to interstitial fibrosis, magnified in subpleural zones and interlobular septa, UIP includes characteristic **fibroblastic foci** and typically shows prominent type 2 pneumocyte hyperplasia. End-stage UIP shows dilated airspaces lined by cuboidal or low columnar epithelium separated by inflamed fibrous tissue. Patients with IPF typically present in the fifth to eighth decade with increasing dyspnea on exertion and dry cough, followed by hypoxemia, cyanosis, and digital clubbing. Progression of IPF is unpredictable, but the mean survival time is approximately three years. The only definitive therapy for IPF is lung transplantation.

**FIGURE 23.4**

Usual interstitial pneumonia in idiopathic pulmonary fibrosis. (a) Cystically dilated airspaces are separated by fibrotic and thickened septa. (b) A characteristic finding in UIP is the fibroblastic focus (arrow). (b): *From Travis et al. Atlas of Nontumor Pathology: Volume 2: Non-Neoplastic Disorders of the Lower Respiratory Tract, American Registry of Pathology; 2002.*
CLINICAL CORRELATION 23.1

By turning up the brightness on a computed tomogram, the resulting CT images of the lungs can demonstrate severity of interstitial disease. The settings used to image lung parenchyma are the lung windows and blur detail in surrounding soft tissue. Fig. 23.5(a) is high-resolution CT of UIP, with subpleural distribution of abnormalities. Fig. 23.5(b) is an HRCT of end-stage UIP with honeycombing that is more pronounced on the patient's left side (right side of image).

FIGURE 23.5


Non-specific interstitial pneumonia (NSIP) is an idiopathic, nongranulomatous lung disease without the defining diagnostic features of better-characterized diseases. Histologically, NSIP can show a cellular pattern with mild to moderate expansion of the interstitium by lymphocytes and plasma cells with either a uniform or patchy distribution [Fig. 23.6(a)]. Alternatively, a fibrosing pattern with diffuse or patchy interstitial fibrosis is noted [Fig. 23.6(b)]. In contrast to UIP, the fibrosing pattern of NSIP does typically not show fibroblastic foci or the regional/temporal heterogeneity of disease.

FIGURE 23.6

Sarcoidosis is an idiopathic multisystem disease characterized by granulomatous inflammation (typically noncaseating) in many tissues and organs. Since there are many causes of granulomatous inflammation—including foreign body, mycobacterial infection, and fungal infection—sarcoidosis is a diagnosis of exclusion. Though its presentation can include involvement of virtually any organ, patients typically have bilateral hilar lymphadenopathy and/or lung involvement. Sarcoidosis shows a racial bias (black:white of about 10:1) and a female gender bias. Though the etiology of sarcoidosis is unknown, its pathogenesis likely involves a type IV hypersensitivity reaction (cell-mediated, delayed) to a currently unknown antigen. Familial and racial clustering and association with certain HLA subtypes imply that development of sarcoidosis may require a genetic predisposition. Many features of sarcoidosis suggest that it is an infectious disease, but there is no unequivocal evidence that sarcoidosis has an infectious etiology. The morphology of sarcoidosis is nonspecific: noncaseating granulomatous inflammation (Fig. 23.7). A granuloma is a circumscribed collection of epithelioid histiocytes [Fig. 23.7(c)]; the term "epithelioid" is used to describe cells that have more cytoplasm than typical histiocytes, imparting a resemblance to squamous epithelial cells. Epithelioid histiocytes can merge with each other, producing a multinucleated giant cell. While multinucleated giant cells are common in granulomata, not all granulomata contain them. In sarcoidosis, the granulomata often contain Schaumann bodies [laminated concretions of calcium and protein, Fig. 23.7(d)] and asteroid bodies [stellate inclusions within giant cells, Fig. 23.7(e)]. However, neither Schaumann bodies nor asteroid bodies are specific for sarcoidosis.

