Imaging of Small Airways Disease

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Abstract: Small airways disease includes a spectrum of inflammatory and fibrotic pulmonary diseases centered on the small conducting airways. High-resolution computed tomography plays a key role in the detection and classification of small airways disease and, when combined with relevant clinical and pathologic findings, leads to more accurate diagnosis. The imaging manifestations of small airways disease on high-resolution computed tomography may be direct or indirect signs of small airway involvement and include centrilobular nodules and branching nodular (tree-in-bud) opacities, or the demonstration of mosaic attenuation that is typically exaggerated on expiratory computed tomography. This article reviews the normal anatomy and histology of bronchioles and the clinical, pathologic, and imaging features of small airways diseases.

Key Words: small airways disease, bronchioles, bronchiolitis, constricitive bronchiolitis (J Thorac Imaging 2009;24:285–298)

The term bronchiolitis has been used to refer to a broad spectrum of inflammatory and fibrotic pulmonary diseases centered on the small conducting airways. Several classification schemes of bronchiolitis have been proposed. Some of these are based on clinical features and take into consideration the clinical setting and the etiologic factors associated with bronchiolitis. Others are based on histologic features and others on high-resolution computed tomography (HRCT) findings of small airways disease. HRCT plays a key role in the detection and classification of small airways disease and, when combined with relevant clinical and pathologic findings, leads to a more accurate diagnosis. This article will review the normal anatomy and histology of bronchioles and the clinical, pathologic, and imaging features of small airways diseases.

NORMAL ANATOMY

The designation “small airways” refers to the membranous and respiratory bronchioles. In addition to their small size (<2 mm internal diameter), the small airways are also distinguished by their lack of cartilage and submucosal glands.2,3 The terms bronchioles and small airways are used here interchangeably, although they are not strictly synonymous.

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SECONDARY PULMONARY LOBULE

The secondary pulmonary lobule (SPL) is a key structure in the lung anatomy and is distinguished as the smallest functioning subunit of lung that is bound by connective tissue septa, supplied by a lobular bronchi ole and arteriole, and drained by veins and lymphatics in the interlobular septa. Each SPL measures 1 to 2.5 cm and contains 3 to 12 acini. The SPL are better formed and more easily recognized in the peripheral subpleural lung and are smaller and less regular in the central lung. The SPL are not normally visible on radiography or computed tomography (CT)/HRCT (Fig. 1). The small airways are arrayed within the SPL, branching successively from a central, lobular bronchi ole (1 mm diameter) that in turn supplies 3 to 12 terminal bronchioles, respiratory bronchioles, and alveolar ducts.3,4

BRONCHIOLES

The axial pathway of human conducting airways extends from the main bronchus of each lung to the terminal bronchi ole and may contain as many as 25 airway generations or as few as 5. The number of generations may vary among different pulmonary lobes and segments according to their proximity or distance from the pulmonary hilum. Small bronchi give rise to membranous bronchioles, so-called because cartilage disappears from the airway wall at that level, and the airway diameter decreases to approximately 1 mm. The last conducting membranous bronchiole, the terminal bronchi ole, leads into the pulmonary acinus, a structural unit of lung distal to the terminal bronchi ole, supplied by first-order respiratory bronchioles, which in turn supply alveolar ducts, alveolar sacs, and alveoli. The acinus is the largest unit of lung in which all airways participate in the gas exchange.

The membranous bronchioles, including the terminal bronchi ole, are lined by epithelial cells consisting of ciliated columnar cells and nonciliated Clara cells (Fig. 2). Elastic fibers attached to the adventitia of bronchioles from adjacent alveoli provide mechanical support and prevent small airway collapse in the final phase of expiration.3,4

Respiratory bronchioles arise from the distal aspects of terminal bronchioles or as branches of other respiratory bronchioles: they are partially alveolated, transitional airways—both conductive and respiratory—and measure in the range of 0.5 mm in diameter. The respiratory bronchioles branch into multiple alveolar ducts, characterized by walls that are totally alveolated and terminate in a semicircular blind end called the alveolar sac, each surrounded by 4 or more alveoli.

