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State of the Art

Bronchiolar Disorders

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Bronchiolar abnormalities are relatively common and occur in a variety of clinical settings. Various histopathologic patterns of bronchiolar injury have been described and have led to confusing nomenclature with redundant and overlapping terms. Some histopathologic patterns of bronchiolar disease may be relatively unique to a specific clinical context but others are nonspecific with respect to either etiology or pathogenesis. Herein, we present a scheme separating (*1*) those disorders in which the bronchiolar disease is the predominant abnormality (primary bronchiolar disorders) from (*2*) parenchymal disorders with prominent bronchiolar involvement and (*3*) bronchiolar involvement in large airway diseases. Primary bronchiolar disorders include constrictive bronchiolitis (obliterative bronchiolitis, bronchiolitis obliterans), acute bronchiolitis, diffuse panbronchiolitis, respiratory bronchiolitis, mineral dust airway disease, follicular bronchiolitis, and a few other rare variants. Prominent bronchiolar involvement may be seen in several interstitial lung diseases, including hypersensitivity pneumonitis, respiratory bronchiolitis–associated interstitial lung disease, cryptogenic organizing pneumonia (idiopathic bronchiolitis obliterans organizing pneumonia), and pulmonary Langerhans' cell histiocytosis. Large airway diseases that commonly involve bronchioles include bronchiectasis, asthma, and chronic obstructive pulmonary disease. The clinical relevance of a bronchiolar lesion is best determined by identifying the underlying histopathologic pattern and assessing the correlative clinico–physiologic–radiologic context.

Keywords: bronchiolitis; bronchiolitis obliterans; organizing pneumonia

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Bronchiolar abnormalities are relatively common and occur in a variety of clinical settings, including infections, connective tissue diseases and other immunologic disorders, inhalational injuries, drug reactions, allograft transplantations, and many others. Some histopathologic patterns of bronchiolar disease may be relatively unique to a specific clinical context, such as respiratory bronchiolitis caused by cigarette smoking. More often, however, the microscopic features of airway injury are nonspecific with respect to either etiology or pathogenesis (1, 2).

A confusing array of terms has been used in referring to bronchiolar disorders. Some of these descriptive terms are synonymous, whereas others overlap in their intended meaning. For example, the term "bronchiolitis obliterans" has been applied to two distinct histopathologic patterns of bronchiolar fibrosis as well as various clinical syndromes ranging from progressive airflow obstruction (i.e., constrictive or obliterative bronchiolitis) to a predominantly infiltrative process associated with restricted lung volumes (i.e., bronchiolitis obliterans organizing pneumonia [BOOP] or cryptogenic organizing pneumonia) (3–5). In addition, it should be noted that bronchiolar abnormalities may at times represent a component of a pathologic process primarily affecting more distal lung parenchyma (e.g., bronchopneumonia and chronic eosinophilic pneumonia) or larger, proximal airways (e.g., bronchiectasis) (1, 6, 7).

No single classification scheme for bronchiolar diseases has been widely accepted. Attempts have been made to classify bronchiolar disorders from different viewpoints including those of the clinician, pathologist, and radiologist (1, 2, 4–7). Most commonly, classification is performed according to histopathologic patterns or etiology (2, 7). Over 10 years ago in this journal, Wright and colleagues (7) provided an authoritative review on "Diseases of the Small Airways" that included small airways disease caused by cigarette smoke and mineral dusts, transplant bronchiolitis, bronchiolitis obliterans, and BOOP. After this publication, there have been a number of publications suggesting that the spectrum of bronchiolar disorders may be more heterogenous than previously recognized. In addition, we have come to appreciate bronchiolar involvement occurring in large airway diseases and interstitial lung diseases.

The purpose of this review is to provide a framework to better conceptualize the spectrum of primary bronchiolar diseases, diverse clinical settings in which they occur, and their potential significance in these varying clinical contexts. We define primary bronchiolar disorders as those diseases in which an isolated pathologic process is limited to bronchioles anatomically. Primary bronchiolar disorders are separated from diseases primarily affecting more distal components of the pulmonary acinus and large airway diseases in which prominent secondary bronchiolar changes may be seen (Table 1). Most of the primary

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bronchiolar disorders and large airway diseases are associated with obstructive physiologic defects. In contrast, most of the distal acinar interstitial diseases with secondary bronchiolar involvement cause restrictive lung disease, although superimposed obstructive features may also be seen. In some cases, interstitial lung disease such as pulmonary Langerhans' cell histiocytosis can present with a purely obstructive physiologic defect (8). Thus, the pattern of pulmonary function abnormality may not always distinguish primary bronchiolar disease from a predominantly parenchymal process. Under such circumstances, radiologic features demonstrated by high-resolution computed tomography (HRCT) scanning can help distinguish primary bronchiolar disorders from bronchiolar involvement occurring in interstitial lung diseases and large airway diseases. This correlative construct helps us organize the wide array of histologic, physiologic, clinical, and radiologic features that have been used to describe various bronchiolar disorders. Ultimately, the evaluation of a patient with suspected bronchiolar disease attempts to identify the underlying histopathologic pattern of bronchiolar injury in an effort to understand its cause and likely natural history.

GENERAL FEATURES OF BRONCHIOLAR DISORDERS

Bronchioles are small airways (internal diameter of 2 mm or less) that do not contain cartilage in their walls (1). These airways consist of membranous and terminal bronchioles that are purely air conducting and respiratory bronchioles containing alveoli in their walls (6, 7, 9). Respiratory bronchioles communicate directly with alveolar ducts and are in the range of 0.5 mm or less in diameter (1). The acinus or primary pulmonary lobule (the basic unit of gas exchange) consists of one terminal bronchiole, two to five generations of respiratory bronchioles, alveolar ducts, alveolar sacs, and alveoli (1, 6). Bronchioles contribute little to airway resistance in normal lungs because the total cross-sectional area of the small airways is much greater than the total cross-sectional area of the central airways (10, 11). In disease states, however, abnormalities at the level of small airways contribute disproportionately to increased airway resistance (10, 11).

Bronchiolitis, a generic term applied to various inflammatory diseases affecting the bronchioles, is the most common form of disease affecting small airways (1, 2). Bronchiolitis is a common lesion but is rarely extensive enough to cause clinical symptoms. Several patterns of primary bronchiolitis have been delineated, including constrictive bronchiolitis (also called obliterative bronchiolitis or bronchiolitis obliterans), acute bronchiolitis, diffuse panbronchiolitis, respiratory bronchiolitis, mineral dust airway disease, and follicular bronchiolitis (Table 1). Only the first three are typically associated with evidence of airflow limitation.

Radiologic imaging of the chest, especially HRCT, is a very useful tool in the diagnostic evaluation of a patient with suspected small airways disease (12–15). Chest radiography demonstrates normal findings or mainly hyperinflation in purely obstructive bronchiolar lesions such as constrictive bronchiolitis (13–15). In other primary bronchiolar disorders, small nodules or reticulonodular infiltrates may be observed (13–15). In distal acinar interstitial diseases with secondary bronchiolar involvement, chest radiography usually demonstrates features of the underlying parenchymal disease process such as cryptogenic organizing pneumonia or hypersensitivity pneumonitis.

Most HRCT protocols use thin (0.63–1.25 mm) collimation (at intervals or continuously) from apices to costophrenic angles in the supine position with image reconstruction using an edge-enhancement algorithm (12, 13). Prone imaging is performed when needed to distinguish gravity-dependent atelectasis from early infiltrative lung disease. HRCT at full expiration should routinely be performed when airway disease is suspected or documented clinically. Because visibility on CT is limited to airways more than 2 mm in diameter, normal bronchioles cannot be seen on CT scans (13, 15). However, diseased bronchioles with dilated lumen ($>$ 2 mm in diameter) or thickened walls can be visualized (14, 15). Aside from demonstrating evidence of bronchiolar disease, HRCT of the chest helps identify those cases in which an interstitial lung disease or large airway disease may be the predominant underlying process.

Features of bronchiolar disease on HRCT can be broadly categorized into direct and indirect signs (12–15). Direct CT findings of bronchiolar disease include bronchiolar wall thickening, bronchiolar dilatation (bronchiolectasis), and luminal impaction that render affected airways directly visible in the lung periphery (14, 15). Bronchiolar wall thickening may occur due to inflammation or fibrosis. Bronchiolar luminal impaction with secretions or fibrotic material manifests as 2 to 4 mm nodular and linear branching centrilobular opacities on CT (Figure 1). The "tree-in-bud" pattern represents a form of bronchiolar impaction in which branching linear structures have more than one contiguous branching site (15). Indirect signs of bronchiolar disease on CT include subsegmental atelectasis and air trapping (13–15). Air trapping due to small airway disease often results in a "mosaic pattern" of lung attenuation (multilobular, geographic density differences of the lung parenchyma), which, however, is not specific for bronchiolar diseases (14). In bronchiolar diseases, the mosaic pattern is caused by hypoventilation of alveoli distal to bronchiolar obstruction (cicatricial scarring of many bronchioles), which leads to secondary vasoconstriction (consequently, underperfused lung) and is seen on CT scans as areas of decreased attenuation. Uninvolved segments of lung show normal or increased perfusion with resulting normal or increased attenuation,

TABLE 1. CLASSIFICATION OF BRONCHIOLAR DISORDERS

Primary bronchiolar disorders
Constrictive bronchiolitis (obliterative bronchiolitis, bronchiolitis obliterans)
Acute bronchiolitis
Diffuse panbronchiolitis
Respiratory bronchiolitis (smoker's bronchiolitis)
Mineral dust airway disease
Follicular bronchiolitis
Other primary bronchiolar disorders (e.g., diffuse aspiration bronchiolitis, lymphocytic bronchiolitis)
Interstitial lung diseases with a prominent bronchiolar involvement
Hypersensitivity pneumonitis
Respiratory bronchiolitis–associated interstitial lung disease/desquamative interstitial pneumonia
Cryptogenic organizing pneumonia (idiopathic bronchiolitis obliterans organizing pneumonia or proliferative bronchiolitis)
Other interstitial lung diseases (pulmonary Langerhans' cell histiocytosis, sarcoidosis, bronchiolocentric interstitial pneumonia)
Bronchiolar involvement in large airway diseases (chronic bronchitis, bronchiectasis, asthma)

respectively. Paired CT scans performed in inspiration and expiration are useful for distinguishing bronchiolar disease from pulmonary vascular disease and some diffuse infiltrative diseases that may also cause a mosaic pattern. In bronchiolar disease, the lucent regions of lung seen at inspiration remain lucent at expiration due to air trapping and show little increase in lung attenuation or decrease in volume as seen for primary vascular lung disease.