**FIGURE 23.7**

Sarcoidosis. (a) Grossly, numerous white nodules are associated with bronchovascular bundles. (b) At low magnification, the numerous granulomata appear as eosinophilic nodules. (c) At higher magnification, these nodules are seen to be composed of epithelioid histiocytes and multinucleated giant cells (arrow). Though nonspecific, Schaumann bodies [(d), arrow] and asteroid bodies [(e), arrow] also can be present. (a), (b), (d), and (e): From Travis et al. Atlas of Nontumor Pathology: Volume 2: Non-Neoplastic Disorders of the Lower Respiratory Tract, American Registry of Pathology; 2002. (c): From Klatt. Robbins and Cotran Atlas of Pathology, 2nd ed. 2010.
As mentioned above, the granulomata in sarcoidosis can involve virtually any organ but typically involve the pulmonary interstitium and hilar lymph nodes. Pulmonary involvement is often complicated by interstitial fibrosis. Other organs that are commonly involved include skin, eyes, lacrimal glands, salivary glands, spleen, liver, and skeletal muscle. Clinically, sarcoidosis is often asymptomatic. If symptomatic, sarcoidosis ranges from progressive chronicity to periods of activity separated by periods of remission. Presentation is typically due to respiratory involvement, with dyspnea, cough, chest pain, and hemoptysis; alternatively, constitutional signs and symptoms (fever, fatigue, weight loss, anorexia, night sweats) may dominate the clinical scenario. Specific symptoms at presentation are markedly variable due to the complex of sites showing involvement. Approximately 65%-70% of patients recover spontaneously or with steroid therapy and have minimal or no residual disease, ~20% of patients develop permanent lung dysfunction or visual impairment, and 10%-15% develop progressive pulmonary fibrosis with subsequent cor pulmonale or central nervous system damage.

**Hypersensitivity pneumonitis** is typically an occupational disease that begins with alveolar damage from exposure to an organic antigen. The acute phase of the disease occurs 4-6 hours after antigen exposure in a previously sensitized host, likely represents a **type III hypersensitivity reaction** (immune complex), and is typified by diffuse and nodular infiltrates on chest radiograph, restrictive pattern of pulmonary function tests, and neutrophilic inflammation. With continuous antigen exposure, the disease enters its chronic phase with respiratory failure, dyspnea, cyanosis, decreased lung compliance, and decreased total lung capacity. The chronic phase is a type IV hypersensitivity reaction (delayed, cell-mediated) characterized histologically by lymphocytes, plasma cells, and foamy histiocytes in alveoli, alveolar walls, and around terminal bronchioles; interstitial fibrosis; obliterative bronchiolitis; and, in about two-thirds of cases, granulomata. Of note, the eosinophilia that is typical of type I hypersensitivity reactions is not a significant feature of hypersensitivity pneumonitis. If the offending antigen is removed during the acute phase, the disease resolves in weeks. Once the disease has progressed to its chronic phase, resolution can be slow, and approximately 5% of patients develop respiratory failure and die. Table 23.2 summarizes the myriad diseases that represent forms of hypersensitivity pneumonitis.

**Table 23.2 Typical presentations of hypersensitivity pneumonitis**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Exposure</th>
<th>Antigens</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fungal/Bacterial Antigens</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Farmer's lung</td>
<td>Moldy hay</td>
<td><em>Micropolyspora faeni</em></td>
</tr>
<tr>
<td>Bagassosis</td>
<td>Moldy sugar cane</td>
<td><em>Thermoactinomyces sacchari</em></td>
</tr>
<tr>
<td>Maple bark disease</td>
<td>Moldy maple tree bark</td>
<td><em>Cryptostroma corticale</em></td>
</tr>
<tr>
<td>Humidifier lung</td>
<td>Cool-mist humidifier</td>
<td>Thermophilic <em>Actinomycetes, Aureobasidium pullulans</em></td>
</tr>
<tr>
<td>Malt worker's lung</td>
<td>Moldy barley grain</td>
<td><em>Aspergillus clavatus</em></td>
</tr>
<tr>
<td>Cheese washer's lung</td>
<td>Moldy cheeses</td>
<td><em>Penicillium casei</em></td>
</tr>
<tr>
<td><strong>Insect Products</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miller's lung</td>
<td>Dust-contaminated grain</td>
<td><em>Sitophilus granarius</em> (wheat weevil)</td>
</tr>
<tr>
<td><strong>Animal Products</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bird fancier's lung</td>
<td>Pigeon, parakeet, chicken</td>
<td>Serum proteins in droppings</td>
</tr>
<tr>
<td><strong>Chemicals</strong></td>
<td></td>
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</tr>
</tbody>
</table>
Chemical worker's lung  Chemical industries  Trimellitic anhydride, isocyanates