The canals of Lambert are direct, epithelial-lined channels between membranous bronchioles and adjacent alveoli that provide an alternate route for collateral ventilation and allow passage of macrophages from the
alveolus to the respiratory and terminal bronchioles where ciliated cells can clear them from the lungs.4

RELATIONSHIP WITH VASCULAR AND LYMPHATIC STRUCTURES

Throughout its course, each bronchiole is paired with a homologous arteriole of equivalent size to form a bronchovascular bundle that is further supplied by accompanying lymphatic vessels until reaching the alveolar-capillary network. In chronic inflammatory processes, lymphoid follicles along small airways form the mucosa-associated lymphoid tissue reaction, designated as chronic bronchiolitis. When germinal centers are also present, the condition is termed follicular bronchiolitis (FB).2,3

IMAGING OF SMALL AIRWAYS DISEASE

Small airways disease is difficult to detect by conventional radiographic imaging and physiologic testing until widespread involvement has occurred. In recent decades, the utilization of thin-section and high-resolution CT has advanced our understanding of small airways diseases and, when correlated with clinical features and pathologic

FIGURE 1. Normal anatomy. A, Illustration depicts normal CT anatomy showing polyhedral secondary pulmonary lobules that are better defined peripherally and less regular centrally. Gray lines outline the boundaries of the secondary pulmonary lobules, the interlobular septa. The small airways are not visible. B, Illustration depicts the typical findings on normal chest CT. Note that the interlobular septa are not normally visible.

FIGURE 2. Microscopic anatomy of normal small airways. A, Intermediate power photomicrograph (hematoxylin and eosin stain) shows a normal membranous bronchiole lined by a single layer of low-cuboidal epithelium with a circumferential layer of smooth muscle and no cartilage in the airway wall. B, High-power photomicrograph (hematoxylin and eosin stain) shows a terminal bronchiole with surrounding normal alveoli. The bronchiole is partially lined by a single layer of low-columnar epithelium in continuity with the alveolar walls. Note the absence of smooth muscle surrounding the bronchiole and its communication with adjacent respiratory bronchioles.
findings, has greatly enhanced diagnostic accuracy in the evaluation of patients suspected of having small airways disease.

The imaging evaluation of patients suspected of having small airways disease should include inspiratory and expiratory HRCT obtained using thin collimation (1.25 mm or less) acquired as either noncontiguous images at 1 cm or 2 cm intervals, or reconstructed from a spiral/helical volumetric acquisition. Volumetric image acquisition requires a higher radiation dose, but allows for evaluation of larger airways for the presence of bronchiectasis and optimizes the detection and characterization of airway abnormalities by utilization of reconstructed multiplanar or postprocessed images. Multidetector row CT of the chest enables production of multiplanar volume reconstructions that may be manipulated to encode the minimum-intensity or maximum-intensity voxels of a scanned volume of tissue onto a 2-dimensional image. Minimum-intensity projection (MinIP) techniques project voxels with the lowest attenuation value, improving the detection of subtle areas of low attenuation and the conspicuity of regional heterogeneity (mosaic attenuation) of lung parenchyma that may be manifestations of small airways disease. Projection of voxels with the highest attenuation values produces maximum-intensity projection (MIP) images that facilitate the recognition of small centrilobular nodules, tree-in-bud opacities, and poorly defined centrilobular nodules.

**DIRECT AND INDIRECT CT SIGNS OF SMALL AIRWAYS DISEASE**

**Centrilobular Nodules and Tree-in-bud Opacities**

The small airways are not normally visible on HRCT. Their location may be inferred from visualization of their accompanying small lobular arteries. They may become visible at the center of the SPL when there is abnormal increased soft-tissue density in or around the bronchiole and thickening of the bronchiolar wall. The soft tissue density may form direct CT signs of small airways disease as centrilobular nodules and/or V-shaped or Y-shaped branching linear opacities that resemble the early seasonal appearance of a budding tree in springtime (“tree-in-bud” pattern) (Fig. 3). Poorly defined centrilobular nodules, often of a CT attenuation less than that of soft tissue, may occur when inflammatory cellular infiltrates involve the peribronchiolar alveoli [eg, hypersensitivity pneumonitis (HP) or respiratory bronchiolitis (RB)]. A less common direct sign of bronchiolitis is the presence of bronchiolitis, representing dilated bronchioles that are usually associated with a chronic, fibrotic process and are most easily recognized in the subpleural lung.