PRIMARY BRONCHIOLAR DISORDERS

Certain forms of bronchiolitis are histologically distinctive. Some of these histologically defined patterns of bronchiolitis can occur in very disparate clinical settings. For example, constrictive bronchiolitis may be seen in patients with connective tissue diseases, transplant recipients, as well as in an idiopathic form (cryptogenic constrictive bronchiolitis). Other forms of bronchiolitis, including diffuse panbronchiolitis, respiratory bronchiolitis, mineral dust bronchiolitis, and follicular bronchiolitis, are more limited in terms of potential etiologies and associations.

A subset of primary bronchiolar disorders is associated with airflow obstruction. Constrictive bronchiolitis is the prototype of an obstructive bronchiolar process resulting in airflow obstruction that can occur in various clinical settings.

Constrictive Bronchiolitis (Obliterative Bronchiolitis, Bronchiolitis Obliterans)

Lange's original description of "bronchiolitis obliterans" in 1901 (16) was that of two patients with what would now be termed "cryptogenic organizing pneumonia." In 1973 Gosink and colleagues (17) applied the term "bronchiolitis obliterans" to a heterogeneous group of patients some of whom had submucosal and peribronchiolar fibrosis resulting in extrinsic narrowing and obliteration of bronchiolar lumens referred to as constrictive bronchiolitis. Most of the patients described by these authors likely had cryptogenic organizing pneumonia. In the years since these reports, the term "bronchiolitis obliterans" has been used for a variety of unrelated clinicopathologic conditions.

Pathologically, constrictive bronchiolitis is characterized by a distinctive pattern of peribronchiolar fibrosis ultimately resulting in complete cicatrization of the bronchiolar lumen (1, 2, 16, 18). The fibrosing inflammatory process surrounds rather than fills the lumen, resulting in extrinsic compression and obliteration of the airway (Figure 2). Areas of fibrosis are patchy and subtle, even in severely affected patients, and thus the diagnosis can be missed if lesions are inadequately sampled (16, 19, 20). Transbronchial lung biopsy is a relatively insensitive diagnostic tool, and for those patients in whom histologic confirmation is required, a surgical lung biopsy is necessary (1, 2, 7).

Known causes and associations with constrictive bronchiolitis include connective tissue disorders (most common), infections (7, 21, 22), inhalational injury (7, 18), chronic hypersensitivity pneumonitis (18), drugs (23, 24), organ transplantation (25), and many others (Table 2). Evidence underlying some of these associations is relatively tenuous and consists of case reports or small case series. Rheumatoid arthritis–associated constrictive bronchiolitis occurs principally in women in their fifth to sixth decades of life (26–29). Most have had long-standing rheumatoid arthritis, although in rare cases pulmonary abnormalities antedate rheumatologic manifestations. Although earlier reports of constrictive bronchiolitis in rheumatoid arthritis were marked by a rapidly progressive course that was often fatal, more recently, it has become clear that there is considerable heterogeneity in the rapidity of progression, with a number of patients deteriorating slowly (30). Minor degrees of constrictive bronchiolitis are probably present and subclinical in many patients with rheumatoid arthritis (30). Penicillamine therapy has been implicated as a potential etiologic factor in some of these patients (27).

Constrictive bronchiolitis with airflow obstruction has been known to complicate a variety of pulmonary infections and inhalational injury (7, 21, 22). Viral infections, particularly adenovirus,

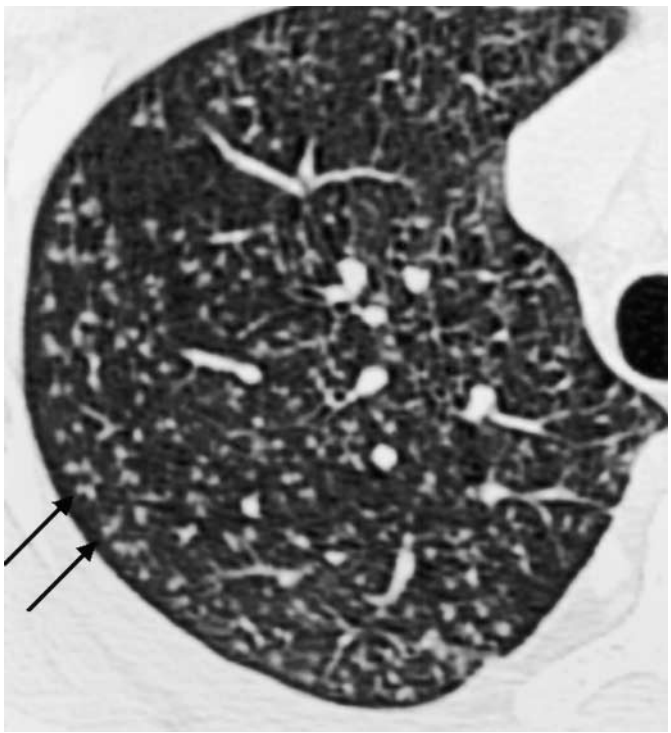

Figure 1. Bronchiolar disease. High-resolution computed tomography (HRCT) shows characteristic findings of chronic bronchiolitis in this case due to silo filler's disease. Note well-circumscribed centrilobular nodules and branched opacities that have the characteristic "tree-in-bud" appearance (*arrows*).

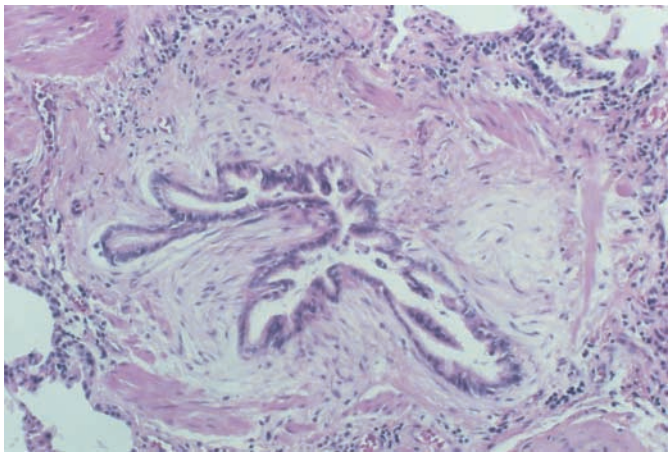

Figure 2. Constrictive bronchiolitis. Intermediate-magnification photomicrograph illustrating constrictive (obliterative) bronchiolitis in a patient with underlying rheumatoid arthritis. Fibroblast proliferation and stromal edema with associated collagen deposition thicken the submucosa resulting in constriction of the airway lumen.

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TABLE 2. CAUSES AND UNDERLYING DISORDERS ASSOCIATED WITH CONSTRICTIVE BRONCHIOLITIS

Cryptogenic constrictive bronchiolitis (20)
Postinfectious including most commonly viruses (7, 21, 22) (adenovirus, respiratory syncytial virus, influenza, parainfluenza, etc.) and mycoplasma (21)
Connective tissue diseases (26–30) (rheumatoid arthritis and eosinophilic fasciitis)
Inhalational injury (7, 18, 32, 47) (nitrogen dioxide, sulfur dioxide, ammonia, chlorine, phosgene, hot gases, fly ash)
Ingested toxins (48) (e.g., *Sauropus androgynus*)
Allograft recipients (25, 33–39) (heart–lung or lung transplant, bone marrow transplant)
Drugs (23, 24) (penicillamine, lomustine, cocaine, gold, penicillamine, etc.)
Other associations—inflammatory bowel diseases (45, 46), neuroendocrine cell hyperplasia and multiple carcinoid tumorlets (40–43), and paraneoplastic pemphigus (44)

have been most frequently implicated (7, 21, 22). One of the long-term complications of postinfectious constrictive bronchiolitis occurring in childhood is the development of the Swyer–James (or MacLeod's) syndrome, that is, unilateral hyperlucent lung with evidence of air trapping and decreased vascularity (6, 21, 31). Constrictive bronchiolitis after noxious inhalational injury, e.g., ammonia, presents as cough and progressive dyspnea beginning days to weeks after recovery from acute exposure (32).

Patients with allogeneic or autologous bone marrow transplantation, heart–lung transplantation, or lung transplantation may develop constrictive bronchiolitis as a chronic rejection phenomenon (7, 25, 33–39). This problem is a major threat to long-term survival in these transplant recipients and may affect up to 65% of patients at 5 years after lung transplantation (33). Constrictive bronchiolitis is the primary cause of late death after lung transplantation (25, 33). Confirming the diagnosis of constrictive bronchiolitis in transplant recipients by transbronchial lung biopsies is problematic because of the patchy distribution of lesions and difficulties in obtaining adequate samples of bronchioles (25, 33). Thus, the phenomenon of progressive airway obstruction in transplant recipients is termed "bronchiolitis obliterans syndrome," a clinical diagnosis, and is defined physiologically by a decrement in FEV_1 of 20% or more below a stable baseline (25, 36).

Other causes and associations with constrictive bronchiolitis have included neuroendocrine cell hyperplasia or multiple carcinoid tumorlets (40–43), paraneoplastic pemphigus (44), inflammatory bowel disease (45, 46), exposure to incinerator fly ash (47), *Sauropus androgynus* ingestion (48), gold therapy (23), and penicillamine therapy (24).

It is likely that pathogenetic mechanisms vary according to the cause or underlying disease associated with constrictive bronchiolitis. However, various forms of insults can eventually lead to a similar histopathologic lesion. For example, in bronchiolitis obliterans syndrome associated with lung transplantation, alloreactivity directed toward human leukocyte antigens, airway ischemia, viral infections, and airway inflammation are major factors that lead to accumulation of profibrotic cytokines and the development of bronchiolar fibrosis (33, 49, 50). Constrictive bronchiolitis occurring in patients with paraneoplastic pemphigus, however, involves deposition of IgG autoantibodies on the surface of bronchial epithelial cells and acantholytic changes (44). There are likely multiple mechanisms through which the lesion of constrictive bronchiolitis takes form.