CLINICAL CORRELATION 23.2

A 13-year-old boy with a history of congenital heart disease presents with interstitial lung disease of unknown etiology. A wedge biopsy of lung is procured and shows interstitial non-necrotizing granulomatous inflammation with multinucleated giant cells (Fig. 23.8). Special stains for acid-fast microorganisms and fungi are negative. Histologic findings are nonspecific but suggestive of hypersensitivity pneumonitis. Subsequently, additional history is obtained: the patient lives in a home with 17 birds. Combining the clinical scenario with histologic findings, a diagnosis of hypersensitivity pneumonitis (bird fancier's disease) is made, establishing the etiology for the patient's interstitial lung disease.

FIGURE 23.8

See Clinical Correlation 23.2 for details.

![Micrograph of interstitial non-necrotizing granulomatous inflammation with multinucleated giant cells.](source)

Pulmonary eosinophilia is a collection of diseases with similar morphologies of eosinophilic infiltration of the pulmonary interstitium and/or alveolar spaces (Fig. 23.9) and similar clinical scenarios of corticosteroid-responsive fever, night sweats, and dyspnea. Acute eosinophilic pneumonia with respiratory failure is an idiopathic illness with rapid onset of fever, dyspnea, and potentially fatal hypoxemic respiratory failure. Simple pulmonary eosinophilia (Löffler syndrome) is characterized by transient pulmonary eosinophilic infiltrates and peripheral blood eosinophilia. Tropical eosinophilia represents a microfilarial infection. Secondary chronic pulmonary eosinophilia occurs in a number of settings, including certain infections (parasitic, fungal, bacterial), drug allergies, asthma, allergic bronchopulmonary aspergillosis (Chap. 20), and polyarteritis nodosa.
**Idiopathic chronic eosinophilic pneumonia** is characterized by interstitial and intra-alveolar lymphocytic and eosinophilic infiltrates in peripheral lung fields. From the morphologic perspective, many of these diseases are indistinguishable, thus giving rise to the morphologic term pulmonary eosinophilia.

**FIGURE 23.9**

Pulmonary eosinophilia. (a) Intra-alveolar eosinophil-rich exudates dominate this example of idiopathic chronic eosinophilic pneumonia. (b) In this example of acute eosinophilic pneumonia, eosinophils are in the interstitium. *From Travis et al. Atlas of Nontumor Pathology: Volume 2: Non-Neoplastic Disorders of the Lower Respiratory Tract, American Registry of Pathology; 2002.*

Though smoking-related lung disease is frequently obstructive (see Chap. 20 for discussions of emphysema and chronic bronchitis), there are several smoking-related restrictive lung diseases. **Desquamative interstitial pneumonitis (DIP)** and **respiratory bronchiolitis-associated interstitial lung disease** are thought of as opposite ends of a spectrum of interstitial lung disease that may develop in smokers; the pathogenesis of both is unknown. In DIP *[Fig 23.10(a), (b)]*, there is mononuclear interstitial inflammation, an abundance of airspace macrophages with dusty brown cytoplasmic pigment, and type 2 pneumocyte hyperplasia. The airspace macrophages in DIP typically clump together, resulting in an appearance that was historically (and erroneously) interpreted as desquamated alveolar epithelium. In respiratory bronchiolitis-associated interstitial lung disease, there is patchy bronchiolocentric distribution of pigmented macrophages *[Fig. 23.10(c)]*, and there can be histologic overlap with DIP. Both DIP and respiratory bronchiolitis-associated interstitial lung disease present in the fourth to fifth decade, show a male gender bias (male:female ratio of about 2:1), may occur with insidious onset of dyspnea and cough, and improve with cessation of smoking and steroid therapy.