**Air Trapping and Mosaic Attenuation**

The CT findings of mosaic attenuation and/or air trapping may be indirect signs of small airways disease. The term mosaic attenuation refers to a patchwork of regions of differing attenuation detected on inspiratory CT images, and may represent obliterative small airways disease, patchy interstitial disease, or occlusive vascular disease. Air trapping is seen on end-expiration CT scans as parenchymal areas with less than the normal increase in attenuation and a lack of volume reduction and manifests on expiratory HRCT as sharply defined geographic areas of low attenuation with contours that follow the outlines of the underlying polyhedral SPLs (Fig. 4). Subtle or diffuse areas of air trapping may be more easily differentiated by comparison between inspiratory and expiratory CT scans and thus it is important to include expiratory imaging in the CT evaluation of individuals suspected of having small airways disease.
SMALL AIRWAYS DISEASE

Definition
The term small airways disease refers to pathologic conditions that involve the bronchioles primarily, or as components of interstitial or alveolar lung disease. Bronchiolitis occurs in a heterogeneous group of lesions that vary in their etiology, clinical settings, and pathologic features but are centered on small conducting airways.1

Historic Perspective
The term ‘small airway disease’ was first used by Hogg and colleagues11 in 1968, in a study, that showed that the main site of airflow resistance in patients with chronic airflow obstruction was in airways less than 2 mm in diameter. They also confirmed in humans what Macklem and Mead had shown in dogs—that the peripheral airways normally contribute only 10% to 20% of total airway resistance because the total cross-sectional area of the small airways is much greater than the total cross-sectional area of the central airways. When diseased, however, the small airways contribute disproportionately to increased airway resistance.11 As a consequence, measurement of airway resistance might be normal in the setting of considerable obstruction in the peripheral airways. For this reason, the small airways have been described as the ‘silent zone’ of the lungs, and diseases affecting these structures may not be evident on pulmonary function tests until late in their course.11

Classification of Small Airways Disease
Small airways disease (bronchiolitis) may be classified according to its clinical setting, its histologic pattern, or on the basis of HRCT imaging findings. The clinical classification is on the basis of the proven or presumed etiology, or on associated systemic conditions. Histologic classification into proliferative (cellular) or fibrotic (constrictive) bronchiolitis correlates most directly with the imaging features of small airways disease.9,12 This article will emphasize the imaging appearances of bronchiolitis and review those lesions that produce direct and indirect imaging features of small airways disease.

Cellular bronchiolitis refers to bronchiolitis in which inflammatory cells (acute, chronic, or acute and chronic) are the predominant histopathologic finding and is a common pattern found in many clinicopathologic settings. Bronchioles are not visible on normal HRCT but may become visible at the center of the SPL as a direct sign of bronchiolitis when their walls are thickened by inflammatory cell infiltrates. Cellular infiltrates in the peribronchiolar alveoli may manifest as poorly defined centrilobular nodules that may be of soft tissue or ground glass attenuation.2,9,13

Constrictive bronchiolitis (syn. bronchiolitis obliterans) is a purely bronchiolar lesion with luminal narrowing by collagenous fibrosis and scarring that may be subtle or result in complete luminal obliteration. Constrictive bronchiolitis can be seen in a variety of disorders and in some specific clinical settings.2

CELLULAR BRONCHIOLITIS

Infectious Bronchiolitis
General Features
The imaging features of bronchiolitis are relatively common on chest CT but are often nonspecific, typically manifesting as centrilobular nodules and branching nodular (tree-in-bud) opacities, and have been described in viral infection, bacterial pneumonia, tuberculosis, nontuberculous mycobacterial infection, and aspergillosis. Some disease entities, however, have associated findings that provide clues to the diagnosis. Detection of associated cavitory lesions, for instance, suggests the diagnosis of

FIGURE 4. Indirect signs of small airways disease. A, Illustration depicts mosaic attenuation/air trapping characterized by sharply defined geographic areas of low attenuation (darker lung) with contours that follow the polyhedral outlines of the underlying secondary pulmonary lobules, depicted by gray lines. B, Illustration depicts the same findings as in A without the underlying pulmonary architecture and, therefore more closely approximates the findings seen on CT and HRCT.
**Mycobacterium tuberculosis**, atypical mycobacterial, or fungal infection, whereas findings of bronchiolitis associated with bronchiectasis, particularly with involvement of the middle lobe and lingula, suggest the diagnosis of atypical mycobacterial infection. The combination of centrilobular nodules and lobular areas of ground-glass opacity on chest CT is suggestive of *Mycoplasma pneumoniae* pneumonia.

Acute infectious bronchiolitis most commonly affects children and is most often caused by viruses (respiratory syncytial virus, adenoviruses, parainfluenza virus, influenza virus, and human metapneumovirus) and *M. pneumoniae* pneumonia. Less common etiologies include chlamydia, bacteria, and fungi (eg, aspergillus in immunocompromised individuals).

