Pathology of Small Airways

Philip T. Cagle and Victor L. Roggli

The small conducting airways consist of the membranous bronchioles and the respiratory bronchioles. Bronchiolitis is a generic term for inflammatory and fibrotic injuries of these small airways. The histology of normal bronchioles is discussed in detail in Chapter 2. A brief review is warranted here before discussing the histopathologic patterns associated with small airway injury.

Bronchioles are defined as conducting airways less than 1 mm in diameter that lack cartilage in their walls. Bronchioles are divided into two groups: the larger (average 0.5 to 1 mm diameter) membranous bronchioles branch from the smallest bronchi and give rise to the smaller (average 0.15 to 0.2 mm diameter) respiratory bronchioles. The final smallest division of the membranous bronchioles that branches into the first tier of respiratory bronchioles is often called the terminal bronchiole. The membranous bronchioles only conduct air similar to bronchi, whereas the respiratory bronchioles both conduct air and participate in gas exchange via the alveoli in their walls. The respiratory bronchioles branch into about two more generations of respiratory bronchioles with increasing numbers of alveoli in their walls and give rise to the alveolar ducts.

Respiratory bronchioles have a bronchiolar wall with simple columnar to cuboidal bronchiolar epithelium and alveoli budding from their walls. The alveoli budding from the bronchiolar walls increase in number the higher the generation of the respiratory bronchiole. In two-dimensional longitudinal sections on glass slides, respiratory bronchioles often appear to have a bronchiolar mucosa and wall on one side of their lumen and alveolar spaces on the opposite side of their lumen. Respiratory bronchioles represent the first generation of airways in which exchange of gases occurs.

The histopathology of small airways may primarily involve the bronchioles alone or may be a component of a pulmonary disease characterized by other histopathologic changes. Focal small airways histopathology may be observed as a result of a localized acute injury such as a focal infection or bronchopneumonia. Further discussion of small airway injury as it relates to diseases and conditions involving the lungs can be found in other chapters, as follows: infections, Chapters 8 through 14; acute lung injury, Chapters 4; bronchial obstruction, including aspiration and asthma, Chapters 5 and 15; connective tissue diseases and inflammatory bowel disease, Chapters 20; interstitial pneumonias, Chapters 19; lung transplant, Chapters 23; exposures such as hypersensitivity pneumonitis, Chapters 17; eosinophilic pneumonia, Chapters 15; drug reactions and radiation, Chapters 22; pneumoconioses, Chapters 26 and 27; Langerhans histiocytosis, Chapters 16; sarcoidosis, Chapter 18; and neuroendocrine cell hyperplasia, Chapter 34. General patterns of small airway injury and those entities not discussed in detail in these other chapters are discussed in this chapter. Causes of small airways histopathology are listed in Table 25.1.
TABLE 25.1. Causes of small airway histopathology

| Idiopathic                                      |
|------------------------------------------------|
| Organizing pneumonia/bronchiolitis obliterans-organizing pneumonia/bronchiolitis obliterans with intraluminal polyps |
| Constrictive bronchiolitis obliterans/obliterative bronchiolitis |

| Tobacco-related small airways disease          |
|------------------------------------------------|
| Respiratory bronchiolitis and respiratory bronchiolitis associated interstitial lung disease |
| Membranous bronchiolitis                       |
| Pulmonary Langerhans' cell histiocytosis/histiocytosis X |

| Secondary to specific exposures                |
|------------------------------------------------|
| Fumes, chemicals, and toxins                   |
| Sauropus androgynus ingestion                  |
| Drug reactions                                 |
| Mineral dust-associated small airways disease  |
| Hypersensitivity pneumonitis                   |
| Flock worker's lung                            |
| Eosinophilic pneumonia                         |

| Secondary to diseases/conditions involving the lungs |
|-----------------------------------------------------|
| Asthma                                               |
| Bronchiectasis                                      |
| Chronic bronchitis/emphysema                        |
| Collagen-vascular disease                           |
| Post-obstruction                                    |
| Infections/bronchopneumonia/healed infections       |
| Diffuse alveolar damage/bronchopulmonary dysplasia  |
| Aspiration                                          |
| Inflammatory bowel disease                         |
| Sarcoidosis                                         |
| Bronchocentric granulomatosis                      |
| Wegener's granulomatosis                           |
| Post-lung transplant                                |
| Post-bone marrow transplant (graft versus host disease) |
| Airway-centered interstitial lung disease           |
| Swyer-James (Macleod) syndrome                     |

FIGURE 25.1. Medium power view of a bronchiole shows fibrosis in the wall and adjacent tiers of alveolar septa. There is metaplastic bronchiolar epithelium (Lambertosis) lining the fibrotic alveolar septa.

TABLE 25.2. Basic patterns of small airway histopathology

| Cellular bronchiolitis                                      |
|-------------------------------------------------------------|
| Acute bronchiolitis                                         |
| Chronic bronchiolitis                                       |
| Mixed acute and chronic bronchiolitis                       |
| Follicular bronchiolitis                                    |
| Diffuse panbronchiolitis and variants                       |
| Diffuse panbronchiolitis-like lesions                       |

| Granulomatous bronchiolitis                                |
|-------------------------------------------------------------|
| Organizing pneumonia/bronchiolitis obliterans-organizing pneumonia/bronchiolitis obliterans with intraluminal polyps |

| Constrictive bronchiolitis obliterans/obliterative bronchiolitis |
|------------------------------------------------------------------|
| Respiratory bronchiolitis and respiratory bronchiolitis associated interstitial lung disease |
| Membranous bronchiolitis                                        |
| Pulmonary Langerhans' cell histiocytosis/histiocytosis X        |

| Tobacco-related small airways disease                      |
|-------------------------------------------------------------|
| Respiratory bronchiolitis and respiratory bronchiolitis associated interstitial lung disease |
| Membranous bronchiolitis                                    |
| Pulmonary Langerhans' cell histiocytosis/histiocytosis X     |

| Mineral dust-associated small airways disease              |
|-------------------------------------------------------------|
| Hypersensitivity pneumonitis                                |

Histopathologic Patterns in Small Airways

Bronchiolar and Peribronchiolar Inflammation, Fibrosis, and Metaplasia

Several general histopathologic patterns are common to small airway injury regardless of etiology. Inflammation and fibrosis may involve the bronchiolar lumen, mucosa or wall, or the adjacent (peribronchiolar) tiers of alveolar septa. The bronchiolar epithelium or epithelium of peribronchiolar alveoli may also undergo metaplastic changes in association with inflammation and fibrosis, primarily with scarring as in constrictive bronchiolitis (Fig. 25.1). These findings may be seen with both focal and diffuse airways injury. The basic patterns of small airway histopathology are listed in Table 25.2. The types of metaplastic epithelium are listed in Table 25.3.