**FIGURE 23.10**

Smoking-related restrictive lung disease. (a) DIP at low magnification. Airspaces are difficult to discern due to accumulated clumps of intra-alveolar macrophages. (b) DIP at high magnification. Clumping of faintly pigmented intra-alveolar macrophages resembles the cohesion of epithelial cells. (c) In respiratory bronchiolitis, there is patchy distribution of macrophages in the bronchiolar lumen and adjacent airspaces. *From Travis et al. Atlas of Nontumor Pathology: Volume 2: Non-Neoplastic Disorders of the Lower Respiratory Tract, American Registry of Pathology; 2002.*
Pulmonary amyloidosis can show diffuse deposition of amyloid in alveolar septa, a pattern typically associated with disseminated primary amyloidosis or multiple myeloma, or there may be nodular deposition of amyloid. Pulmonary symptoms are usually not severe. Morphologically, amyloid is hyaline and stains with Congo red stain [Fig. 23.11(a), (b)]. Amyloid shows apple-green birefringence when stained with Congo red and viewed through a polarized light source [Fig. 23.11(c)].

**FIGURE 23.11**

Pulmonary amyloidosis. (a) By routine H&E staining, amyloid appears as eosinophilic amorphous material, shown here (arrow) surrounding two blood vessels. (b) Amyloid stains deep red with Congo red stain. (c) When stained with Congo red stain and viewed with polarized light, amyloid shows "apple-green" birefringence. (b) and (c): From Travis et al. Atlas of Nontumor Pathology: Volume 2: Non-Neoplastic Disorders of the Lower Respiratory Tract, American Registry of Pathology; 2002.

Cryptogenic organizing pneumonia (COP) is a nonspecific pattern of lung injury characterized by polypoid plugs of loose fibrous tissue. In contrast to the majority of diseases discussed in this chapter, in COP the fibrous tissue is not in the interstitium but rather within lumina of alveolar ducts, alveoli, and often bronchioles (Fig. 23.12). The distribution of lesions is typically more peripheral than distal. There are many etiologies of COP including infection (viral, bacterial), collagen vascular diseases, drug toxicity, toxic inhalants, and bronchial obstruction. Most patients show gradual improvement with steroid therapy.

**FIGURE 23.12**

Pulmonary alveolar proteinosis (PAP) is a rare disease with bilateral, patchy, and asymmetric lung involvement manifesting as opacification on chest radiograph. PAP can be acquired (being most common with ~90% of cases), congenital, or secondary. Acquired PAP appears to result from an autoantibody that inhibits the activity of GM-CSF, thereby impairing macrophage clearance of pulmonary surfactant. Congenital PAP is genetically heterogeneous, with the genetic lesion unknown in most cases; alternatively, congenital PAP can arise in the setting of mutations in the genes for ATP-binding cassette protein member A3 (ABCA3), surfactant protein B, GM-CSF, or the GM-CSF receptor β chain. Secondary PAP can arise in the setting of hematopoietic disease, malignancy, immunodeficiency, lysinuric protein intolerance, or acute silicosis (and other pneumoconioses, see below). Morphologically, whether acquired, congenital, or secondary, PAP is characterized by enlarged and abnormally heavy lungs which exude turbid fluid on sectioning. Microscopically (Fig. 23.13), there is intra-alveolar accumulation of dense, granular, eosinophilic material containing lipid and PAS-positive material. Clinically, PAP presents with insidious respiratory difficulty and a cough productive of abundant gelatinous chunks. With disease progression, dyspnea, cyanosis, and respiratory insufficiency can develop. Therapy for adult PAP involves lung lavage, and approximately one-half of adults benefit from recombinant GM-CSF therapy. Congenital PAP is fatal in 3–6 months without lung transplantation.