**Clinical Presentation**

The clinical presentation of adults with infectious bronchiolitis is typically less severe than that of affected infants and children, but may sometimes be severe and fatal. Children affected by infectious bronchiolitis often present with symptoms of an upper respiratory tract infection followed 2 to 3 days later by the abrupt onset of dyspnea, tachypnea, and fever.

**Pathology**

Histologically, infectious bronchiolitis is characterized by the presence of inflammatory cells, mainly neutrophils, in the walls of airways and inflammatory exudates in the airway lumens (Fig. 5). In some instances, specific histologic or microbiologic findings may indicate a specific diagnosis (eg, hyphae in aspergillus infection, observation of acid-fast bacilli in *M. tuberculosis* infection).

**Imaging Findings**

**Radiography**

Chest radiographs may reveal bilateral, often subtle, nodular, or reticulonodular opacities. In children, airway wall thickening and peribronchial consolidations are common. Partial small airway obstruction may manifest as hyperinflation; patchy bilateral consolidation often indicates the presence of bronchopneumonia.

**CT/HRCT Features**

In adults, infectious bronchiolitis typically manifests on HRCT as well-defined centrilobular nodules and tree-in-bud opacities that may be patchy and unilateral or bilateral and asymmetric. The presence of tree-in-bud nodules is highly suggestive of infectious bronchiolitis but may be a manifestation of noninfectious conditions (eg, aspiration, cystic fibrosis) (Figs. 6–9).

**Hypersensitivity Pneumonitis**

Cellular bronchiolitis is a prominent feature of hypersensitivity pneumonitis (HP) (syn. extrinsic allergic alveolitis), an allergic lung disease caused by the inhalation of organic or inorganic agents and of some chemicals. In affected individuals, the small organism or protein complex lodges in the terminal and respiratory bronchioles and

**FIGURE 5.** Microscopic features of cellular bronchiolitis. A, Intermediate power photomicrograph (hematoxylin and eosin stain) shows dilated branching bronchioles surrounded by a dense acute and chronic inflammatory cellular infiltrate. B, High-power photomicrograph (hematoxylin and eosin stain) shows the inflammatory cellular infiltrate involving the bronchiolar epithelium and wall.

**FIGURE 6.** Purulent bronchiolitis. Unenhanced axial thin-section chest CT (lung window) demonstrates diffuse bilateral centrilobular nodules and tree-in-bud opacities consistent with the cellular bronchiolitis characteristically seen in bacterial infections. Note the centrilobular nodules do not abut the pleural surfaces.
alveoli, and induces an alveolitis and inflammatory granulomatous bronchiolitis of variable severity.18–21

Patients with subacute HP may experience an insidious onset of symptoms over a period of weeks or months and may present with cough and dyspnea on exertion, or experience loss of appetite, weight loss, and fatigue.22

Acute HP manifests as pulmonary edema and diffuse airspace consolidation. Subacute HP manifests as bilateral ground-glass opacities and poorly defined centrilobular nodules that correlate, respectively, with the histologic presence of alveolitis and bronchiolitis. The findings are often diffuse, or predominantly involve the middle and lower lung zones. Lobular areas of decreased attenuation and perfusion manifest as air trapping on expiratory CT imaging. (Figs. 10, 11).8,9,21 HP is discussed in detail elsewhere in this issue (see Sirajuddin and Kanne).

Aspiration Bronchiolitis

General Features
Diffuse aspiration bronchiolitis (DAB) is a recently described clinical entity characterized by chronic inflammation of bronchioles as a result of recurrent aspiration of foreign material.23

Clinical Presentation
Half of all the patients affected with DAB have oropharyngeal dysphagia; many are elderly or bedridden patients, or individuals with neurologic disorders or dementia. Many present with bronchorrhea, bronchospasm, wheezing, and dyspnea—signs and symptoms that are often associated with oral food intake. Patients with DAB often present with a persistent respiratory illness and radiographic findings of diffuse small nodular opacities.23,24

Pathology
DAB is characterized histologically by chronic mural inflammation of bronchioles with foreign body reaction. Evidence of cryptogenic organizing pneumonia or bronchopneumonia may be seen within associated patchy areas of consolidation.24

Imaging Findings

Radiography
Chest radiographs demonstrate diffuse small (< 5 mm) nodular opacities that may be unilateral or bilateral, and mild-to-moderate hyperinflation.23 The small nodular pattern on radiography may be misleading and resemble an interstitial, rather than an airways-related disease.6