Inflammation or scarring in bronchiolar walls or peribronchiolar tissue may result in decreased airflow that can often be measured physiologically as an obstructive

TABLE 25.3. Histopathologic types of metaplastic epithelium

| Bronchiolar epithelium metaplasia                          |
|-------------------------------------------------------------|
| Goblet cell (mucinous) metaplasia                           |
| Squamous metaplasia                                         |

| Peribronchiolar alveolar epithelium metaplasia              |
|-------------------------------------------------------------|
| Cuboidal metaplasia                                         |
| Bronchiolar metaplasia                                      |
| Goblet cell (mucinous) metaplasia                           |
| Squamous metaplasia                                         |
change in the forced expiratory volume in 1 second (FEV₁), and more specifically in forced expiratory flow after 25% to 75% of vital capacity has been expelled (FEF₂₅–₇₅) or forced expiratory flow after 75% of vital capacity has been expelled (FEF₇₅). However, small airways histopathologic changes may be associated with restrictive changes instead of or in addition to obstructive changes. The frequency with which bronchiolitis causes clinical symptoms is fairly uncommon compared to the frequency with which pathologists may encounter histopathologic lesions because of the large total cross-sectional area of the bronchioles. On the other hand, clinical symptoms may be severe despite what appears to be relatively mild small airway histopathology.¹⁰⁵–¹⁰⁷

Bronchiolitis is recognized at low power as an inflammation or fibrosis that is centered in and around the bronchioles. In many cases of bronchiolitis, inflammatory infiltrates precede airway scarring, but this is not always the case and some lesions consist primarily or totally of scarring from the beginning of their course. Fibroblastic granulation tissue may precede mature scars. Findings of bronchiolitis may be nonspecific and it may be difficult to ascertain the underlying cause of either inflamed or scarred bronchioles. Additional nonspecific findings such as intraalveolar foamy macrophages due to small airway obstruction may be present, regardless of the etiology.

Surface bronchiolar metaplasia of peribronchiolar fibrotic alveoli has been referred to as Lambertosis (Fig. 25.2). This term derives from an older concept that this metaplastic epithelium “grew out” from the adjacent bronchiole via the canals of Lambert.¹⁰⁸

**FIGURE 25.2.** Higher power of Lambertosis shows bronchiolar-type epithelium lining alveolar septa thickened by fibrosis.

Organizing Pneumonia, Bronchiolitis Obliterans–Organizing Pneumonia, and Bronchiolitis Obliterans with Intraluminal Polyps

Organizing pneumonia or bronchiolitis obliterans with intraluminal polyps (formerly referred to as bronchiolitis obliterans–organizing pneumonia [BOOP]) is seen secondary to a variety of lung injuries and as a component of several specific lung diseases. The same histologic pattern occurs as an idiopathic clinical syndrome called cryptogenic organizing pneumonia (COP; formerly referred to as idiopathic BOOP), classified with the idiopathic interstitial pneumonias.¹⁰⁹–¹³⁶

Organizing pneumonia may occur in viral or other infections, as a drug reaction, as a reaction to chemotherapy or radiation therapy, after inhalation of fumes or toxic compounds, as a postobstructive finding distal to an obstructed airway, as a result of aspiration, and in bone marrow transplant recipients. It is proposed that this pattern may represent acute lung transplant rejection in some lung transplant patients. This pattern can also be a component of specific lung diseases including hypersensitivity pneumonitis, eosinophilic pneumonia, collagen vascular diseases involving the lungs, and Wegener’s granulomatosis.¹³² The causes of organizing pneumonia are listed in Table 25.4.

Organizing pneumonia (Fig. 25.3) consists of plugs of granulation tissue (fibroblasts in an edematous or myxoid stroma) in the lumina of bronchioles (Fig. 25.4), alveolar ducts (Fig. 25.5), and adjacent alveoli. These rounded nodules of granulation tissue are called Masson bodies. There may be accompanying interstitial lymphocytes or other inflammation. A transbronchial biopsy may fail to sample bronchioles, and the only finding may be the granulation tissue in the alveoli. Intraalveolar collections of foamy macrophages may result from the bronchiolar obstruction. There may be findings that suggest

| TABLE 25.4. Causes of organizing pneumonia |
|------------------------------------------|
| Idiopathic (cryptogenic organizing pneumonia [COP]) |
| Infections |
| Exposures to fumes, chemicals, and toxins |
| Drug reactions |
| Aspiration |
| Radiation therapy |
| Postobstructive |
| Transplant recipients |
| Inflammatory bowel disease |
| Hematologic malignancies |
| Component of: |
| Collagen vascular disease |
| Hypersensitivity pneumonitis |
| Eosinophilic pneumonia |
| Wegener’s granulomatosis |
the etiology (for example, viral inclusions in viral pneumonias, foreign-body giant cells in aspiration, poorly formed granulomas and multinucleated giant cells in hypersensitivity pneumonitis, etc.). Histopathologic clues to the etiology of organizing pneumonia may not be present, and clinical correlation is often necessary to determine the underlying cause. If an identifiable etiology is excluded, then the diagnosis is cryptogenic organizing pneumonia. The organizing pneumonia may resolve with or without residual scarring. Histopathologic features of organizing pneumonia are listed in Table 25.5.

### Cryptogenic Organizing Pneumonia

Cryptogenic organizing pneumonia (COP), formerly termed idiopathic BOOP, consists of proliferation of granulation tissue within small airways, alveolar ducts, and alveoli, and is classified with the idiopathic interstitial pneumonias (Chapters 4 and 19). The clinical syndrome occurs most often in middle-aged to older adults and is often preceded by a flu-like illness. Persistent nonproductive cough and shortness of breath are the usual presenting symptoms. Most, but not all, patients respond rapidly to steroids and in most cases prognosis is excellent.