**FIGURE 23.13**

Pulmonary alveolar proteinosis. Alveolar septa are normal, but airspaces are filled with granular eosinophilic material. Pulmonary edema fluid (Chap. 26) is less granular than PAP material and typically does not contain PAS-positive debris that is present in PAP. *From Klatt. Robbins & Cotran Atlas of Pathology, 2nd ed. 2010.*
Collagen vascular diseases can be complicated by pulmonary involvement. In **progressive systemic sclerosis (scleroderma)**, pulmonary injury is typified by diffuse interstitial fibrosis. In **systemic lupus erythematosus (SLE)**, pulmonary histopathology typically consists of patchy, transient parenchymal infiltrates. In **rheumatoid arthritis**, pulmonary involvement can manifest as chronic pleuritis (with or without a pleural effusion), diffuse interstitial pneumonitis and fibrosis, pulmonary hypertension (**Chap. 26**), or intrapulmonary rheumatoid nodules. The presence of rheumatoid nodules in the setting of pneumoconiosis (see below) is known as **Caplan syndrome**.

**PNEUMOCONIOSES**

The term pneumoconiosis is broad and refers to non-neoplastic lung reactions to the inhalation of irritants to the lung. Nonetheless, many use this term to refer to such lung reactions to the inhalation of nonorganic mineral dusts. The development of pneumoconiosis depends on the amount of dust retained in the lung, particle solubility and physical/chemical reactivity, and the possible additive effects of other irritants such as cigarette smoke. The amount of dust retained in the lung following inhalation has much to do with particle size (**Chap. 10**). Particles <0.5 μm may remain suspended in inhaled air and are subsequently exhaled. Particles that are 1-5 μm in size are the most dangerous, as these are small enough to pass the vibrissae in the nose and mucociliary clearance action by the conducting portion of the respiratory tract to become deposited in small distal airspaces. Particles exceeding 10 μm are filtered by the vibrissae or are deposited in mucus of the conducting portion of the respiratory tract and cleared through ciliary action. Smaller particles have a greater surface area/volume ratio and so will show more rapid development of toxic levels in fluids. Some dust particles cause direct cell injury, while others can cross the epithelium to directly interact with septal fibroblasts and macrophages.

**Coal worker's pneumoconiosis (CWP)** can develop with inhalation of carbon dust. Low-level exposure to coal dust leads to **anthracosis**, an asymptomatic accumulation of carbon pigment with no significant cellular response. With moderate coal dust exposure, **simple CWP** can develop that shows little or no pulmonary dysfunction. With heavy exposure, however, simple CWP can progress to complicated CWP with respiratory...
insufficiency. Morphologically, anthracosis is characterized by accumulation of black pigment in alveolar macrophages, interstitial histiocytes [Fig. 23.14(a)], and lymph nodes, especially hilar. Simple CWP is characterized by 1-2 mm coal macules and larger coal nodules that have a delicate collagen network [Fig. 23.14(b)]. These are found predominantly in the upper lung lobes and the upper portions of lower lobes. The macules and nodules of simple CWP are typically adjacent to respiratory bronchioles. After many years of simple CWP, black scars >2 cm in greatest dimension herald the development of complicated CWP, that can be further complicated by progressive massive fibrosis (PMF) [Fig. 23.14(c)]. Microscopically, these black scars represent carbon pigment and dense collagen, often with a region of central necrosis. Most cases of simple CWP and mild complicated CWP show normal pulmonary function tests. In a minority of cases of complicated CWP, PMF leads to pulmonary dysfunction, pulmonary hypertension (Chap. 26), and cor pulmonale. Of note, once PMF has begun, it can progress despite cessation of coal dust exposure.

**FIGURE 23.14**

Carbon-related pulmonary disease. (a) In anthracosis, black pigment (carbon) accumulates in interstitial histiocytes as well as alveolar macrophages (not shown) and regional lymph nodes (not shown). (b) In simple CWP, carbon pigment in macrophages is associated with delicate fibrosis. (c) In complicated CWP, larger black scars, predominantly in the upper lung, are present and can lead to PMF as shown in this thin section of an entire lung (N = large coal nodules with PMF). (b) and (c): From Stevens et al. Core Pathology, 3rd ed. 2010.