CT/HRCT Features
DAB manifests on HRCT as disseminated small centrilobular branching linear opacities (tree-in-bud pattern), often associated with adjacent areas of lobular consolidation. The distribution of abnormalities revealed on HRCT is usually associated with the patient’s body position at the times of recurrent aspiration and may predominantly involve the lower lungs in individuals who remain mostly in the supine position while awake or asleep, or be predominantly right or left-sided abnormalities in patients who sleep or spend extended time on their right or left side, respectively (Fig. 12).8,24

Respiratory Bronchiolitis (RB) and Respiratory Bronchiolitis-associated Interstitial Lung Disease (RB-ILD)

RB and RB-associate interstitial lung disease (RB-ILD) occur in patients who smoke and are characterized histologically by submucosal inflammation and fibrosis of the respiratory bronchioles and the presence of pigmented macrophages in bronchiolar lumens, alveolar ducts, and alveolar spaces. On HRCT, RB, and RB-ILD manifest as poorly defined centrilobular nodules that resemble those seen in HP and are frequently accompanied by patchy areas of ground-glass opacity. The abnormalities may predominantly involve the upper lobes.25 RB and RB-ILD are discussed in detail elsewhere in this issue (see Galvin and Franks).
Follicular Bronchiolitis

General Features

Follicular bronchiolitis (FB), also known as pulmonary lymphoid hyperplasia, hyperplasia of the bronchus-associated lymphoid tissue, or hyperplasia of the mucosa-associated lymphoid tissue, is a cellular bronchiolitis characterized histologically by peribronchial and peribronchiolar lymphoid follicles. The detection of FB in lung-biopsy specimens suggests the possibility of congenital or acquired immunodeficiency syndromes, including HIV infection and acquired immunoglobulin deficiencies. However, FB may also be found in patients with collagen vascular disease (e.g., rheumatoid arthritis, Sjögren syndrome), systemic hypersensitivity reactions, infection, lymphoproliferative disease, and diffuse panbronchiolitis (DBP), and as a reactive process distal to bronchiectasis or in association with middle-lobe syndrome (Fig. 13).2,17,26

Clinical Presentation

FB occurs most commonly in middle-aged adults but may occasionally be found in children. Affected patients typically present with progressive shortness of breath and cough. Fever, recurrent pneumonia, and weight loss are less common clinical manifestations of FB. Pulmonary function tests may reveal obstruction, restriction, or a mixed pattern of functional abnormalities.26,27

Clinical conditions associated with FB are similar to those associated with lymphoid interstitial pneumonia and...
include: (1) immunological disorders (Sjögren syndrome, Hashimoto thyroiditis, pernicious anemia, autoimmune hemolytic anemia, chronic active hepatitis, primary biliary cirrhosis, and myasthenia gravis), (2) immunodeficiency (HIV, AIDS), (3) allergy, including asthma, and (4) allogeneic bone-marrow transplantation.

Pathology
Histologically, FB is characterized by abundant lymphoid follicles with abundant germinal centers in the walls of bronchioles and, less extensively, along bronchi, interlobular septa, and the pleura. Obstructive pneumonia may be seen as a result of airway compression.

Imaging Findings

Radiography
FB manifests on chest radiography as bilateral reticular or reticulonodular opacities. However, the findings may be subtle and in some cases the radiograph may be interpreted as normal.

CT/HRCT Features
CT/HRCT demonstrates small, poorly defined centrilobular nodules that are diffusely distributed. Additional but variable findings include peribronchial and subpleural nodules, patchy areas of ground-glass attenuation, bronchial wall thickening, and patchy areas of low attenuation. In 1 study of 12 patients with FB, HRCT findings included bilateral centrilobular nodules (100%), patchy ground-glass opacities (75%), peribronchial nodules (42%), and subpleural nodules (25%) (Fig. 14).

Diffuse Panbronchiolitis

General Features
Diffuse panbronchiolitis (DPB) is a progressive form of cellular bronchiolitis that occurs almost exclusively in adults of Japanese heritage and is associated with chronic inflammation of the paranasal sinuses. The imaging features of DPB may have considerable overlap with those of other inflammatory airway diseases, including cystic fibrosis, inflammatory bowel disease, idiopathic bronchiectasis, constrictive bronchiolitis (CB), and FB.
Clinical Presentation

Patients with DPB typically present with cough and dyspnea on exertion and may have symptoms of sinusitis. *Pseudomonas aeruginosa* frequently colonizes the respiratory tract of affected patients. Pulmonary function tests reveal marked obstruction and mild restrictive disease.