Typical radiologic features of cryptogenic organizing pneumonia are patchy bilateral alveolar infiltrates with a ground-glass appearance that sometimes may be transient and recurring in different locations. Diffuse interstitial infiltrates, focal consolidation, and small, rounded opacities are less frequently observed. On

| Table 25.5. Histopathologic features of organizing pneumonia |
|-------------------------------------------------------------|
| Lumens of bronchioles and alveolar ducts contain plugs of granulation tissue |
| Rounded nodules of granulation tissue are found in alveolar spaces adjacent to involved bronchioles and alveolar ducts |
| The interstitium may have lymphocytic or other inflammatory cell infiltrates |
| Bronchiolar obstruction may cause intraalveolar collections of foamy macrophages |
| Transbronchial biopsies may sample only involved alveoli and not the involved bronchioles |
| Clues to the etiology of the organizing pneumonia (viral inclusions, aspirated squames, and vegetable matter, etc.) may sometimes be identified |
FIGURE 25.6. Low power shows nodules of bronchiolocentric granulation tissue surrounded by relatively normal lung parenchyma in cryptogenic organizing pneumonia.

high-resolution computed tomography (HRCT), there are patchy bilateral areas of alveolar consolidation and ground-glass attenuation, often prominent in a peribronchial or subpleural distribution.\textsuperscript{138-144}

The histopathologic features are essentially the same as those of organizing pneumonia due to identifiable causes. At low power, COP consists of a patchy pattern of nodules of granulation tissue that typically center on a small airway surrounded by normal or near-normal lung (Fig. 25.6). At higher power there are arborizing branches of granulation tissue (fibroblasts in an edematous or myxoid stroma) that fill the lumina of bronchioles, alveolar ducts, and adjacent alveoli (Fig. 25.7). Rounded plugs of granulation tissue in the alveolar spaces are referred to as Masson bodies. The general architecture of the lung is preserved, with no significant interstitial fibrosis or honeycombing. There may be small foci of lymphocytes, plasma cells, and macrophages in some bronchioles, and interstitial inflammation is usually minimal to moderate. Transbronchial biopsies may fail to sample bronchioles and sample only alveoli with organizing pneumonia. Intraalveolar collections of foamy macrophages may result from the bronchiolar obstruction. When an organizing pneumonia pattern is present, the pathologist should examine the tissue for viral inclusions, poorly formed granulomas, isolated giant cells (hypersensitivity pneumonitis), foreign-body giant cells (aspiration), and other entities.\textsuperscript{1,6,7,9,10,17,19,22,109-137}

Constrictive Bronchiolitis

Constrictive bronchiolitis is a condition in which the bronchiolar lumina are severely narrowed or obliterated by submucosal scarring. Constrictive bronchiolitis is also called bronchiolitis obliterans and obliterative bronchiolitis.\textsuperscript{145-147} Constrictive bronchiolitis results from scarring caused by infections (especially viral infections that affect the bronchioles) (see Chapters 8 to 14),\textsuperscript{23-27} collagen vascular diseases involving the lungs (particularly rheumatoid arthritis) (Chapter 20),\textsuperscript{45-47} drug reactions (Chapter 22),\textsuperscript{81-87} exposures to fumes and toxins (Chapter 4),\textsuperscript{1,6,7,9,10,17,19,22} and bone marrow transplant\textsuperscript{718} (Chapter 23). Constrictive bronchiolitis is a major histopathologic finding in chronic lung transplant rejection (Chapter 23).\textsuperscript{7,61-64,66-72} It may be a component of bronchiectasis, cystic fibrosis, or asthma\textsuperscript{36-44} (Chapters 5 and 15), and it is also seen in some rare conditions—in inflammatory bowel disease with lung involvement (Chapter 20)\textsuperscript{58,52} and in diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (Chapter 34).\textsuperscript{108-103} Idiopathic cases also occur and are discussed below.\textsuperscript{148-151} The causes of constrictive bronchiolitis are listed in Table 25.6.

In constrictive bronchiolitis there is narrowing of the bronchiolar lumen by submucosal fibrous tissue or fibrous tissue in the adventitia or adjacent alveolar septa, which may display metaplastic epithelium or Lambertosis.

| TABLE 25.6. Causes of constrictive bronchiolitis |
|-----------------------------------------------|
| Idiopathic                                      |
| Postinfection scarring (especially viruses)    |
| Exposure to fumes and toxins                    |
| Ingestion of Sauropus androgynus                |
| Drug reactions                                  |
| Chronic lung transplant rejection               |
| Bone marrow transplant                          |
| Collagen vascular disease (especially rheumatoid arthritis) |
| Component of bronchiectasis, cystic fibrosis, or asthma |
| Inflammatory bowel disease                      |
| Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia |
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FIGURE 25.8. Low power of constrictive bronchiolitis shows mural and peribronchial scarring surrounded by normal lung parenchyma.

FIGURE 25.9. Constrictive bronchiolitis with mural and peribronchial fibrosis and metaplastic epithelium (Lambertosis) lining the adjacent tiers of fibrotic alveolar septa.

FIGURE 25.10. Mural fibrosis and smooth muscle hypertrophy cause more subtle narrowing of the bronchiolar lumen in this example of constrictive bronchiolitis.

FIGURE 25.11. Obliteration of a bronchiolar lumen by fibrosis leaves residual foci of bronchiolar epithelium in this example of constrictive bronchiolitis.

(Figs. 25.8 and 25.9). The narrowing may be subtle and the clinical symptoms and findings may be disproportionate to the histologic narrowing (Fig. 25.10). In other cases, some of the bronchiolar lumina may be completely obliterated leaving only a scarred remnant of the airway (Fig. 25.11). However, in contrast to COP, there is concentric constriction of the lumen without intraluminal granulation tissue plugs and, in contrast to granulation tissue plugs, the mature submucosal fibrosis does not potentially resolve and disappear. There may also be adventitial scarring and smooth muscle hypertrophy. Inflammation may be present or it may be minimal or absent. Trichrome stain may assist in identifying bronchioles by highlighting their muscle when their lumina have been replaced by scar.\cite{1,6,7,8,9,10,17,19,22} Histopathologic features of constrictive bronchiolitis are listed in Table 25.7.