When constrictive bronchiolitis occurs with no identifiable cause, it is referred to as cryptogenic constrictive bronchiolitis (20). It is rare and occurs mostly in women (20). Patients with constrictive bronchiolitis present with persistent cough and worsening dyspnea. Basilar inspiratory crackles may be heard on auscultation of the lungs in some patients (20). Progressive airway obstruction, often associated with air trapping, is seen by pulmonary function testing in the majority of affected patients (1, 2, 7, 20). Diffusing capacity is commonly reduced, and there is no significant response to bronchodilators during pulmonary function testing (1, 2, 7, 20, 29).

Chest radiography in patients with constrictive bronchiolitis demonstrates normal findings or nonspecific abnormalities including variable degrees of hyperinflation, peripheral attenuation of the vascular markings, and, sometimes, nodular or reticulonodular opacities (6, 12–16, 19, 20). If serial radiographs are available, progressive increase in lung volumes may be appreciated. Bronchial wall thickening and bronchiectasis may occasionally be seen.

HRCT demonstrates mosaic (multilobular) areas of decreased attenuation and vascularity, evidence of air-trapping (accentuated on expiratory views), and peripheral cylindric bronchiectasis (Figure 3) (12–15, 18). Marked heterogeneity of lung density (mosaic attenuation) may be seen due to decreased perfusion of areas with bronchiolar obstruction and blood flow redistribution to normal areas (51). Although these HRCT findings are not specific for constrictive bronchiolitis, this constellation of features can be diagnostic in the appropriate clinical setting. Radiologic finding of mosaic pattern of lung attenuation can be due to pulmonary vascular disease and diffuse parenchy-

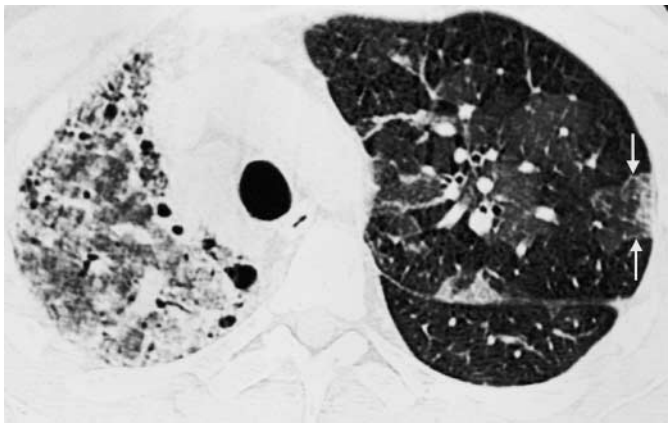

Figure 3. Constrictive bronchiolitis. HRCT of constrictive bronchiolitis in a lung transplant patient. Note native right lung with findings characteristic of usual interstitial pneumonia, including peripheral honeycombing and reticulation with restriction of right lung size due to fibrotic changes. Image of transplanted left lung shows mosaic pattern of lung attenuation due to constrictive bronchiolitis. Note lobular and multilobular regions of increased lung attenuation (*arrows*); this is normal lung that is appropriately ventilated and slightly hyperperfused. The multilobular regions of lower attenuation lung are oligemic and hypoventilated with air trapping secondary to constrictive bronchiolitis. Findings of bronchiectasis are common in this condition but are not demonstrated on this image.

mal disease as well as small airway disease. Expiratory HRCT imaging and contrast enhancement of vasculature can distinguish these differential diagnostic possibilities (52). Additional features may be seen on HRCT of constrictive bronchiolitis depending on the underlying cause.

In most clinical settings, constrictive bronchiolitis tends to be progressive and is poorly responsive to corticosteroid therapy (1, 2, 7, 29, 53). Progressive airflow limitation may result in respiratory failure and death. Management of posttransplant constrictive bronchiolitis involves augmentation of immunosuppression that is often ineffective, thus requiring consideration of retransplantation in some patients (33, 34). Use of statin medications has been associated with a reduced incidence of bronchiolitis obliterans syndrome after lung transplantation (54).

Acute Bronchiolitis

Acute bronchiolitis is a term most often used to describe an illness in infants and children characterized by acute wheezing with concomitant signs of respiratory viral infection (55, 56). Acute bronchiolitis is the most common disease of the respiratory tract during the first year of life and occurs in annual epidemics during winter. Respiratory syncytial virus is the etiologic agent in the majority of patients, but other viruses (adenovirus, influenza, parainfluenza) and nonviral pathogens (mycoplasma, chlamydia) can cause a similar syndrome (22, 55–58). Respiratory syncytial virus is estimated to be responsible for 125,000 hospital admissions per year in the United States, and approximately 1% of infants with lower respiratory tract infections require hospitalization (57). Eighty percent of these hospitalizations occur in infants less than 1 year of age, with peak incidence at 2 to 8 months of age. Other pathogens including fungal and mycobacterial infections also may cause infectious bronchiolitis (14).

Symptomatic acute bronchiolitis in adults is relatively rare but can be caused by infectious agents such as respiratory syncytial virus. Because small airways in adults contribute less to total pulmonary resistance, acute infectious bronchiolitis may spare adults the severe symptoms characteristic of bronchiolitis in infants. Acute bronchiolitis in adults may also be seen with aspiration, toxic inhalation, connective tissue diseases, lung and bone marrow transplantation, and Stevens–Johnson syndrome (58).

Pathologic studies of acute infectious bronchiolitis have shown intense acute and chronic inflammation of small bronchioles with associated epithelial necrosis and sloughing (Figure 4).

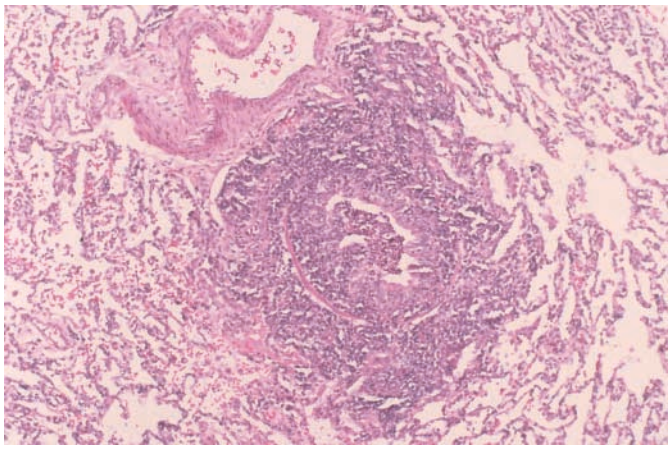

Figure 4. Acute bronchiolitis. Low-magnification photomicrograph illustrating acute bronchiolitis in a patient with underlying ulcerative colitis. A dense peribronchiolar infiltrate of acute and chronic inflammatory cells is associated with an intraluminal exudate rich in neutrophils.

There may be associated edema as well as inflammatory exudate and mucus in the bronchiolar lumen (54).

In respiratory syncytial virus bronchiolitis, respiratory epithelial cells respond to viral infection by producing several chemokines including macrophage inflammatory protein-1-α, interleukin (IL)-8, IL-6, IL-1β, and RANTES (regulated upon activation, normal T cell expressed and secreted) (59, 60). These cytokines recruit and activate neutrophils, lymphocytes, macrophages, eosinophils, and natural killer cells at the site of infection (59, 60). In addition, chemokine receptor CXCR2 may contribute to mucus production and airway hyperreactivity associated with respiratory syncytial virus bronchiolitis (61).

The major clinical findings in acute bronchiolitis include tachypnea, tachycardia, and prolonged expiration (55, 58). Wheezing and crackles are usually present and may be accompanied by nasal flaring and chest retractions in infants (55, 58). Pulmonary function testing demonstrates findings of airway obstruction (62).

The radiologic pattern of acute bronchiolitis is variable. Chest radiography typically demonstrates only hyperinflation (54, 63). Tiny nodules, linear opacities, patchy ground-glass opacities or consolidation and collapse (atelectasis) may sometimes be seen (55, 63). HRCT in acute infectious bronchiolitis demonstrates small, ill-defined centrilobular nodules representing bronchioles impacted with inflammatory material and peribronchiolar inflammation, branching linear opacities corresponding to inflamed airway walls, and focal areas of consolidation due to bronchopneumonia. (14, 55, 63).

Most patients with acute bronchiolitis can be managed at home with supportive care because respiratory symptoms are generally mild. When the illness is more severe, hospitalization, supplemental oxygen, antiviral agents, corticosteroid therapy, and bronchodilators will need to be considered (57, 62).

Overall, the mortality rate of acute bronchiolitis is less than 1% (57, 62). In a small subset of patients, healing of acute bronchiolitis can lead to fibrous obliteration of small airways resulting in chronic airflow limitation, i.e., constrictive bronchiolitis (57, 62). This phenomenon is seen most often after adenovirus infection but also after measles, pertussis, mycoplasma, influenza A, and other infections (22). In some of these cases, unilateral hyperlucent lung and/or a combination of geographic hyperlucency, central bronchiectasis, and vascular attenuation may be seen (Swyer–James syndrome) (57, 62).

Diffuse Panbronchiolitis

Diffuse panbronchiolitis is a rare form of bronchiolitis identified mainly in Asia, particularly in Japanese adults, and is characterized by bronchiolar inflammation and chronic sinusitis (64–66). Few cases occurring in non-Asian patients have been described in the United States (66–68). The cause is unknown, but an association with human leukocyte antigen Bw54 antigen has been reported in Japanese patients (64). Pathogenesis is not well understood, but the racial tendency of this disease suggests genetic predisposition. Neutrophils and T-lymphocytes, particularly $CD8^+$ cells, together with cytokines IL-8 and macrophage inflammatory protein-1-α are believed to play key roles in the development of this disease (64, 69). Accumulation of activated neutrophils in the airways appears to be an important mechanism of injury in this disease (66).