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**Silicosis**, the most common chronic occupational disease in the world, is caused by inhalation of silicon dioxide (silica), which can be crystalline or amorphous. Crystalline silica is much more fibrogenic than amorphous silica and exists in the following forms: quartz (the most common), crystobalite, and tridymite. Silicosis manifests as slowly progressive nodular fibrosis developing after decades of exposure. Pathogenetically, the SiOH groups on particle surfaces bind to membrane proteins and phospholipids, leading to protein denaturation and lipid damage. Exposure of macrophages to silica can result in macrophage death or in macrophage activation with release of numerous signaling molecules including IL-1, TNF-α, fibronectin, lipid mediators, oxygen-derived free radicals, and fibrogenic cytokines. Similar to CWP, silicosis lesions localize in the upper lung zones; in contrast, silicosis lesions are more fibrotic and less cellular than the lesions of CWP. Early in the development of silicosis, small, barely palpable, pale nodules appear in upper lung zones [Fig. 23.15(a)]. With progression, these nodules coalesce into hard, collagenous scars (silicotic nodules) [Fig. 23.15(b)] that can undergo cavitation. Microscopically, the silicotic nodule is composed of concentric layers of hyalinized collagen surrounded by a dense collagen capsule [Fig. 23.15(c)]. The intervening lung parenchyma can be compressed or overexpanded. Silicotic nodules can also develop in regional lymph nodes, where they typically undergo peripheral calcification, imparting an eggshell appearance radiographically. In some cases, silicosis evolves into PMF. Clinically, presentation is usually radiographic identification of fine upper lung nodularity in an asymptomatic worker, at which time pulmonary function tests are usually normal or near normal. If complicated by PMF, there
can be progression without additional silica exposure. The relationship of silicosis to the development of lung cancer in humans is controversial.

FIGURE 23.15

Silicosis. (a) In early silicosis, small pale nodules appear, predominantly in the upper lung. (b) As silicosis progresses, the nodules coalesce into silicotic nodules. (c) Histologically, silicotic nodules are composed of concentric layers of hyalinized collagen; the fibrotic nodules of silicosis are paucicellular. *From Travis et al. Atlas of Nontumor Pathology: Volume 2: Non-Neoplastic Disorders of the Lower Respiratory Tract, American Registry of Pathology; 2002.*

Asbestos represents a family of crystalline hydrated silicates that form fibers of two general forms: serpentine chrysotile fibers, which are curly and flexible, and amphibole fibers, which are straight, stiff, and brittle. Though less prevalent than chrysotile fibers, amphibole fibers are more pathogenic, likely due to aerodynamic properties that allow straight fibers to align in the airstream and be deposited more deeply in the lung. Amphibole fibers are less soluble than chrysotile fibers, and so chrysotile fibers are leached from tissue more quickly. Asbestos shows activity as a tumor initiator and tumor promoter, in part due to adsorption of toxic chemicals. Asbestos causes or contributes to the development of many diseases, one of which—is asbestosis—is characterized by restrictive lung disease with interstitial fibrosis.

Asbestosis begins with inhalation of asbestos fibers, which impact and penetrate tissue at the bifurcation of small airways and ducts. Subsequently, macrophages attempt to ingest and clear the fibers and release chemotactic and fibrogenic mediators. Chronic fiber deposition, causing persistent mediator release, culminates in interstitial fibrosis and interstitial inflammation [Fig. 23.16(a), (b)]. The fibrosis begins around respiratory bronchioles and alveolar ducts. Later fibrosis extends into adjacent alveolar sacs and alveoli, with progressive distortion of the architecture and eventual development of a honeycomb appearance typical of many end-stage chronic restrictive lung diseases. In addition to the interstitial changes, asbestosis is typified by fibrous thickening of the visceral pleura, often leading to adhesions to the parietal pleura with anchoring of the lung to the chest wall. In contrast to CWP and silicosis, the pathologic findings in asbestosis are more prominent in the lower lung zones but may extend to the middle and upper zones. Microscopically, within the interstitial fibrosis will be asbestos bodies, which are golden brown and fusiform or beaded rods with a translucent core [Fig. 23.16(c)]. Asbestos bodies are composed of an asbestos fiber coated with iron-containing, proteinaceous material. Of note, other inorganic material may become coated with similar iron-containing material. When seen outside the setting of asbestos-related disease, such structures are called ferruginous bodies, a less specific designation. Clinically, the presentation of asbestosis is usually 10 to more than 20 years after initial exposure and is characterized by dyspnea and productive cough. Though asbestosis can remain static, it may progress and lead to congestive heart failure, cor pulmonale, and death.