Idiopathic Constrictive Bronchiolitis

Idiopathic constrictive bronchiolitis, in which patients lack any identifiable predisposing condition or exposure known to cause bronchiolitis, occurs primarily in non-smoking middle-aged women. Patients present with a few months’ history of cough and shortness of breath, often...
after an exacerbation of obstructive symptoms. Clinical findings of wheezing are often minimal. There is hyperinflation with vascular attenuation on chest x-ray and a mosaic pattern of attenuation on HRCT. Prognosis varies from rapid deterioration to slow, sometimes stable disease. Histopathologic findings, including submucosal and adventitial fibrosis with narrowing or loss of bronchiolar lumina, are those of constrictive bronchiolitis but with minimal or mild inflammation.148-151

Cellular Bronchiolitis

Cellular bronchiolitis refers to bronchiolitis in which acute, chronic, or acute and chronic inflammatory infiltrates, or both types, are the primary histopathologic pattern.152,153 There is considerable overlap of the etiologies of these histopathologic patterns. Radiologic patterns vary and include the so-called tree-in-bud pattern.154-156 Follicular bronchiolitis is a somewhat more distinct pattern associated with several different etiologies.157-170 More detailed discussions of the etiologies of these patterns of bronchiolitis can be found in the respective chapters dealing with these underlying conditions. For our purposes, this section serves as a brief overview of these relatively nonspecific patterns of cellular bronchiolitis, and the reader is referred to the respective chapters for more detailed discussion of the underlying conditions. Specific patterns of bronchiolitis are discussed in the next section.

Acute Bronchiolitis, and Acute and Chronic Bronchiolitis

Etiology

Acute bronchiolitis is typically an infectious respiratory disease in infants, as described in Chapters 7 and 11. The most common infectious agent in both children and adults is respiratory syncytial virus.23-33,35 In adults, acute bronchiolitis may be caused not only by infectious agents but also by other etiologies in which the infiltrates are often mixed acute and chronic inflammatory cells (acute and chronic bronchiolitis).1,6,7,9,10,17,19,22 Causes of acute bronchiolitis and acute and chronic bronchiolitis are listed in Table 25.8. Further discussion of bronchiolitis associated with these specific etiologies can be found in Chapters 4, 20, 23, and 29.

Clinical and Radiologic Features

Acute bronchiolitis usually requires only symptomatic treatment, but patients, particularly infants, may sometimes require hospitalization. Patients present with tachypnea, wheezing, prolonged expiration, and tachycardia. Chest x-ray shows hyperinflation in most cases.1,6,7,9,10,17,19,22 Radiographic findings are summarized in Table 25.9.

Idiopathic cases are characterized by a chronic history (several years) of shortness of breath or cough, and an obstructive pattern on pulmonary function tests. Recurrent infections may be an associated finding.1,6,7,9,10,17,19,22

| Table 25.7. Histopathologic features of constrictive bronchiolitis |
|-----------------------------------------------|
| Submucosal fibrous tissue narrows bronchiolar lumina |
| Adventitial scarring and smooth muscle hypertrophy may also be present |
| Luminal narrowing may be subtle |
| Airflow obstruction may be disproportionate to the amount of luminal narrowing by histologic examination |
| Complete obliteration of bronchiolar lumina may occur leaving only residual scars |
| Trichrome stain may help identify obliterated bronchioles by highlighting smooth muscle in their walls |
| Chronic inflammation may be present but in many cases may be minimal or absent |

| Table 25.8. Causes of acute bronchiolitis and acute and chronic bronchiolitis |
|-----------------------------------------------|
| Infectious agents |
| Viruses |
| Respiratory syncytial virus |
| Adenovirus |
| Influenza |
| Parainfluenza |
| Measles |
| Chlamydia |
| Mycoplasma |
| Bordetella pertussis |
| Acute inhalation of toxic fumes |
| Acute aspiration |
| Lung transplant |
| Bone marrow transplant |
| Collagen vascular diseases |
| Inflammatory bowel disease |
| Wegener’s granulomatosis |
| Stevens-Johnson syndrome |
| Idiopathic |

| Table 25.9. Radiographic features of acute bronchiolitis |
|-----------------------------------------------|
| Chest radiograph |
| Hyperinflation |
| Small nodules |
| Linear or patchy ground-glass opacities |
| Atelectasis |
| High-resolution computed tomography scan |
| Small centriflobular nodules |
| Branching linear opacities |
| Focal consolidation |
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25.12. Acute bronchiolitis shows filling of this bronchiolar lumen by purulent material and infiltration of the bronchiolar wall and mucosa by neutrophils.

Histopathologic Features
In acute bronchiolitis, there is filling of bronchiolar lumina by necropurulent exudates, and necrosis with sloughing of bronchiolar mucosa (Fig. 25.12). In acute and chronic bronchiolitis there is bronchiolar and peribronchiolar infiltration by both acute and chronic inflammatory cells along with purulent exudates in the bronchiolar lumina (Fig. 25.13). Occasional patients may have residual constrictive bronchiolitis.\textsuperscript{1,6,7,9,10,17,19,22}

25.13. Acute and chronic bronchiolitis shows permeation of the bronchiolar mucosa and wall by both neutrophilic and lymphoplasmacytic infiltrates and filling of the lumen with purulent debris.

In idiopathic cases, there are intraluminal purulent exudates and typically mural chronic inflammatory infiltrates, sometimes with follicular bronchiolitis. Bronchoalveolar lavage (BAL) specimens contain a large percentage of neutrophils.\textsuperscript{1,6,7,9,10,17,19,22}

Prognosis
Most patients fully recover from acute bronchiolitis, although a few may have residual constrictive bronchiolitis as noted above. Fewer than 1% of patients die as a result of acute bronchiolitis.

Patients with idiopathic acute and chronic bronchiolitis may respond to antibiotics and may sometimes temporarily respond to immunosuppressive therapy. Most will have residual impairment of pulmonary function.\textsuperscript{1,6,7,9,10,17,19,22}

Chronic Bronchiolitis

Etiology
Chronic bronchiolitis has overlapping etiologies with other patterns of cellular bronchiolitis.\textsuperscript{1,6,7,9,10,17,19,22} Causes of chronic bronchiolitis are listed in Table 25.10 and detailed discussions of these underlying conditions can be found in each of their respective chapters. Follicular bronchiolitis has some distinctive associations and is discussed separately.