Histopathologic findings in diffuse panbronchiolitis are characteristic and consist of bronchiolocentric infiltration of lymphocytes, plasma cells, and foamy macrophages at the level of the respiratory bronchioles (Figure 5) (1, 67, 70). Intraluminal neutrophils can be prominent. Organization of intraluminal exudates may form polypoid plugs. In addition, marked increase in the number of dendritic cells has been found in both the bronchiolar epithelium and submucosal tissues of patients with diffuse

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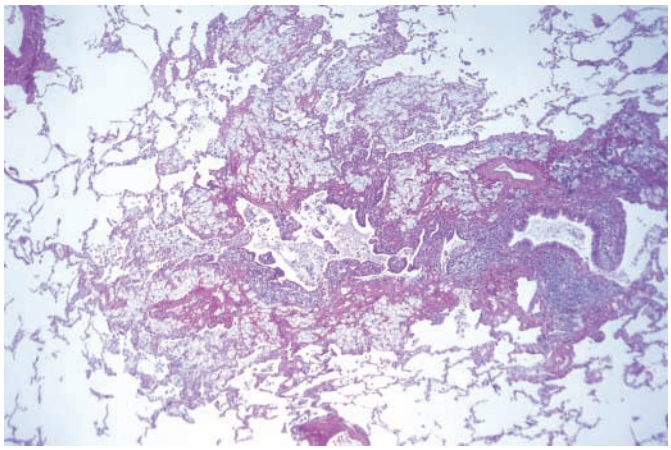

Figure 5. Diffuse panbronchiolitis. Low-magnification photomicrograph demonstrating the "index lesion" of diffuse panbronchiolitis. A dense peribronchiolar infiltrate of mainly mononuclear cells is associated with a striking infiltrate of finely vacuolated histiocytes. Vacuolated, lipid-laden histiocytes extend and expand contiguous peribronchiolar alveolar septa.

panbronchiolitis (71). Although this pattern of bronchiolitis is characteristic of diffuse panbronchiolitis, nearly identical changes have been described in a broad range of airway-centered disease processes including bronchiectasis and rheumatoid arthritis–related bronchiolitis (70, 72).

Patients present with subacute onset of cough productive of purulent sputum, dyspnea, and evidence of airflow obstruction. The majority of patients also complain of chronic sinusitis, suggesting that there may be an underlying abnormality of ciliary function (64). Chest examination may reveal decreased breath sounds with coarse crackles or wheezing present (67). Digital clubbing is unusual (67).

The most characteristic laboratory feature associated with diffuse panbronchiolitis is the persistent elevation of cold agglutinins, but tests for *Mycoplasma pneumoniae* are negative (64). Elevated leukocyte count and erythrocyte sedimentation rate are common (67). In the early stages of the disease, the sputum generally contains normal flora or *Hemophilus influenzae*. Colonization with *Pseudomonas aeruginosa* eventually occurs, which appears to accelerate the destructive process (67).

Pulmonary function testing generally demonstrates marked obstructive impairment (64). In some patients, a superimposed mild to moderate restriction may also be seen (65, 67).

On chest radiography, diffuse panbronchiolitis is characterized by diffuse small (up to 5 mm in diameter), ill-defined nodular opacities most prominent over the lung bases and symmetrically distributed. Mild to moderate hyperinflation may be seen. In late stages, the radiographic features of cylindric bronchiectasis may become evident (64, 65, 67).

Findings on HRCT depend on the stage of the disease and include centrilobular nodules, thickened and ectatic bronchioles, and peripheral air trapping (Figure 6) (64, 65, 67). Centrilobular nodules are poorly defined and measure less than 5 mm in diameter; some of these nodules are connected to distal branching structures that represent secretion-filled bronchioles (tree-in-bud appearance). In later stages, cystic dilatation of the nodules that corresponds to bronchiolectasis is seen (13).

The natural history of diffuse panbronchiolitis is characterized by progressive respiratory dysfunction with episodic bacterial superinfection, often with *P. aeruginosa* (64, 67). In advanced

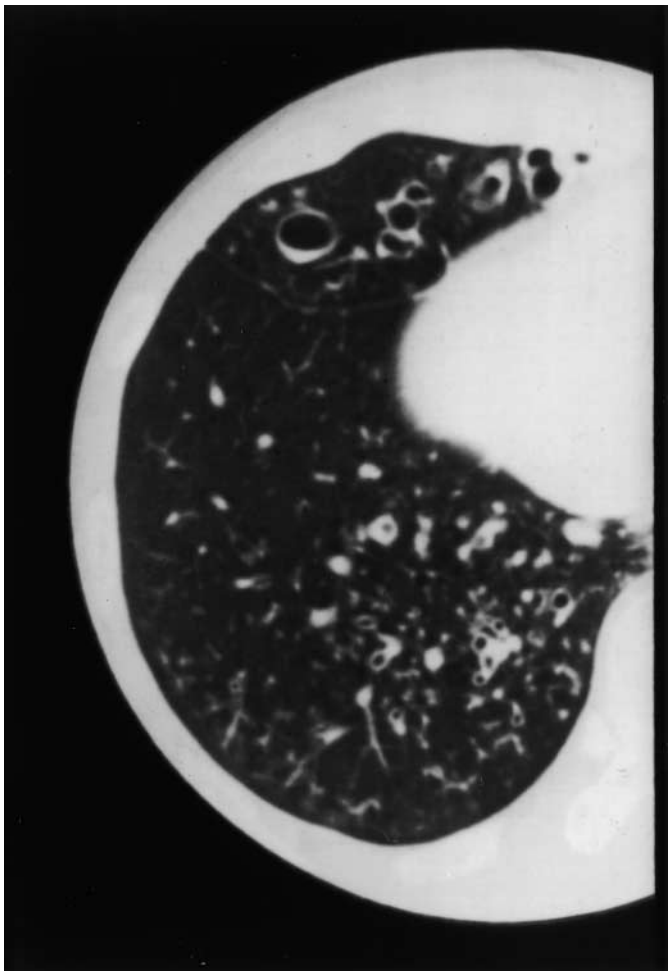

Figure 6. Diffuse panbronchiolitis. HRCT shows findings of bronchiolitis including centrilobular nodularity and branched tubular opacities with a "tree-in-bud" appearance. There are also several regions of bronchiectasis characteristic of this condition. (Courtesy of Dr. Koichi Nishimura, Department of Respiratory Medicine, Kyoto Katsura Hospital, Kyoto, and Dr. Harumi Itoh, Department of Radiology, Fukui Medical School, Fukui, Japan.)

disease, patients succumb to chronic respiratory failure and cor pulmonale leading to death. Low-dose erythromycin therapy, 400 to 600 mg per day, is the preferred therapy and has shown some efficacy (64, 65, 66, 73, 74). Therapeutic efficacy of macrolides in the treatment of patients with diffuse panbronchiolitis may be based on the ability of these antibiotics to impair the production of proinflammatory cytokines, including IL-1β and IL-8, rather than their antibacterial properties (66, 74–76). Decreased levels of chemokines reduce neutrophil influx and associated inflammatory mediators in the airways (66). Macrolide therapy has also been demonstrated to inhibit mucus and water secretion from airway epithelial cells (66). Lung transplantation has been used in some patients, and diffuse panbronchiolitis has recurred in the allograft of one patient (77).

Respiratory Bronchiolitis

Exposure to cigarette smoke results in various alterations of bronchioles ranging from potentially reversible inflammatory reactions to fixed scarring (11, 78). Respiratory bronchiolitis is a specific form of smoking-related small airways disease and was first described by Niewoehner and colleagues (79) as an

incidental finding at autopsy in young cigarette smokers. Respiratory bronchiolitis has been rarely reported in nonsmokers with other inhalational exposures, especially asbestos and nonasbestos dusts as well as various fumes (7, 80).

The most distinctive feature of respiratory bronchiolitis is the prominent accumulation of pigmented macrophages in the lumen of respiratory bronchioles and adjacent alveoli (Figure 7) (1). Respiratory bronchiolitis usually occurs without symptoms or physiologic evidence of lung disease. In some patients, however, respiratory bronchiolitis can cause symptomatic diffuse parenchymal lung infiltrates, a syndrome referred to as respiratory bronchiolitis–associated interstitial lung disease (RB-ILD) as discussed later (1, 80–83).

Chest radiographs are usually normal, with no clear evidence of lung infiltrates or apparent airway abnormalities (84). On HRCT, respiratory bronchiolitis correlates with centrilobular micronodules (Figure 8) (85, 86).

Respiratory bronchiolitis is suspected when HRCT of the chest demonstrates parenchymal micronodules in a smoker who undergoes CT of the chest, usually for an unrelated indication. Many such patients are asymptomatic with the exception of a "smoker's cough" and do not need any specific treatment other than smoking cessation. The term RB-ILD is reserved for those patients who have additional findings of interstitial lung disease (*see below*).

Mineral Dust Airway Disease

Mineral dust exposure is classically associated with restrictive lung disease due to parenchymal fibrosis (pneumoconiosis) (7). However, mineral dusts can also produce abnormalities in the small airways and airflow obstruction (87). Mineral dust airway disease refers to deposition of inhaled dust around small airways, with some associated fibrosis (1, 7, 87). This condition primarily affects respiratory bronchioles and sometimes alveolar ducts with increased fibrous tissue in the walls of the bronchioles with luminal narrowing (Figure 9) (1, 7, 87, 88). There is usually a chronic inflammatory response. The morphologic features are distinguishable from respiratory bronchiolitis induced by tobacco smoke. This form of bronchiolar disease may occur with inhalation of a number of inorganic dusts, including asbestos, iron oxide, aluminum oxide, talc, mica, silica, silicate, and coal (88). The degree of fibrosis in the bronchiolar wall appears to be closely linked to local dust burden (7, 87).

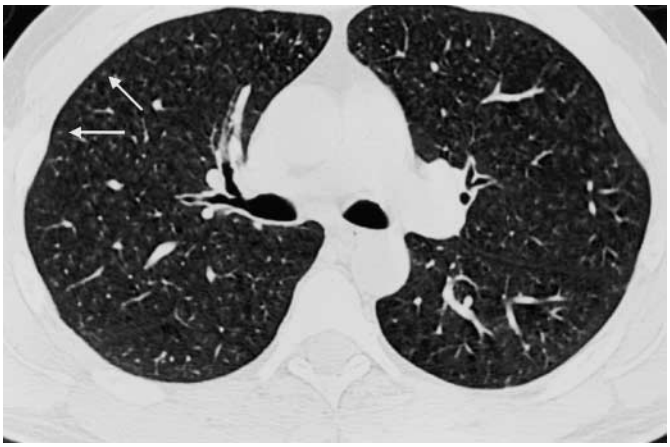

Figure 8. Respiratory bronchiolitis. HRCT shows diffuse, poorly circumscribed centrilobular nodular opacities (*arrows*). In acute respiratory bronchiolitis the nodular opacities tend to be more poorly circumscribed than in chronic bronchiolitis where the centrilobular nodular opacities and branched tubular opacities tend to be better circumscribed.