FIGURE 23.16
Asbestosis. (a) Grossly, asbestosis is characterized by interstitial fibrosis that is more pronounced peripherally and especially subpleurally; in contrast to CWP and silicosis, the pathologic findings in asbestosis are more predominant in lower lung zones. (b) Histologically, asbestosis is characterized by expansion of the interstitium by fibrosis. (c) Shown here are macrophages stained green (GMS stain) attempting to phagocytize an asbestos body. (a): *From Travis et al. Atlas of Nontumor Pathology: Volume 2: Non-Neoplastic Disorders of the Lower Respiratory Tract, American Registry of Pathology; 2002.*

In addition to asbestosis, asbestos exposure is implicated in the development of pleural plaques, pleural fibrosis, pleural effusion, bronchogenic carcinoma, malignant mesothelioma, and laryngeal and other extrapulmonary cancer. **Pleural plaques** ([Fig. 23.17](#)) are the most common asbestos-related lesion and consist of a well-circumscribed focus of dense collagen, often calcified, on the parietal pleura (usually posterolaterally and over the diaphragm). Such plaques are a morphologic indication of asbestos exposure but otherwise are clinically inconsequential. Asbestos exposure increases the risk of malignant mesothelioma ~1,000-fold and increases the risk of bronchogenic carcinoma fivefold in nonsmokers and 55-fold among smokers; mesothelioma and bronchogenic carcinoma are discussed further in **Chap. 31**.

**FIGURE 23.17**

Pleural plaque. (a) Though clinically insignificant, parietal pleural plaques (arrows) indicate prior asbestos exposure. (b) Histologically, pleural plaques are composed of paucicellular fibrous connective tissue, often, as in this image, with a "basket weave" appearance. (a): *From Kemp et al. Pathology: The Big Picture; 2008.* (b): *From Travis et al. Atlas of Nontumor Pathology: Volume 2: Non-Neoplastic Disorders of the Lower Respiratory Tract, American Registry of Pathology; 2002.*
**Talcosis** can result from inhalation of large amounts of talc, a magnesium silicate used widely in industry and cosmetics. Morphologically, talcosis is characterized by granulomatous inflammation, hyaline nodules, and interstitial fibrosis (rarely with PMF). Talc is highly birefringent when examined with polarized light.

**Berylliosis** is caused by exposure to airborne dusts or fumes of metallic beryllium (atomic number 4) or its oxides or salts, many of which are used in the electronics and aviation industries. Acutely, berylliosis is characterized by acute pneumonitis with DAD. Chronically, there is granulomatous inflammation and interstitial fibrosis. Heavy beryllium exposure is associated with bronchogenic carcinoma (Chap. 31).

Additional pneumoconioses include the **hard metal diseases** that are associated with tungsten carbide and cobalt exposure and characterized by giant cell interstitial pneumonitis. **Welder's pneumoconiosis** is most often associated with oxides of aluminum, iron, titanium, or manganese, and patients may show varying degrees of interstitial fibrosis depending on the specific metal oxide involved.

**SUGGESTED READINGS**

1. Travis WD, Colby TV, Koss MN, Rosado-de-Christenson ML, Müller NL, King TE. *Atlas of Nontumor Pathology: Volume 2: Non-Neoplastic Disorders of the Lower Respiratory Tract*, American Registry of Pathology; 2002. For many years, the Armed Forces Institute of Pathology (AFIP) was responsible for the publication of numerous tumor atlases, frequently referred to as "The Fascicles." Later, the AFIP expanded its atlas publication to include non-neoplastic disease. This text offers well-organized and exceedingly well-illustrated discussions of pulmonary disease with a focus on morphology but with generous clinical and radiographic coverage. In accordance with the 2005 Defense Base Realignment and Closure (BRAC) law, the AFIP is on track to disestablish and permanently close by September 15, 2011.