Clinical and Radiologic Features
Clinical features include those of airway obstruction and radiographic features include small nodules on HRCT. Some forms of chronic bronchiolitis such as respiratory bronchiolitis are specific conditions discussed later.

Histopathologic Features
In chronic bronchiolitis, bronchiolar walls and peribronchiolar tissues are infiltrated by chronic inflammatory cells (Fig. 25.14). Germinal centers may be present in the chronic inflammation in follicular bronchiolitis (discussed below). Changes of constrictive bronchiolitis may be

| Table 25.10. Causes of chronic bronchiolitis |
|---------------------------------------------|
| Asthma                                      |
| Bronchiectasis                              |
| Chronic aspiration                          |
| Lung transplant                             |
| Collagen-vascular disease                   |
| Inflammatory bowel disease                  |
| Lymphoproliferative diseases                |
| Idiopathic                                  |
Chronic bronchiolitis shows infiltration of bronchiolar mucosa and wall by chronic inflammatory cells.

observed in some cases as the process progresses to airway scarring. 1,6,7,9,10,17,19,22

Follicular Bronchiolitis

Etiology
Follicular bronchiolitis is lymphoid hyperplasia of the bronchus-associated lymphoid tissue (BALT) as a result of immune stimulus or altered immune response. Hence, follicular bronchiolitis may be seen in collagen vascular diseases, especially rheumatoid arthritis, immunodeficiency states, and lymphoproliferative disorders. 1,7,19,22,157–170

Causes of follicular bronchiolitis are listed in Table 25.11.

Clinical and Radiologic Features
With follicular bronchiolitis, most patients have progressive shortness of breath and may present with obstructive, restrictive, or mixed pulmonary functions. 2,157–170

Radiographic changes are bilateral and are listed in Table 25.12.

Granulomatous Bronchiolitis

Etiology
Granulomatous bronchiolitis may be due to any of several causes of granulomatous inflammation including infections. 1,71–180 Potential etiologies of granulomatous bronchiolitis are listed in Table 25.13.

Histopathologic Features
There is lymphoid hyperplasia around the bronchi and bronchioles with reactive germinal centers (Fig. 25.15). Lymphocytic infiltrates may extend into the adjacent interstitium. 1,7,19,22,157–170

Prognosis
Treatment of the underlying condition is indicated. In idiopathic cases, therapy may include steroids, bronchodilators, and erythromycin. 1,7,19,22,157–170

Table 25.11. Causes of follicular bronchiolitis

| Causes of follicular bronchiolitis |
|-----------------------------------|
| Collagen vascular diseases (especially rheumatoid arthritis) |
| Immunodeficiency syndromes (AIDS, congenital, etc.) |
| Lymphoproliferative disorders |
| Bronchiectasis |
| Middle lobe syndrome |
| Idiopathic |

Table 25.12. Radiographic features of follicular bronchiolitis

| Radiographic features of follicular bronchiolitis |
|-----------------------------------------------|
| Chest radiograph |
| Small nodules |
| Reticulonodular infiltrates |
| Lymphadenopathy |
| Normal |
| High-resolution computed tomography scan |
| Centrilobular nodules |
| Peribronchial nodules |
| Patchy ground-glass opacities |

Figure 25.15. A membranous bronchiole is surrounded and infiltrated by lymphoid aggregates with a poorly formed reactive follicle in an example of follicular bronchiolitis.
TABLE 25.13. Causes of granulomatous bronchiolitis

| Infections, especially mycobacteria and fungus |
| Sarcoïdosis |
| Hypersensitivity pneumonitis |
| Aspiration |
| Wegener’s granulomatosis |
| Bronchocentric granulomatosis |

Clinical and Radiologic Features

Generally, the clinical and radiologic features are those of the underlying disease. These are discussed in the respective chapters on each disease.

Histopathologic Features

The histopathology varies with the underlying disease. Well-formed granulomas with caseous necrosis in the walls of bronchioles are relatively classic for granulomatous infections; well-formed granulomas with no necrosis or only punctuate necrosis are suggestive of sarcoidosis; and poorly formed granulomas associated with interstitial infiltrates are typical of hypersensitivity pneumonitis (Fig. 25.16). Foreign material including squamous cells, vegetable matter, and skeletal muscle may be seen in association with aspiration (see Chapter 5).

Prognosis

Prognosis depends on the underlying etiology and its treatment. Prognosis for the underlying diseases is discussed in the respective chapters on each disease.

Specific Types of Bronchiolitis

Diffuse Panbronchiolitis

Etiology

Diffuse panbronchiolitis (DPB) is a distinct, idiopathic syndrome characterized by progressive obstructive and supplicative airway disease. The majority of cases occur in Japan, although there are increasing numbers of reports from other nations and regions that include patients of Japanese descent and patients of non-Japanese descent. Diffuse panbronchiolitis was first described in Japan in 1969, and it was studied in a large nationwide survey in Japan in 1983, but it was not recognized in North American patients until several years later.

Association with human leukocyte antigen (HLA)-Bw54 has been reported in Japan, leading to the proposal that HLA alleles or closely linked genes may contribute to a genetic predisposition to DPB. This might partly explain why this disorder is found primarily in Asians.

Clinical and Radiologic Features

Patients typically have a history of chronic sinusitis, dyspnea on exertion, and cough. Over time, they develop purulent sputum production, obstructive pattern on pulmonary function tests, bilateral small nodular opacities on chest x-ray, and centrilobular lesions on HRCT. Highly elevated serum cold agglutinins are also typical. There is a slight male preponderance, and a wide age range with a mean of 50 years. Patients are commonly colonized with Haemophilus influenzae or Pseudomonas aeruginosa.

Prognosis

Pseudomonas infection may develop and is associated with poor prognosis. Untreated cases of DPB typically progress to bronchiectasis and respiratory failure. Prolonged survival is frequently reported with chronic low-dose macrolide therapy. Although treatment of patients with macrolide antibiotics for infections began in 1983, Kudoh et al. reported that chronic low-dose macrolide antibiotic therapy improved the course of DPB through mechanisms not related to treatment of infection. This is presumably as a result of nonspecific antiinflammatory effects of these antibiotics since they are effective even when Pseudomonas or other infections are not present. Recurrence of DPB was reported by Baz et al. in a patient who underwent lung transplantation.