This bronchiolar lesion appears to be a specific marker of mineral dust exposure (87). Little information is available regarding the pathogenesis of mineral dust airway disease. It has been suggested that the two factors at play include local dust accumulation and the inflammatory response to the dust (88). Among those subjects exposed to mineral dusts, susceptibility to this bronchiolar lesion may be determined by individual ability to clear these particles from the airways (88). Inflammatory response induced by the dust likely lead to local production of fibrogenic factors and morphogenesis of this lesion (88).

Mineral dust bronchiolitis may be associated with an obstructive defect, although cigarette smoking and the presence of associated emphysema have confounded interpretation of some studies in this regard (1, 5, 7, 87, 88). Chest radiography and HRCT may demonstrate tiny ill-defined punctate opacities (89, 90). There is

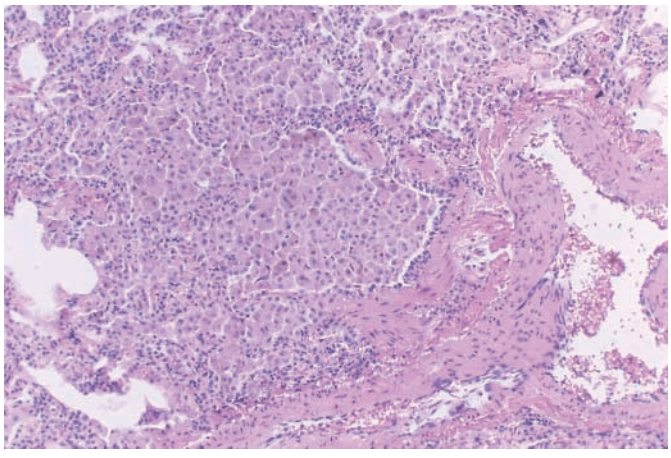

Figure 7. Respiratory bronchiolitis. Intermediate-magnification photomicrograph showing respiratory bronchiolitis in a heavy cigarette smoker. Lightly pigmented histiocytes fill the distal lumen and spill into adjacent peribronchiolar air spaces.

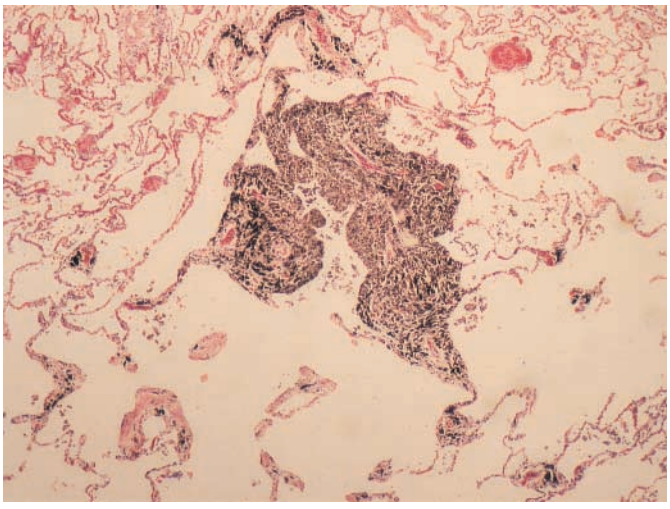

Figure 9. Low-magnification photomicrograph demonstrating mineral dust–associated small airways disease in a hard rock miner. Peribronchiolar interstitium is expanded by dust-laden macrophages and extracellular dust deposits with mild fibrosis. (Photomicrograph courtesy of Andrew Churg, M.D., Ph.D., University of British Columbia, Vancouver, Canada.)

little else known regarding the clinical and radiologic correlates of this bronchiolar disorder.

Follicular Bronchiolitis

Follicular bronchiolitis is defined by the presence of hyperplastic lymphoid follicles with reactive germinal centers distributed along bronchovascular bundles (Figure 10) (91–93). Grossly, lungs show peribronchial nodules, 1 to 2 mm in diameter. This form of pulmonary lymphoid hyperplasia is a common secondary finding in patients with bronchiectasis affecting proximal large airways. In others, however, follicular bronchiolitis is a manifestation of primary pulmonary lymphoid hyperplasia. In patients with primary lymphoid hyperplasia, peribronchiolar lymphocytic infiltration into the interstitium often accompanies the peribronchiolar lymphoid aggregates and overlaps with lymphoid interstitial pneumonia (93).

Follicular bronchiolitis can be idiopathic or occur in association with connective tissue diseases (particularly rheumatoid arthritis), immunodeficiency syndromes including AIDS, pulmonary infections, or ill-defined hypersensitivity reactions (91, 94, 95). Follicular bronchiolitis represents lymphoid hyperplasia in response to an extrinsic immune stimulus or altered systemic immune response as seen in patients with rheumatoid arthritis (96).

Patients usually present with progressive dyspnea (13, 97). Variable pulmonary function abnormalities have been reported, including obstructive, restrictive, and mixed patterns (98–100). The predominant finding on chest radiography is bilateral, small nodular, or reticulonodular infiltrates with intrathoracic adenopathy (13). Chest radiographs may sometimes look normal (13). The cardinal features of follicular bronchiolitis on HRCT consist of centrilobular nodules measuring 1 to 12 mm in diameter, variably associated with peribronchial nodules and patchy areas of ground-glass opacity (93). Nodules and ground-glass opacities are generally bilateral and diffuse in distribution. Mild bronchial dilatation with wall thickening is seen in some cases. Mosaic perfusion, pleural effusions, or areas of honeycombing are not seen (93).

Prognostic implication of follicular bronchiolitis is unclear. Treatment is generally directed to the underlying disease when such association is recognized. Those patients with no identifiable underlying cause have generally been treated with bronchodilators and corticosteroids. More recently, erythromycin therapy has been reported to be of benefit (94).

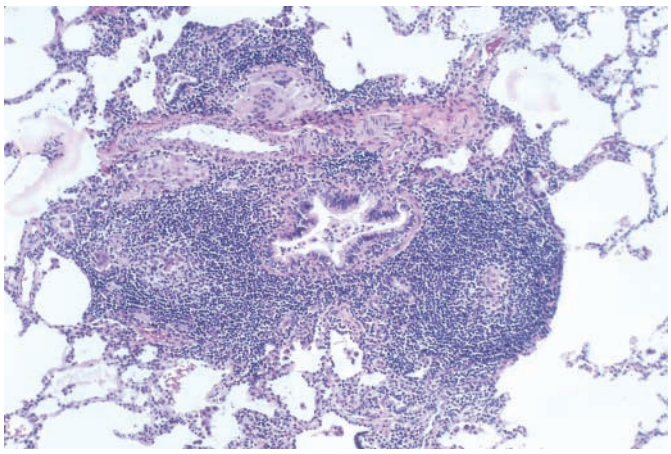

Figure 10. Follicular bronchiolitis. Intermediate-magnification photomicrograph showing follicular bronchiolitis characterized by prominent peribronchiolar lymphoid aggregates with secondary germinal centers.

Other Forms of Primary Bronchiolitis

There are few other entities that deserve mention in this section but do not easily fit into the primary bronchiolar disorders already discussed. Diffuse aspiration bronchiolitis is a term recently proposed to define a clinical entity characterized by chronic inflammation of bronchioles caused by recurrent aspiration of foreign particles (101). Most of these patients are elderly and bedridden.

A distinctive pattern of lymphocytic bronchiolitis and peribronchiolitis with lymphoid hyperplasia has been observed in the lung biopsies of nylon flocking industry workers (102). This reaction pattern appears to represent a chronic immunologic response to the inhaled material. Flocking is a widely used industrial process in which short lengths of synthetic fibers are applied to backing fabric to produce plush material.

A form of "clinical bronchiolitis obliterans" was recently described in workers at a microwave popcorn plant (103). The underlying histopathologic lesion is not known. These patients present with cough and progressive dyspnea. Pulmonary function testing demonstrates fixed airway obstruction with no abnormalities seen on chest radiography (103). This bronchiolar disorder is associated with exposure to diacetyl, an organic compound used to impart buttery flavor.

INTERSTITIAL LUNG DISEASES WITH A PROMINENT BRONCHIOLAR COMPONENT

Many parenchymal lung diseases can involve the bronchioles with varying degrees of inflammation and scarring. Pulmonary function testing and HRCT of the chest may yield evidence of bronchiolar involvement in these predominantly parenchymal diseases. There are several of these disorders in which bronchiolar involvement may cause diagnostic confusion. These interstitial lung diseases include hypersensitivity pneumonitis, RB-ILD, desquamative interstitial pneumonia (DIP), and cryptogenic organizing pneumonia.

Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis is an immunologically induced inflammatory disease involving the lung parenchyma and terminal airways secondary to repeated inhalation of a variety of organic dusts and other agents in a sensitized host (104). Immunopathogenesis of this disorder in which macrophages and $CD8^+$ cytotoxic lymphocytes play a central role was recently summarized in another review article (104). Hypersensitivity pneumonitis is one of the more common forms of interstitial lung disease. Aside from the obvious parenchymal involvement, histologic evidence of bronchiolitis is seen in virtually all cases (105–108). Bronchiolitis in hypersensitivity pneumonitis is characterized by patchy peribronchiolar infiltrate of mainly lymphocytes with variable numbers of poorly formed granulomas or isolated multinucleated histiocytes (Figure 11) (105). In about half of patients, the bronchiolitis is accompanied by intraluminal fibrosis resembling that seen in organizing pneumonia. Smooth muscle hypertrophy associated with peribronchiolar fibrosis contributes to extrinsic bronchiolar narrowing (106). This inflammatory reaction may produce scarring of the airway wall and may be associated with mild airflow abnormalities. Bronchiolar involvement is the basis of airflow obstruction that is observed in varying degrees in all stages of hypersensitivity pneumonitis (109). In general, the degree of bronchiolar involvement tends to be proportional to the severity of fibrosis seen in the lung parenchyma (106). The spectrum of bronchiolar changes seen in some forms of hypersensitivity pneumonitis such as chronic pigeon breeder's disease is similar to that described for constrictive bronchiolitis (106). Thus, it is not uncommon for pulmonary function testing to

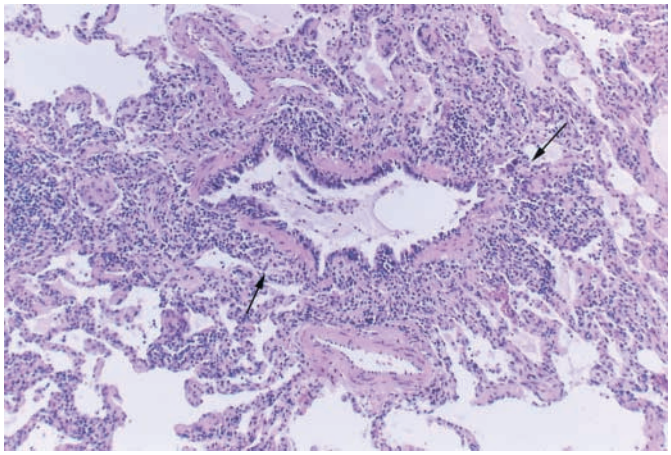

Figure 11. Hypersensitivity pneumonitis. Intermediate-magnification photomicrograph showing chronic bronchiolitis in a patient with hypersensitivity pneumonitis resulting from exposure to pigeons. Variable number of histiocytes, including occasional isolated multinucleated giant cells (*see arrows*) accompany a dense peribronchiolar infiltrate of mainly lymphocytes.

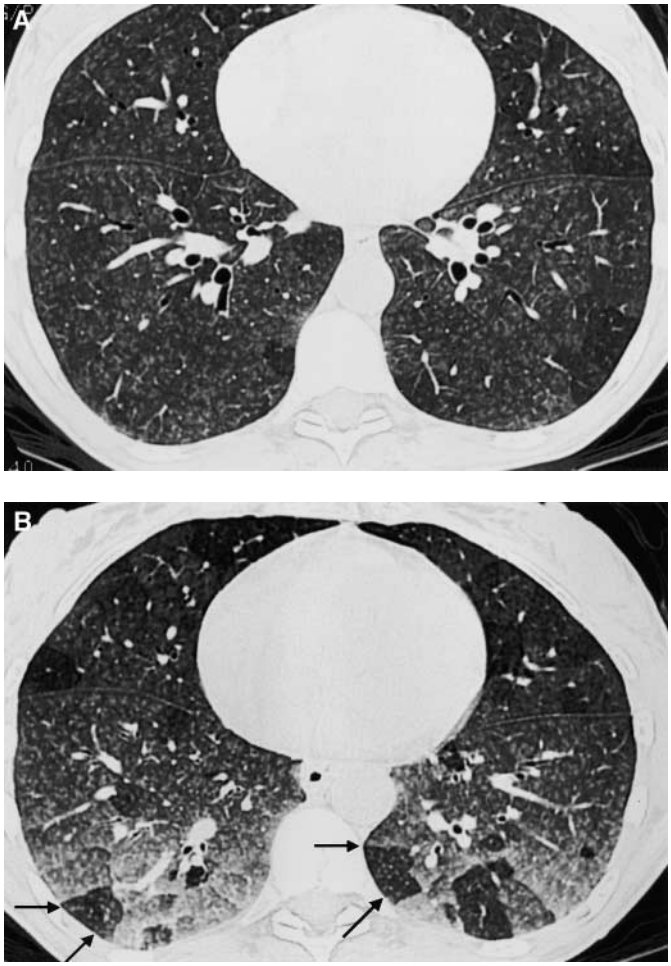

Figure 12. Hypersensitivity pneumonitis. (*A*) Full-inspiration HRCT of hypersensitivity pneumonitis shows diffuse, small, poorly circumscribed centrilobular nodular opacities. There are subtle changes of mosaic lung attenuation. (*B*) Expiratory HRCT in same patient shows air trapping in multiple lobules throughout both lungs with background of diffuse poorly circumscribed centrilobular nodular opacities. Note lobules of lower attenuation where there is air trapping (*arrows*) secondary to the bronchiolitis component of hypersensitivity.

reveal a mixed obstructive and restrictive pattern in patients with hypersensitivity pneumonitis (109, 110). In other forms of hypersensitivity pneumonitis, e.g., farmer's lung disease, bronchiolar involvement may appear closer to the pattern of organizing pneumonia (107).

On HRCT, the most frequent features of hypersensitivity pneumonitis are areas of decreased attenuation in a mosaic pattern (caused by small airways obstruction), followed by ground-glass opacities, poorly circumscribed centrilobular nodules (1–5 mm in diameter), and a reticular pattern (Figures 12A and 12B) (109). Areas of decreased attenuation and mosaic perfusion (mosaic pattern) suggesting air trapping are indirect signs of bronchiolar obstruction (13, 109). The poorly defined nodules and micronodules seen in hypersensitivity pneumonitis have a predominantly centrilobular distribution and represent intraluminal granulation tissue in the bronchioles and adjacent alveoli (109). Parenchymal inflammation and fibrosis are manifest as areas of ground-glass opacities and reticular densities (6).

Management of hypersensitivity pneumonitis mainly involves avoidance of exposure to the inciting agent, when the cause can be identified (104). If the cause is unknown or respiratory impairment is substantial, corticosteroid therapy may be needed (104).

RB-ILD and DIP

As discussed earlier, respiratory bronchiolitis is common in cigarette smokers and usually occurs without significant accompanying interstitial lung disease (79). In a small portion of smokers, symptomatic interstitial lung disease may occur in association with respiratory bronchiolitis. In 1987, Myers and colleagues (82) described what was subsequently labeled RB-ILD. This is a clinicopathologic entity seen almost exclusively in current or former cigarette smokers and may be confused with other interstitial lung diseases, in particular, idiopathic pulmonary fibrosis (80–83, 111–113).

Histologically, RB-ILD is characterized by the presence of pigmented macrophages and mild interstitial inflammatory changes centering on respiratory bronchioles (Figure 7) and neighboring alveoli (peribronchiolar air spaces) with sparing of more distal air spaces (1, 2, 81, 82, 111, 112, 114). The changes are patchy and have a bronchiolocentric distribution. Alveolar septa in the peribronchiolar region may be mildly thickened. DIP is highly related, differing mainly in that the airspace macrophages and interstitial thickening are more extensive and diffuse (1, 2, 81, 86, 111, 112, 114). That is, respiratory bronchiolitis, RB-ILD, and DIP represent a continuous spectrum of smoking-related interstitial lung disease (83, 86, 115). Because respiratory bronchiolitis and "DIP-like" changes are common incidental findings in cigarette smokers, ascribing clinical significance requires careful correlation with the clinical and radiographic findings (116). These histopathologic changes are presumably triggered by epithelial damage induced by cigarette smoke. Initial events in the pathogenesis of these lesions have not been clarified.

For the majority of patients with RB-ILD and DIP, the onset of symptoms is usually in the fourth or fifth decades of life and is considerably earlier than that noted in patients with idiopathic pulmonary fibrosis/usual interstitial pneumonia (80–83, 111, 112). There is a slight male predominance, and these patients have average exposures of over 30 pack-years of cigarette smoking (80–82, 112). Patients with RB-ILD and DIP commonly present with gradual onset of cough and dyspnea (80–83). Most

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patients with RB-ILD have relatively mild symptoms compared with those with DIP who commonly have significant dyspnea and hypoxemia (80–83, 117). Auscultation of the lungs reveals inspiratory crackles in about one-half of patients (80–83, 118). Digital clubbing is occasionally seen in patients with RB-ILD compared with nearly 50% of those with DIP (80–83, 117, 118).

Pulmonary function results in patients with RB-ILD may be normal but more commonly show a mixed obstructive and restrictive pattern of mild to moderate degree (80–82, 118). Most patients with DIP have a restrictive defect with reduced diffusing capacity (80–83, 118).

Chest radiographs are usually abnormal in both RB-ILD and DIP (80–82, 118–121). Diffuse, fine reticular, or reticulonodular opacities are the most common radiographic findings in patients with RB-ILD and DIP, but ground-glass pattern may be the predominant abnormality in some patients (80–83, 111, 112, 118–121). Thickening of the walls of central and peripheral bronchi is also a common radiographic feature in RB-ILD (120, 121). Lung volumes are usually preserved in RB-ILD but tend to appear reduced in DIP unless there is coexisting obstructive lung disease such as emphysema (81–83). Normal chest radiographs have been reported in up to 20% of patients with RB-ILD and DIP (81, 83, 120).

Areas of ground-glass attenuation are the most common finding on HRCT for both RB-ILD and DIP (Figure 13), but fine centrilobular nodules may also be seen in RB-ILD (80, 84, 113, 120–125). The extent of centrilobular nodules on CT correlates with the degree of macrophage accumulation and chronic inflammation in respiratory bronchioles, whereas ground-glass attenuation correlates with macrophage accumulation in the alveolar spaces and alveolar ducts (83, 84, 113, 120, 121). Associated centrilobular emphysematous changes may be present, particularly in the upper lobes, but signs of idiopathic pulmonary fibrosis, such as subpleural honeycombing and traction bronchiectasis, are generally absent. Septal thickening and irregular linear opacities are infrequently reported (120, 121, 123–125).

The mainstay of therapy for RB-ILD and DIP is smoking cessation after which the lesion appears to stabilize or to resolve slowly and generally does not show progression to fibrotic lung disease (80–83). However, some of these patients may experience continuing deterioration despite treatment (80). No deaths have been attributed to RB-ILD but have occurred with DIP (80–83, 119, 126). Corticosteroid therapy has been employed in a few anecdotal cases of RB-ILD, and more widely in DIP, with beneficial results reported (81–83, 126).