Pathology

The gross pathologic features of DPB are yellow 1 to 3 mm nodules. Histologically, there is transmural infiltration of the bronchiolar interstitium and peribronchiolar tissue by foamy macrophages, lymphocytes, and plasma cells. The involved small airways may include respiratory bronchioles, terminal (membranous) bronchioles, and alveolar ducts. Terminal bronchioles may be ectatic. Follicular bronchiolitis may be present, and acute inflammation may occur in bronchiolar lumens. Superimposed acute or organizing pneumonia and bronchiectasis may also occur.

Imaging Findings

Radiography

Chest radiography reveals diffuse nodules (<5 mm) that predominantly involve the lower lungs, and mild-to-moderate hyperinflation.

CT/HRCT Features

CT/HRCT demonstrates small centrilobular nodules and branching linear opacities (tree-in-bud pattern), bronchiolectasis, cylindrical bronchiectasis, and areas of mosaic attenuation. In the early stages of DPB, the tree-in-bud pattern is the predominant finding, followed by thick-walled centrilobular lucencies. In later stages, HRCT reveals large, cystic spaces, bullae, air trapping, and peripheral areas of decreased attenuation (Fig. 15).

**CONSTRUCTIVE BRONCHIOLITIS**

General Features

The published terminology regarding CB can at times be confusing and inconsistent. For example, the term “bronchiolitis obliterans” has been used to refer to both CB and bronchiolitis obliterans organizing pneumonia (more usefully designated as cryptogenic organizing pneumonia or organizing pneumonia). The former is a relatively rare condition characterized by collagen deposition extrinsic to the airway lumen and is considered irreversible, whereas the latter is a more frequently diagnosed often multifocal cellular process characterized by active fibroblast proliferation within the airspace lumens that typically responds to therapy. Some advocate the use of the term “obliterative bronchiolitis” to refer to the clinical syndrome of airflow obstruction associated with CT or HRCT findings of small airways disease with or without pathologic confirmation of CB. In addition, the term bronchiolitis obliterans syndrome (BOS) has been proposed for the clinical syndrome of chronic rejection that can follow lung transplantation and may be associated with HRCT abnormalities.

Clinical Features and Etiology

Patients with CB typically present with dyspnea and chronic cough. In some cases, the symptoms follow a lower respiratory tract infection. Characteristic findings on auscultation include mid-inspiratory squeaks, wheezes, and crackles. The disease typically follows a chronic and slowly progressive course; although rapidly progressive disease is also described. Pulmonary function typically demonstrates airflow obstruction with mixed restrictive and obstructive abnormalities.

There are many pulmonary and systemic conditions that have been associated with CB. Thus, some employ a “clinical” classification of CB based on etiologic factors. CB may rarely be idiopathic. Affected patients are usually older women with a variable history of cigarette smoking who often experience a rapid progression of clinical symptoms with eventual respiratory failure. A series of etiologic factors has also been described that include...
infection, transplantation, collagen vascular disorders, inhalational lung injury, and ingested toxins.

Infection
Childhood infection is a rare cause of CB. The causative infection typically occurs in children under 8 years of age. Typical infections are viral (respiratory syncytial virus, parainfluenza virus, adenovirus), but \textit{M. pneumoniae} has also been implicated. Some affected patients may go on to exhibit imaging features of the Swyer-James syndrome or MacLeod syndrome as adults. It is postulated that viral bronchiolitis of childhood may interfere with the normal development of the affected lung with resultant CB. These patients may be asymptomatic or may present with cough, recurrent infection, or hemoptysis. CB may also be seen in cases of cystic fibrosis and is felt to represent the sequelae of recurrent episodes of pulmonary infection (Figs. 16, 17).

Transplantation
Lung Transplantation
CB is a known complication of lung and heart-lung transplantation that impacts the morbidity and limits the survival of affected patients. CB is considered a manifestation of chronic allograft dysfunction or chronic rejection. The major risk factor for CB is acute rejection, particularly when severe or recurrent. Severe infection, particularly cytomegalovirus pneumonia is also associated with the development of CB. CB is a late complication of transplantation that occurs at least 3 months (median 16 to 20 mo) after the transplant. The onset of symptoms may be insidious or rapid. The mechanism of rejection is related to the activity of the recipient immune system against the transplanted lung tissue.