Gross and Histopathologic Features

Grossly, in DPB, cut surfaces of the lungs demonstrate scattered 1- to 4-mm yellow nodules. There may also be gross findings of bronchiectasis or pneumonia (Fig. 25.17).
Histopathologically, DPB is characterized by (1) diffuse, bilateral chronic airway inflammation; (2) centrilobular, bronchiolocentric chronic interstitial inflammation; and (3) accumulation of foam cells and lymphoplasmacytic infiltrates throughout the full thickness of the walls of the respiratory bronchioles and their adjacent alveolar ducts and alveoli (Figs. 25.18 and 25.19). The panbronchiolitis (PB) unit lesion is the defining histopathologic feature of DPB and is defined as the involvement of the distal centrilobular conducting/gas exchange unit. Membranous bronchioles may also be involved and may be ectatic. Follicular bronchiolitis, intraluminal acute inflammation, bronchiectasis, acute or organizing pneumonia, or postobstructive lipoid pneumonia may also be present.

**Differential Diagnosis**

The conditions described in the following subsections, in which the lesions resemble those of DPB, have been reported in the literature:

Rheumatoid Arthritis–Associated Bronchiolar Disease/Diffuse Panbronchiolitis in Rheumatoid Arthritis

Relatively few patients with DPB have overt rheumatoid disease, although rheumatoid factor is often elevated, but a few authors have reported DPB lesions in patients with rheumatoid arthritis. Hayakawa et al. used the term *rheumatoid arthritis–associated bronchiolar disease* (RA-BD) to refer to DPB-like lesions that differed from classic DPB in the following ways: (1) panbronchiolitis lesions were more common in DPB, (2) bronchiolar obliteration occurred at more proximal sites in RA-BD, (3) long-term macrolide therapy had less effect in RA-BD, and (4) HLA-B was more frequent in DPB (50% versus 22.2%).

Pulmonary lesions resembling DPB have also been described in association with other collagen-vascular and autoimmune diseases including microscopic polyangiitis, Lambert-Eaton myasthenic syndrome and idiopathic thrombocytopenic purpura, ulcerative colitis, Churg-Strauss syndrome, Sjögren’s syndrome with malignant thymoma, and thymoma.
Human T-Cell Lymphotropic Virus Type 1–Associated Bronchiolitis and Diffuse Panbronchiolitis

There are reports of clinical and histopathologic findings in patients with human T-cell lymphotropic virus type 1 (HTLV-1) that resemble DPB. In a study of 15 cases of HTLV-1–associated bronchiolitis and 43 cases of DPB, Kadota et al. reported that HTLV-1–associated bronchiolitis had histopathologic features similar to DPB. However, a higher ratio of interleukin-2 receptor expression in T cells from BAL was found in HTLV-1–associated bronchiolitis and it did not respond as well to chronic macrolide therapy as DPB. Patients with adult T-cell leukemia and non-Hodgkin’s lymphoma have also been reported to have DPB-like lesions.

Pulmonary Diseases with Centrilobular Interstitial Foam Cell Accumulations

Iwata et al. found PB-like lesions in 20 of 1336 wedge biopsies, resections, or autopsies of various lung diseases that involve airways. (A summary of these other lung diseases with PB-like lesions are listed in Table 25.14.) Their 20 cases resembled DPB histopathologically, but using established criteria the cases could be differentiated from DPB. In general, foam cells were found in the walls of alveolar ducts and, to a lesser extent, in the walls of respiratory bronchioles. Cases of constrictive bronchiolitis, follicular bronchiolitis, bronchiectasis, and cystic fibrosis showed the greatest foam cell accumulation in membranous bronchioles or small bronchi, typically associated with lymphoid hyperplasia and scarring. Focal poorly developed PB-like lesions or occasional foci of interstitial foam cells associated with acute inflammation and intraluminal granulation tissue were observed in the other conditions.

| Pulmonary diseases                          | Number/total cases and percentage with PB-like lesions |
|--------------------------------------------|-------------------------------------------------------|
| Cystic fibrosis                            | 6/19 = 32%                                            |
| Bronchiectasis                             | 1/7 = 14%                                             |
| Constrictive bronchiolitis obliterans      | 1/15 = 7%                                             |
| Follicular bronchiolitis                   | 1/16 = 6%                                             |
| Bronchocentric granulomatosis              | 1/28 = 4%                                             |
| Aspiration pneumonia                       | 1/54 = 2%                                             |
| Hodgkin’s lymphoma                         | 1/46 = 2%                                             |
| Hypersensitivity pneumonitis               | 2/95 = 2%                                             |
| Non-Hodgkin’s lymphoma                     | 3/189 = 2%                                            |
| Wegener’s granulomatosis                   | 2/85 = 2%                                             |
| Collagen vascular disease                  | 1/162 = 1%                                            |

Idiopathic Bronchiolitis Clinically Mimicking Diffuse Panbronchiolitis

Poletti et al. screened all their patients presenting with clinical, pathophysiologic, and radiologic patterns compatible with DPB. Over a 10-year period they found four cases of DPB and five cases of idiopathic bronchiolitis that had clinical symptoms and HRCT findings indistinguishable from those of DPB but lacking the typical histopathologic features of DPB.

Eosinophilic Bronchiolitis Clinically Mimicking Diffuse Panbronchiolitis

Takayanagi et al. reported a patient diagnosed with DPB 3 years previously who failed to respond to erythromycin. A diagnosis of eosinophilic bronchiolitis was made on a wedge biopsy.