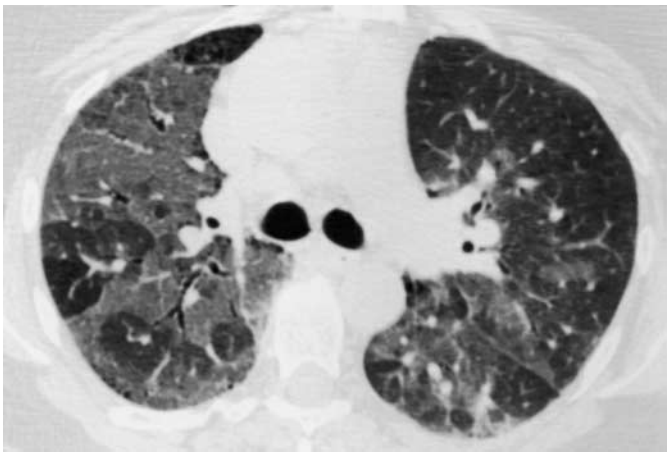

Figure 13. Desquamative interstitial pneumonia. HRCT shows characteristic changes of desquamative interstitial pneumonia. Note diffuse ground-glass opacity that is mildly heterogeneous with several more lucent regions of lung that are relatively spared. Desquamative interstitial pneumonia is on the same spectrum of disease and is related to respiratory bronchiolitis–associated interstitial lung disease.

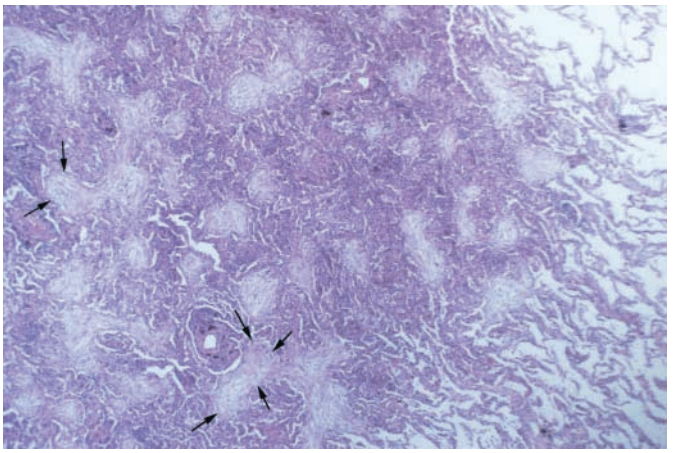

Figure 14. Organizing pneumonia. Low-magnification photomicrograph illustrating organizing pneumonia in a patient with idiopathic disease (i.e., cryptogenic organizing pneumonia). The changes are patchy and comprise pale-staining, intraluminal plugs of proliferating fibroblasts filling distal airways and peribronchiolar air spaces (*arrows*).

Cryptogenic Organizing Pneumonia (Also Known as Idiopathic BOOP)

As already discussed, cases of "bronchiolitis obliterans" in the older literature include a heterogeneous mix of lesions. Organizing pneumonia has been included in older reports under different names such as bronchiolitis obliterans (16), proliferative bronchiolitis (6), or more general terms such as interstitial pneumonias (127). Liebow and Carrington (128) included some examples of organizing pneumonia in their original classification of interstitial pneumonias as "bronchiolitis obliterans with classical interstitial pneumonia." Davidson and coworkers (129) coined the term "cryptogenic organizing pneumonitis" to describe a specific clinicopathologic syndrome with distinctive histopathologic findings. "BOOP" was the term proposed by Epler and colleagues (130) for the same condition in 1985, and since then the term BOOP has become entrenched in popular usage in the United States. Epler and colleagues separated BOOP from a group of 10 patients described as having "bronchiolitis obliterans without organizing pneumonia" (i.e., "pure" bronchiolits obliterans), but this was a heterogenous group including three patients with probable constrictive bronchiolitis and five patients with biopsies that were "not a representative sample of tissue." A recently published classification of the idiopathic interstitial pneumonias developed by an international panel has proposed the term "cryptogenic organizing pneumonia" (121). The term cryptogenic organizing pneumonia has the advantages of being descriptively accurate, both clinically and pathologically, and of avoiding confusion with other entities traditionally included under the heading of bronchiolitis obliterans. The connotation fits the clinical and morphologic features of a mainly alveolar process, rather than an obstructive airway disease.

Organizing pneumonia is a histopathologic pattern characterized by polypoid intraluminal plugs of proliferating fibroblasts and myofibroblasts within alveolar ducts and spaces with varying degrees of bronchiolar involvement (1, 2, 121). The fibroblastic plugs may form "casts" that outline the branching configuration of alveolar ducts and distal airways (Figure 14). The airway

TABLE 3. CAUSES AND UNDERLYING DISORDERS ASSOCIATED WITH ORGANIZING PNEUMONIA

Cryptogenic organizing pneumonia (idiopathic bronchiolitis obliterans organizing pneumonia or proliferative bronchiolitis) (121, 129, 130, 134–137)
Connective tissue disorders and vasculitides (systemic lupus erythematosus, Behçet's disease, rheumatoid arthritis, polymyalgia rheumatica, polymyositis and dermatomyositis, systemic sclerosis, mixed connective tissue disease, Sjögren syndrome) (134, 144)
Hypersensitivity pneumonitis (107)
Eosinophilic pneumonias (121)
Aspiration (1, 121)
Inhalational injury (1, 121) (e.g., silo filler's disease, paint aerosols, paraquat)
Drugs (1, 121, 134, 144) (e.g., amiodarone, nitrofurantoin, bleomycin, acebutolol, L-tryptophan, gold, sulfamethoxypyridazine, amphotericin B, mesalamine, methotrexate, naproxen sodium, sulindac, cephalosporins, hexamethonium, busulfan, cephalosporin, sulfasalazine, free base cocaine, etc.)
Radiation therapy (47)
Infections (bacteria, mycoplasma, cryptococcus, nocardia, viruses) (12, 134, 144)
Allograft recipients (heart–lung, lung and bone marrow) (144)
Hematologic malignancies and myelodysplastic disorders (134, 144)
Inflammatory bowel diseases (121, 144)
Focal organizing pneumonia as an isolated lesion or a reaction around other inflammatory processes, e.g., Wegener's granulomatosis (121, 134, 144)
Obstructive pneumonia (121, 144)
Other associations (2, 144)—IgA nephropathy, mesangiocapillary glomerulonephropathy, Sweet's syndrome, thyroiditis, common variable immunodeficiency, hepatitis C

lumen appears to be occluded from within, as opposed to the concentric narrowing seen in constrictive bronchiolitis. The lung parenchyma is involved in a patchy distribution, and the background architecture is generally preserved. Alveolar septal thickening due to an interstitial infiltrate of chronic inflammatory cells and hyperplasia of alveolar lining epithelium may be seen limited to areas of intraluminal fibrosis. Honeycombing is generally not seen.

Although the pathogenesis of the organizing pneumonia lesion is not fully understood, an animal model study suggests that T-lymphocytes and IFN-γ play important roles in the development of intraluminal fibrosis (131). Bronchoalveolar lavage studies in patients with cryptogenic organizing pneumonia have demonstrated lymphocytic alveolitis with expansion of $CD8^+$ cells and increased levels of Th1-related cytokines including IFN-γ, IL-12, and IL-18 (132). Newly formed intraluminal fibromyxoid tissue in cryptogenic organizing pneumonia demonstrates increased capillarization compared with fibroblastic foci of usual interstitial pneumonia (133). Angiogenesis appears to be mediated by growth factors, vascular endothelial growth factor and basic fibroblast growth factor (133). Regulation of angiogenesis may influence the reversibility of fibrotic lesions.

Although this histologic lesion of organizing pneumonia is morphologically distinctive, it is a nonspecific reparative reaction that may be seen in a variety of clinical contexts (Table 3) (1, 2, 7, 127, 134). In other words, organizing pneumonia may result from a variety of causes or underlying pathologic processes including infections, connective tissue diseases, inhalational injury, hypersensitivity pneumonitis, drugs, radiation, aspiration or as a focal reaction (1, 7). Focal organizing pneumonia may be seen as an isolated lesion or as a reaction around other inflammatory process such as abscess or other infections, pulmonary infarctions, aspiration pneumonia, or Wegener's granulomatosis. Thus, many conditions are included in the differential diagnosis for this histologic pattern, and only a portion of these cases represents the idiopathic syndrome, i.e., cryptogenic organizing pneumonia (135). In the larger case series, one-half or more of patients with organizing pneumonia had no underlying cause or disease association identified (134).

Most patients with cryptogenic organizing pneumonia are generally in their sixth or seventh decade of life but childhood cases have been reported (127, 134, 136). Symptoms most often consist of a new cough and dyspnea of subacute onset (over a few weeks) (127, 130, 134–136). Cough is usually nonproductive and persistent. Other symptoms may include fever, malaise, anorexia, and weight loss. However, cryptogenic organizing pneumonia can occasionally present as acute respiratory distress syndrome and respiratory failure (134, 137, 138).

The most frequent physical findings are fine inspiratory ("Velcro") crackles and tachypnea (130, 134, 136, 137). Clubbing is rarely seen (130, 136). There may be moderate leukocytosis, with an increased proportion of neutrophils (137). The erythrocyte sedimentation rate and C-reactive protein level are increased in many patients (137).

The most common radiographic finding in patients with cryptogenic organizing pneumonia is patchy bilateral alveolar infiltrates that may have a "ground glass" appearance and normal lung volume (130, 134, 137). These infiltrates may come and go in different locations over a course of several weeks or longer (130). The distribution of these patchy infiltrates can be peripheral, resembling chronic eosinophilic pneumonia (138). Sometimes, these infiltrates may look denser and appear as multifocal mass-like regions of consolidation (134). Occasionally, infiltrates may be unilateral. Diffuse interstitial infiltrates are the predominant radiographic abnormality in less than 20% of patients with cryptogenic organizing pneumonia (7, 130, 134, 137, 139). This latter radiographic pattern may be more common in patients with associated connective tissue diseases and tends to be associated with a poorer prognosis (136). Other radiographic presentations include a unifocal region of consolidation or mass as in those patients with "focal" organizing pneumonia (134). Small rounded opacities are described in 18 to 30% of cases (121, 123, 140). Pleural disease is seen in up to one-quarter of subjects (139, 141). Hyperinflation is not a feature of organizing pneumonia.