The International Society of Heart Lung Transplantation has defined the BOS based on deterioration of pulmonary function, specifically, the forced expiratory volume in one second (FEV1) when compared with baseline. A clinical diagnosis of BOS is based on documentation of a decline in FEV1 of more than 20% during the posttransplantation period, after exclusion of other causes of allograft dysfunction. The category of “potential” BOS or stage BOS 0-p is based on a decrease in forced expiratory flow in the mid-expiratory phase (forced expiratory flows between 25% and 75% of forced vital capacity), but its prognostic usefulness is under debate. Although air trapping found on expiratory thin section CT is considered the most sensitive and accurate imaging indicator of CB in lung transplant recipients (Fig. 18), some investigators have found a weak correlation between the BOS stage and the severity of bronchial dilatation, bronchial wall thickening, air trapping and mosaic attenuation seen on CT, particularly in single lung transplant recipients. The prevalence of CB in lung transplant recipients surviving at 5 years is approximately 50% with a 5-year survival after the onset of disease of approximately 30% to 40%

Hematopoietic Stem Cell Transplantation
CB is a known complication of hematopoietic stem cell (HSC) transplantation with a prevalence of approximately 5%. It is one of the late pulmonary complications of HSC.
transplantation and typically develops more than 100 days (median 400 to 450 d) after the transplant.\textsuperscript{29,30} It is thought to result from graft-versus-host disease induced by the donor cells.\textsuperscript{30} However, although it is typically described in patients undergoing allogeneic transplants, it is also reported in those undergoing autologous transplants. Risk factors for the development of CB include older age, chronic graft-versus-host disease and methotrexate therapy. The histologic diagnosis may be difficult to make on transbronchial lung biopsy due to the patchy nature of the disease.\textsuperscript{29}

The prevalence of CB in allogeneic HSC transplant recipients is estimated at approximately 9% with a range of up to 48%.\textsuperscript{29} The mortality of affected patients reported in the literature is variable with reports of 12% to 27% 5-year mortalities in one series and survival of only 10% of patients with CB at 5 years in another.\textsuperscript{29}

**Connective Tissue Disease**

CB may occur in the setting of rheumatoid arthritis with or without penicillamine treatment. Affected patients are typically women in the fifth or sixth decades of life, and most have long-standing disease. The small airways disease may rarely antedate the rheumatologic manifestations of the disease.\textsuperscript{40} It should be noted that FB (a cellular bronchiolitis) has also been described in patients with rheumatoid arthritis. CB has also been described in a few patients with systemic lupus erythematosus.\textsuperscript{29}

**Inhalational Lung Disease**

Although several chemicals have been implicated, the best understood diseases are those related to inhalation of oxides of nitrogen. Silo filler’s disease is related to nitrogen dioxide (NO\textsubscript{2}) and nitric oxide (NO), which are produced during the anaerobic fermentation of silage. Nitrous acids and nitric oxides produce severe injury to tissues. The presentation of exposed individuals will vary with the degree of exposure. Clinical presentation may be accompanied by mild symptoms that may progress to pulmonary edema and acute respiratory distress syndrome. Those patients who recover may become asymptomatic for a short period of time, and subsequently present with progressive cough, dyspnea, and hypoxemia, secondary to the development of CB of variable severity.\textsuperscript{29} Inhalation of fire fumes (Fig. 19) and the butter-flavoring ingredient acetyl in popcorn plant workers have also been associated with the development of CB.\textsuperscript{30,41}

**FIGURE 18.** Constrictive bronchiolitis after lung transplantation. A, Unenhanced inspiratory thin-section chest CT (lung window) of a 52-year-old woman after left lung transplantation demonstrates subtle heterogeneity (mosaic attenuation) of the left lung parenchyma. B, Expiratory thin-section chest CT (lung window) of the same patient shows patchy areas of air trapping.

**FIGURE 19.** Constrictive bronchiolitis after smoke inhalation. A, Unenhanced inspiratory thin-section chest CT (lung window) of a 45-year-old woman after smoke inhalation in a house fire demonstrates mild mosaic attenuation and patchy ground-glass opacity in the left upper lobe. B, Expiratory thin-section CT demonstrates bilateral scattered areas of air trapping.
Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia

Proliferation of pulmonary neuroendocrine cells is typically confined to the bronchial and bronchiolar epithelium. These proliferations may take the form of tumorlets, which can be diffusely distributed throughout the lung. Nodular neuroendocrine cell proliferations measuring more than 5 mm in diameter are usually classified as carcinoid tumors. Affected patients are typically women who may exhibit obstructive and/or restrictive lung function or may be asymptomatic. These patients may exhibit HRCT evidence of small airways disease in which multifocal pulmonary nodules may be associated with mosaic lung attenuation and air trapping (Fig. 20).