Xanthomatous Bronchiolitis

In 1985, a number of years before DPB was recognized as occurring in North America, the case of a 16-year-old girl undergoing lung transplant for bronchiolitis was reported as a case of xanthomatous bronchiolitis. This young patient was not of Japanese or Asian descent and was from rural Texas. She did not have any of the conditions associated with PB-like lesions, and the dramatic accumulations of foam cells in her bronchioles were more severe than those seen secondary to other conditions. This case of xanthomatous bronchiolitis is probably best considered now as a variant of classic DPB. In addition to an absence of some of the expected clinical features, this case differs from classic DPB in that (1) the membranous bronchioles and small bronchi were more severely involved by foam cell infiltrates than expected in DPB, and (2) the quantity of both mural chronic inflammation and intraluminal acute inflammation are less than typically seen in most cases of DPB (Figs. 25.20, 25.21, and 25.22). These differences may be related to the short course of the disease in a young patient, since most studied cases represent long-standing chronic disease in middle-aged to older adults or due to geo-ethnic differences.

Mineral Dust Associated Small Airways Disease

A number of mineral dusts can cause small airways fibrosis and obstruction. These are discussed in greater detail in Chapters 26 and 27.

Bronchiolitis Due to Tobacco Smoke

Etiology

Tobacco smoke often causes inflammatory, sometimes fibrotic, lesions of the membranous bronchioles and
Respiratory bronchioles, designated membranous bronchiolitis and respiratory bronchiolitis, respectively. The term *respiratory bronchiolitis* is most commonly used to encompass the range of changes in bronchioles and their adjacent air spaces caused by tobacco smoke. The extent and severity of these lesions varies widely. These forms of smoking-related bronchiolitis may be accompanied by emphysema, chronic bronchitis, or interstitial lung disease in the form of respiratory bronchiolitis–associated interstitial lung disease or desquamative interstitial pneumonia (Chapters 19 and 24).

**Clinical and Radiologic Features**

Respiratory bronchiolitis is most often an incidental histopathologic finding involving occasional respiratory bronchioles and often also occasional membranous bronchioles in lung specimens from cigarette smokers. These lesions most often do not produce any clinically significant findings, although small airways obstruction may be detected by measurements of FEV₁, FEF₂₅₋₇₅, or FEF₇₅. When clinically significant, small airway obstruction is often referred to as small airways disease. However, FEV₁, FEF₂₅₋₇₅, and FEF₇₅ do not distinguish clinically between obstruction of the proximal (membranous) and distal (respiratory) bronchioles. The severity of obstruction in patients with chronic obstructive pulmonary disease appears to correlate with the severity of bronchiolitis (see Chapter 24). Less frequently, respiratory bronchiolitis may be more extensive and accompanied by clinical changes called respiratory bronchiolitis–associated interstitial lung disease (RBILD), which is probably part of a spectrum from respiratory bronchiolitis to RBILD to desquamative interstitial pneumonia in terms of histopathologic extent and clinical severity. Patients with RBILD typically present with slow onset of cough and dyspnea and diffuse reticular to reticulonodular opacities on chest X-ray and ground-glass attenuation on HRCT. In desquamative interstitial pneumonia, there is involvement of greater volumes of
lungs tissues by collections of pigmented macrophages, and clinical findings are more severe (see Chapter 19). 1,6,7,9,10,17,19,22,95,147,235-261

**Histopathologic Features**

Collections of lightly pigmented macrophages are found within the lumina of the bronchioles in respiratory bronchiolitis (Fig. 25.23). 235-261 The finely granular particles within the macrophage cytoplasm are brown on hematoxylin and eosin (H&E), stain faintly with iron stain, and are known as smoker’s pigment. The lumina of adjacent alveolar ducts and alveoli as well as membranous bronchioles typically contain collections of similarly pigmented macrophages (Fig. 25.24). The walls of the bronchioles also typically contain infiltrates of lymphocytes and histiocytes. The latter contain finely granular smoker’s pigment or coarser black anthracotic pigment. Peribronchiolar fibrosis may also be variably present in the bronchiolar walls and the first tiers of adjacent alveolar septa. The latter may also exhibit type II pneumocyte hyperplasia or metaplastic bronchiolar epithelium (Lambertosis).

In addition to the collections of pigmented macrophages, membranous bronchioles may exhibit mural lymphocytic infiltrates, smooth muscle hyperplasia, adventitial fibrosis, and hyperplasia or metaplasia of the bronchiolar epithelium. Goblet cell metaplasia of the membranous bronchiolar epithelium and mucous plugs may be present. 235–261 Histopathologic features of respiratory bronchiolitis and membranous bronchiolitis are listed in Table 25.15.

**Prognosis**

Cases of respiratory bronchiolitis even when associated with interstitial lung disease are usually self-limited and respond to cessation of smoking. 1,6,7,9,10,17,19,22,95,147,235-261

**Sauropus androgynus Ingestion**

**Etiology**

Progressive difficulty breathing with obstructive ventilatory impairment following consumption of *Sauropus androgynus*, 262–278 was first reported in Taiwan in 1994 and 1995 with reports in the medical literature by Lin et al. 262 and Lai et al. 263 in 1996. *S. androgynus* is a common vegetable food in Malaysia, and consumption of the raw leaf extract or its juice was a fad for losing weight.

| Table 25.15. Histopathologic features of tobacco-related bronchiolitis |
|---------------------------------------------------|
| **Respiratory bronchiolitis**                      |
| Intraluminal collections of macrophages containing finely granular, light brown, iron positive smokers' pigment |
| Pigmented macrophages in adjacent alveolar ducts and alveoli |
| Histiocytes containing finely granular light brown smokers' pigment or coarse black anthracotic pigment in bronchiolar walls |
| Lymphocytic infiltrates in bronchiolar walls |
| Peribronchiolar fibrosis in bronchiolar walls and adjacent alveolar septa with metaplasia (Lambertosis) of the lining epithelium |
| **Membranous bronchiolitis**                       |
| Also includes: Smooth muscle hyperplasia |
| Adventitial fibrosis |
| Goblet cell metaplasia of the bronchiolar epithelium |
FIGURE 25.25. Obliterative bronchiolitis with complete obliteration of the lumen of a membranous bronchiole after *Saurops androgynus* ingestion.