On HRCT, nearly all patients with organizing pneumonia have patchy, unilateral or bilateral, areas of air-space consolidation or ground-glass attenuation (ranging from 2 cm to extensive bilateral disease), with nodules being less common (Figure 15) (6, 123, 127). Subpleural or peribronchial distribution is demonstrated in up to 50% of cases. Linear or reticular opacities may be seen in some subjects (123, 142). A small number of patients with cryptogenic organizing pneumonia will progress to honeycombing (121, 123). As is true in many inflammatory lung dis-

eases, moderate mediastinal adenopathy may occur in organizing pneumonia.

Bronchoalveolar lavage usually reveals an increase in lymphocytes count as the most common pattern (127, 134, 137, 143). Increased numbers of eosinophils and neutrophils may be seen as well (127, 134, 143).

Pulmonary function testing typically shows a predominantly restrictive defect (usually mild to moderate) associated with a diminished diffusing capacity of the lungs for carbon monoxide (137). Obstructive defect (FEV_1/FVC ratio of less than 70%) has been reported in 11 to 28% of subjects with cryptogenic organizing pneumonia and all were current or former smokers (127, 136). Occasionally, lung function measurements are normal. Resting and exercise arterial hypoxemia is seen with extensive lung involvement.

Diagnosis of cryptogenic organizing pneumonia requires identification of the pathologic findings of organizing pneumonia in the appropriate clinical and radiographic context and exclusion of known causes or underlying disease (143, 144). Transbronchial lung biopsy may be sufficient if the specimen is large enough to contain all the elements of the lesion and if the clinical findings are appropriate (121, 134, 143). If not, a surgical lung biopsy may be needed to rule out other diseases such as hypersensitivity pneumonitis, nonspecific interstitial pneumonia, usual interstitial pneumonia, diffuse alveolar damage, or chronic eosinophilic pneumonia (144).

In general, cryptogenic organizing pneumonia is a corticosteroid-responsive disorder. Clinical improvement may be rapid and dramatic, occurring within several days or may take a few weeks (121, 130, 136, 144). Prognosis is generally excellent and two-thirds or more of these patients experience complete resolution of their lung disease (121, 130, 134, 137, 144). The therapy of choice is prednisone, 0.75 mg/kg/day with gradual tapering of dosage in the following several months (137, 144). Several-day course of high-dose parenteral corticosteroid therapy may be needed in patients with rapidly progressive cryptogenic organizing pneumonia (136). The usual duration of corticosteroid therapy is 6 to 12 months (144). Relapse is seen in one-third of the patients if a short treatment course of less than 3 months of corticosteroid therapy is used (130, 137, 144). Prednisone can eventually be given on an alternate day dosage. Some of these patients require low-dose maintenance prednisone therapy for several years to maintain stabilization with chronic symptoms and pulmonary dysfunction. In 10 to 15% of patients, cryptogenic organizing pneumonia remains a progressive disease despite corticosteroid therapy (145). The benefit of cytotoxic agents such as cyclophosphamide has not yet been established (136, 144, 146). A few patients may have spontaneous resolution without therapy over a course of several months (127, 136).

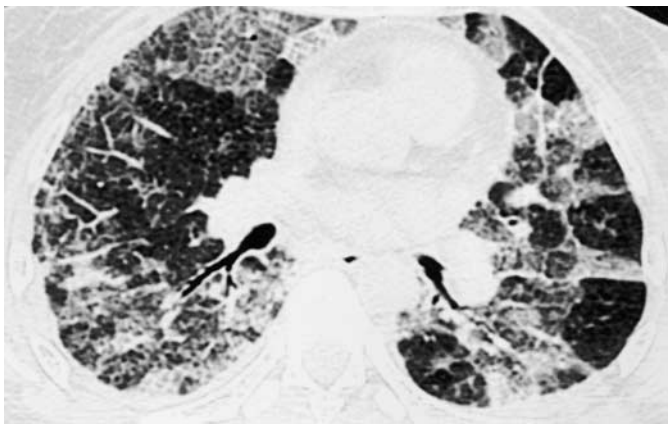

Figure 15. Organizing pneumonia. HRCT of patient with cryptogenic organizing pneumonia shows heterogenous regions of consolidation and ground-glass opacity bilaterally. There are reticular changes, but no honeycombing.

Other Interstitial Lung Diseases

A few other interstitial lung diseases deserve mention in this section with respect to their involvement of bronchioles. Pulmonary Langerhans' cell histiocytosis is a smoking-related interstitial lung disease characterized by excessive proliferation of Langerhans' cells and destructive granulomatous lesions in the lung (147). The earliest lesion in pulmonary Langerhans' cell histiocytosis is accumulation of Langerhans' cells with varying numbers of eosinophils in the submucosa and adjacent interstitium of bronchioles and alveolar ducts (147–149). Recruitment and activation of Langerhans' cells to the lung may result directly from cigarette smoke or may be mediated by cytokines released from other cells including alveolar macrophages and airway neuroendocrine cells (149). This process affects predominantly respiratory bronchioles and to a lesser extent distal terminal bronchioles (148, 149). Some of the cystic lesions seen in pulmonary Langerhans' cell histiocytosis result from this bronchiolocentric process, which results in destruction of the bronchiolar wall (148). Pulmonary function testing in patients with pulmonary Langerhans' cell histiocytosis reveals both obstructive and restrictive changes (147). The effects from cigarette smoking may be superimposed and can be difficult to distinguish from the effects of pulmonary Langerhans' cell histiocytosis itself.

By virtue of their perilymphatic distribution, sarcoid granulomas are concentrated around the airways (150). Small and large airways are frequently involved by granulomas, and measurable airflow obstruction occurs in a small percentage of cases (150). Functional studies using sophisticated tests have suggested airflow obstruction located at the level of small airways to be an early feature of sarcoidosis (13, 150). Supportive evidence may be seen as patchy air trapping on expiratory CT (151, 152). In some cases, air trapping, believed to reflect bronchiolar obstruction, foreshadows more typical parenchymal manifestations of sarcoidosis (152). However, the exact prevalence of this phenomenon and its clinical significance, if any, are as yet unknown.

Inflammation and fibrosis involving bronchioles may also be seen in idiopathic pulmonary fibrosis (106, 153). However, the degree of this reaction is not as severe as that seen in chronic hypersensitivity pneumonitis (106). Bronchiolectasis accounts for some of the cystic changes seen by HRCT in idiopathic pulmonary fibrosis (154).

Recently, Yousem and Dacic (155) described another interstitial lung disease with a prominent bronchiolar component that they named idiopathic bronchiolocentric interstitial pneumonia. Histopathologic features are characterized by chronic inflammatory cell infiltrates with a centrilobular and bronchiolocentric distribution (155). These findings may be similar to hypersensitivity pneumonitis, but there are no interstitial granulomas. Chest radiography demonstrates bibasilar interstitial infiltrates, and restrictive defect is seen on pulmonary function testing (155). Most patients are middle aged, and there appears to be a predilection for women (155). Idiopathic bronchiolocentric interstitial pneumonia is associated with a relatively poor prognosis, including 33% mortality at 4 years follow-up (155).

BRONCHIOLAR INVOLVEMENT IN LARGE AIRWAY DISEASES

Bronchiectasis, chronic bronchitis/emphysema, cystic fibrosis, and similar conditions of the bronchi typically manifest patho-

logic changes at the level of the bronchioles that reflect the full spectrum of bronchiolar pathology. Bronchiolar abnormalities found in these large airway diseases include variable degrees of inflammation in the wall and lumen of bronchioles, smooth muscle hypertrophy, and mucostasis (114, 156). Additional histologic findings in asthma may include mucus plugging, bronchiolar epithelial sloughing, luminal and mural eosinophils, and luminal eosinophil debris (156, 157).

Histopathologic study of lung specimens obtained from patients with severe chronic obstructive pulmonary disease has revealed enhanced inflammatory response in the small airways characterized by increase of T-lymphocytes (both $CD4^+$ and $CD8^+$ cells) in the airway walls and an increase in macrophages in the airway epithelium when compared with smokers with mild or no lung disease (158). Chemokine receptor CXCR3 and its ligand CXCL10 appear to be involved in T-lymphocyte recruitment to bronchioles (159). Correlation was found between the severity of this inflammatory response and the degree of airflow limitation, suggesting a contributory role of small airway inflammation in the development of progressive chronic obstructive pulmonary disease (158).

Obstruction of bronchioles by inflammatory exudates and bronchiolar wall thickening from edema and smooth muscle hyperplasia occurring in these large airway diseases produce the HRCT scan features of atelectasis, air trapping, centrilobular nodules, and bronchiolar wall thickening (160). Thus, air trapping suggestive of bronchiolar disease is not uncommon in patients with bronchiectasis (161). In some cases of severe asthma and air trapping, HRCT features may be difficult to distinguish from that of constrictive bronchiolitis (162). Branching or centrilobular nodules (reflecting the presence of dilated bronchioles with mucus impaction, infection, or peribronchiolar inflammation) and mosaic perfusion are seen in patients with cystic fibrosis (163, 164). Similar signs of bronchiolar disease are also seen in patients with allergic bronchopulmonary aspergillosis (165).

Conclusions

Bronchiolar abnormalities are commonly encountered on lung biopsy specimens and HRCT of the chest. Various histopathologic patterns of bronchiolar injury have been described and have led to confusing nomenclature with redundancies and overlapping terms. There is a need to standardize the terminology and to recognize that bronchiolar disease may not have clinical significance in some clinico–radiologic contexts. Herein, we have presented a scheme to classify those disorders in which the bronchiolar disease can be the predominant (primary bronchiolar disorders) or contributing (i.e., in parenchymal and large airway diseases) pathologic component. When faced with a bronchiolar abnormality the clinician needs to ask three questions: (*1*) is the bronchiolar abnormality the predominant lesion causing disease? (*2*) what is the histopathologic pattern of the bronchiolar lesion? (*3*) what is the clinico–physiologic–radiologic context? The clinical and prognostic significance of a bronchiolar lesion is best determined by identifying the underlying histopathologic pattern and assessing the correlative clinico–physiologic–radiologic context.

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