Miscellaneous Conditions

CB has been reported in association with ingestion of Sauropsis androgynous, a weight control preparation used in Asia. Other associations include inflammatory bowel disease, paraneoplastic pemphigus and gold and penicillamine therapy.

Pathology

CB is characterized by fibrosing bronchiolitis of membranous and respiratory bronchioles with submucosal and peribronchiolar concentric fibrosis and little active inflammation or granulation tissue (Fig. 21). Early disease is characterized by a predominantly lymphocytic inflammatory cellular infiltrate affecting the lumen, mucosa, submucosa, and the tissues surrounding the bronchioles. This progresses to concentric peribronchiolar fibrosis without associated fibroblastic proliferation. The airway involvement tends to be circumferential and results in bronchiolar luminal narrowing and obstruction. Advanced disease may be difficult to diagnose histologically as the bronchioles may become completely obliterated and may be inconspicuous due to the absence of surrounding inflammation. In these cases, elastic stains may be helpful for the identification of affected small airways. Furthermore, the patchy nature of the disease may result in sampling errors on transbronchial biopsy. Thus, there may be subtle pathologic abnormalities in spite of severe symptoms and extensive imaging abnormalities.

Imaging Findings

Radiography

Patients with CB typically have normal or near normal chest radiographs. Previously reported radiographic abnormalities include hyperinflation, air trapping, and peripheral attenuation of pulmonary vascular markings. Nodular and reticular pulmonary opacities have also been described.

Patients with Swyer-James syndrome or MacLeod syndrome may exhibit a unilateral hyperlucent lung with...
findings of CB. Affected patients typically have radiographic predominant involvement of one lobe or lung with decreased pulmonary vascularity and a small ipsilateral hilum. The affected lung parenchyma may exhibit normal or decreased lung volume during inspiration and expiratory air trapping (Fig. 22).32

CT/HRCT Features
The classically described CT feature of CB is a pattern of mosaic pulmonary attenuation characterized by geographic clusters of lung lobules that exhibit alternating increased and decreased lung attenuation (Fig. 4). The mosaic attenuation is typically accentuated on expiratory imaging where air trapping manifests as areas of persistent hyperlucency highlighted by increased pulmonary attenuation in surrounding normal lung. Within low-attenuation areas of air trapping there is often a decrease in the caliber of vascular structures that is likely secondary to hypoxic vasoconstriction. In addition, there is no decrease in the cross-sectional area of the affected hyperlucent lung on expiration. The areas of increased attenuation typically reflect normal lung parenchyma, which exhibits a relative increase in vessel caliber and blood flow. Expiratory thin-section CT facilitates detection of areas of air trapping. The patchy distribution of airway involvement gives rise to mosaic lung attenuation and perfusion. The areas of abnormal attenuation may exhibit well or poorly defined contours. It should be noted that mild-mosaic attenuation and air trapping on expiratory CT has also been described in healthy subjects.45–47 In addition, mosaic attenuation and air trapping that are most evident in the right upper lobe but also affect the left upper and left lower lobes. Note central bronchiectasis and bronchial wall thickening in the left lung.

Associated findings include bronchial dilatation, bronchiectasis, and bronchial wall thickening. Other findings include centrilobular nodules. If pulmonary nodules are seen, diffuse idiopathic neuroendocrine cell hyperplasia should be considered.

Swyer-James syndrome or MacLeod syndrome refers to predominant involvement of one lobe or lung with findings of CB.9 Affected patients typically have radiographic evidence of focal lung hyperlucency and decreased vascularity with normal or decreased volume of the affected lung. Expiratory HRCT typically demonstrates air trapping of the affected lung lobe. However, affected patients typically exhibit air trapping and hyperlucency in other lobes and in the contralateral lung, which is not readily appreciated at radiography.43,50 Bronchiectasis and bronchial wall thickening may also be observed.9

SUMMARY
Small airways disease includes a spectrum of inflammatory and fibrotic pulmonary diseases centered on the small conducting airways. The imaging manifestations of small airways disease on CT/HRCT may be direct or indirect signs of small airway involvement and include centrilobular nodules and branching nodular (tree-in-bud) opacities, or the demonstration of mosaic attenuation that is typically exaggerated on expiratory CT. Some disease entities have distinguishing clinical, pathologic, and/or imaging features that facilitate a more accurate diagnosis.

REFERENCES