**Clinical and Radiologic Features**

Most patients are young to middle-aged women who present within a few months of consumption of *S. androgynus*. Progressive dyspnea and persistent cough are the primary presenting symptoms. Patients have generally been reported to have obstructive ventilatory defects without bronchodilator response, with the severity sometimes reported as dose dependent. Lai et al.\(^2\) reported that chest x-rays were normal, but HRCT showed bilateral bronchiectasis and patchy low attenuation of lung parenchyma with mosaic pattern. Wu et al.\(^2\) and Kao et al.\(^3\) reported that consumption of *S. androgynus* may result in either symptomatic or asymptomatic lung injury. They found that patients had obstructive or restrictive ventilatory impairment on pulmonary function tests and inhomogeneous radio-aerosol distribution as well as increased alveolar epithelial permeability on technetium-99m diethylenetriamine pentaacetic acid (DTPA) lung scan.

**Histopathologic Features**

In the original report by Lin et al.,\(^2\) one open lung biopsy disclosed bronchiolitis obliterans organizing pneumonia. Shortly thereafter, Lai et al.\(^2\) reported bronchiolitis obliterans in open lung biopsies from four patients (Fig. 25.25). They also reported a predominance of T cells by immunohistochemistry. The BAL fluid prior to treatment has been reported to have increased neutrophils and eosinophils. A study of four explanted lungs of patients receiving lung transplants,\(^2\) allowing for more extensive examination than biopsies, disclosed pathologic changes consistent with segmental ischemic necrosis of bronchi at the water-shed zone of bronchial and pulmonary circulation: fibromuscular sclerosis and obliteration of bronchial arteries in the walls of large bronchi, segmental necrosis of small bronchi, fibrosis and atrophy of bronchial structures in immediately proximal bronchi, and obstruction and dilatation in immediately distal bronchi. They reported that most small bronchioles were “little altered.” However, Wang et al.\(^2\) subsequently reported a significant number of constrictive and obliterative bronchioles in one pneumonectomy and four biopsies. They also found fibromuscular intimal sclerosis of bronchial arteries in 15% of bronchi 4 mm or less in diameter, which they proposed was only an indirect contributing factor.

**Prognosis**

Patients with *S. androgynus* bronchiolitis obliterans develop progressive respiratory failure and do not respond to cessation of *S. androgynus* intake, large-dose steroids, bronchodilators, cytotoxic agents, or plasmapheresis.\(^2\) Lung transplantation has been proposed as therapy for end-stage disease.\(^2\)

**Bronchiolitis Due to Chemical Fumes**

**Etiology**

Inhalation of a wide range of chemical fumes and smoke can cause small airways injury.\(^2\) An acute phase, an organizing phase, and a chronic phase of bronchiolar injury can be classically identified in many cases associated with inhalation of toxic fumes, although not all cases progress to a chronic phase. Fumes that can cause bronchiolitis are listed in Table 25.16.

**Clinical and Radiologic Features**

During the acute phase immediately after fume exposure, the patient’s symptoms depend on the type, amount, and circumstances of the exposure.\(^2\) In very severe cases, there may be pulmonary edema or adult respiratory distress syndrome or even death from reflex

| TABLE 25.16. Causes of bronchiolitis due to fume exposure |
|---------------------------------------------------------|
| Smoke from fires |
| Chlorine       |
| Phosgene       |
| Ozone          |
| Nitrogen dioxide |
| Sulfur dioxide |
| Ammonia        |
| Hydrogen sulfide |
| Trichloroethylene |
| Chloropierin   |
| Methyl sulfate |
| Hydrogen fluoride |
| Methyl isocyanate |
laryngospasm and bronchial spasm. With less severe exposures, patients may have cough, dyspnea, hypoxemia, cyanosis, and a variety of other symptoms such as headache, vomiting, and loss of consciousness. Most patients who survive the acute phase recover without long-term consequences. A small number progress to clinical illness over a period of a few weeks, with findings of obstructive disease and symptoms of cough, dyspnea, hypoxemia, and cyanosis. Bronchial wall thickening is commonly seen on the first chest x-ray subsequent to fume exposure. Later, bilateral consolidation may be seen. As noted, most cases resolve, but some cases progress to radiographic findings of constrictive bronchiolitis.

Histopathologically, in the acute phase there is acute inflammation and necrosis of the bronchiolar mucosa, which may or may not be associated with adjacent findings of diffuse alveolar damage or pulmonary edema. The acute phase is followed by an organizing phase, in which the histopathologic features of organizing pneumonia (or bronchiolitis obliterans with intraluminal polyps, formerly referred to as BOOP) are found. The organizing phase resolves in the majority of cases, but some cases progress to constrictive bronchiolitis with narrowing or obliteration of bronchiolar lumina by scar.

Bronchiolitis Associated with Swyer-James Syndrome

Swyer-James (Macleod) syndrome is unilateral radiographically hyperlucent lung associated with constrictive bronchiolitis and bronchiectasis, often as a result of childhood pulmonary infection.

Etiology

Most cases diagnosed as Swyer-James syndrome are rare complications of viral pneumonia and bronchiolitis in childhood, although other infections including *Mycoplasma* and pertussis are sometimes implicated. Patients typically develop bronchiectasis and recurrent infections including bacterial pneumonia, so that there are often multiple clinical and pathologic findings.

Clinical and Radiologic Features

Patients often have chronic cough and wheezing. Clinical and radiologic criteria for diagnosis of this syndrome include (1) unilateral loss of lung volume with hyperlucency on chest x-ray, (2) unilateral reduction in vascularity on computed tomography (CT) scan of the chest, and (3) unilateral loss of perfusion on technetium-99c lung scan.

Histopathologic Features

There are relatively few descriptions of the histopathology of Swyer-James syndrome. Histopathologic features that have been described include emphysema with widespread obliteration of the pulmonary capillary bed, bronchitis and bronchiolitis, peribronchial fibrosis and smooth muscle proliferation, bronchiectasis including cystic cavities lined by ciliated columnar epithelium, interstitial chronic inflammation and fibrosis, lymphoid nodules, and hypertrophy of the pulmonary artery. Marchevsky et al. recently described features from a pneumonectomy specimen including severe mixed centriacinar-panacinar emphysema in all lobes, bullous emphysema in the upper lobe, bronchiectases, mild interstitial pneumonia with fibrosis, and placental transmogrification of the pulmonary parenchyma of all three lobes.

Prognosis

Most patients with Swyer-James syndrome are managed clinically. In one study of 13 patients with Swyer-James (MacLeod) syndrome, patients with saccular bronchiectasis had more frequent pneumonias than those without bronchiectasis or with cylindrical bronchiectasis.

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