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Small Airway Disease

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Although severe cases of chronic obstructive pulmonary disease have lesions of both large and small airways, there is a distinct minority of patients whose airflow obstruction is due, solely or predominantly, to involvement of the small airways. The latter are defined as those airways less than 2 mm in diameter, and corresponding to small cartilaginous bronchi, terminal bronchioles, and respiratory bronchioles.[1] Small airway disease (SAD) represents luminal obstruction by inflammatory and fibrotic changes that increase airway resistance significantly. The obstruction may be transient or permanent; the latter is due to diffuse involvement by dense fibrocollagenous plugs and plaques.

From a pathogenetic perspective, acute and chronic airway inflammation induce insudation of fluid and fibrin, the organization of which causes luminal obstruction of variable degrees. Moreover, papillary epithelial hyperplasia and goblet cell metaplasia of the epithelium may cause excessive mucus in the airways, which disrupts the laminar airflow. Squamous metaplasia may induce functional changes by reducing the ciliary motion of the bronchiolar epithelium essential to clearing mucoid secretions. The smooth muscle of the small airways may be hyperreactive and hypertrophic, causing intermittent bronchoconstriction which also alters airflow mechanics.

The main histologic feature of obstructive SAD is dense fibrocollagenous tissue in the submucosa, lumen, and peribronchiolar zones, which causes reduction or frank obliteration of the small airways. This process has generically been labeled "bronchiolitis obliterans" (BO) and represents the end stage of small airway injury (Color Fig. 30-1).

Most lesions of SAD are associated with diseases of larger airways. Therefore, exclusion of processes that affect large cartilaginous bronchi is essential before SAD can be accepted as a primary cause of the airway obstruction. Specifically, this excludes coexisting chronic bronchitis, bronchiectasis, emphysema, and some cases of asthma.

Inflammatory processes of the small airways may be reversible or irreversible. Patients may present with obstructive changes on pulmonary function testing, but with resolution of the inflammation, pulmonary function abnormalities may resolve. However, the histologic diagnosis of SAD often implies irreversibility of the airway injury, and some functional deficit would remain after treatment. For example, most children who experience respiratory syncytial virus bronchiolitis will have complete reversal of symptoms and functional abnormalities after the viral episode resolves. However, a small minority will have persistent and chronic fibrosis of the small airways and will experience pulmonary limitation for the rest of their lives.

Predicting chronicity of SAD in the acute or subacute phases is difficult, and the best monitor of the fate of injury remains repeated pulmonary function testing over prolonged periods. It is not uncommon in any lung biopsy to document some fibrosis of the small airways that has no functional correlate. Because the lung biopsy provides only a limited sample of the small airways, functional alterations more accurately reflect the severity and extent of the lesions. Clinical correlation is also essential to determine the etiology of SAD.

PATTERNS OF SMALL AIRWAY DISEASE

Bronchiolitis Obliterans

BO, also known as obliterative bronchiolitis, is a clinicopathologic syndrome of progressive SAD that reflects injury to the terminal and respiratory bronchioles, and it is characterized by partial or complete occlusion of their lumens by inflammatory and fibrous tissue.[2,3] A partial list of conditions associated with BO is presented in Display 30-1.

BO is the prototype for SAD.[4] From a pathologic point of view, BO may be analyzed by the series of events that affects the small airways prior to irreversible airway scarring. Presumably, an injurious stimulus affects the small airways and results in epithelial necrosis and ulceration with formation of an intraluminal fibropurulent exudate (Fig. 30-1). This induces the ingrowth of young fibroblasts and myofibroblasts from the denuded submucosa into the exudate and the deposition of young collagen and acid mu-

DISPLAY 30-1. CAUSES OF BRONCHIOLITIS OBLITERANS

Inhalation
Thermal injury
Chlorine
Ammonia
Hydrochloric acid
Mustard gas
Nitrogen dioxide
Sulfuric acid
Hypersensitivity pneumonitis

Infection
Respiratory syncytial virus
Adenovirus types 1, 3, 7, 21
Influenza
Bordetella pertussis
Mycoplasma pneumoniae
Chlamydia spp.
Measles
Haemophilus influenzae

Collagen-Vascular Disease
Rheumatoid arthritis
Sjögren syndrome
Systemic lupus erythematosus
Eosinophilic fasciitis
Scleroderma
Ankylosing spondylitis

Transplantation
Heart-lung transplant recipients
Bone marrow transplant recipients

Drugs
Penicillamine
Sulfa drugs
Methotrexate

Miscellaneous
Aspiration
Lymphoma-leukemia
Cystic fibrosis
Diffuse alveolar damage

Idiopathic

copolysaccharides (Fig. 30-2). Small capillaries and histiocytes also proliferate within the exudate, forming a large intraluminal polyp (*i.e.*, Masson body). At the same time, metaplastic epithelium from adjacent noninjured epithelium grows over the granulation tissue plug, incorporating it into the wall of the airway.

Several consequences of the above injury are possible. With the action of collagenase-secreting histiocytes, the fibrovascular connective tissue may be resorbed and the diameter of the airway regains its original degree of patency. The regenerative epithelium returns to its original form, consisting of ciliated, absorptive, and Clara cells. In other instances, the small airways may be left with a concentric, eccentric, or transluminal scar that severely reduces the patency of the airway (Fig. 30-3). This scar tissue may contain small capillaries, dense eosinophilic collagen, plugs of entrapped metaplastic epithelium, or occasionally hyperplastic neuroendocrine cells (*i.e.*, pulmonary tumorlets). In rare instances, a peribronchiolar collarette of eosinophilic scar tissue may surround the airway and be associated with minimal submucosal scarring. This constrictive form of BO may act in a fashion similar to that of a rubber band entwined around a collapsible cylinder.

The term BO should be reserved for only those cases in which a cicatrix has formed and the airways within the biopsy specimen show fibroobliterative changes. Whether the scarring is clinically relevant or not is determined by the number of airways affected and the severity of the injury to individual bronchioles. Therefore, one must see in the open lung biopsy specimen generalized involvement of the small airways that correlates with obstructive pulmonary function abnormalities.

At the end stage of BO, the diagnosis may be difficult to make. The small airways appear obliterated, and can only be identified by their accompanying pulmonary artery (see Color Fig. 30-1). Sometimes this obliteration can be highlighted by the marked metaplastic bronchiolar epithelium that coats thickened peribronchiolar alveolar septa adjacent to the injured bronchiole, and it is frequently associated with mucus inspissation and acute inflammation. Additional diagnostic information can be provided by van Gieson, trichrome, and elastic tissue stains. Trichrome stains can demonstrate the collagenous tissue within airways and peribronchiolar air spaces, as well as highlight portions of smooth muscle in the walls of the airways. Elastic tissue stains accentuate the basilar elastica of the small airways, areas of reduplication, or loss of such elastica.

Most patients with BO have an idiopathic form; however, as noted in Display 30-1, some causes are well recognized. This is particularly true of infection, in which some viral pathogens may be identified.[5–7] In infants, respiratory syncytial virus and adenovirus may severely and permanently injure the airways. Their presence can be documented by culture, immunohistochemistry,

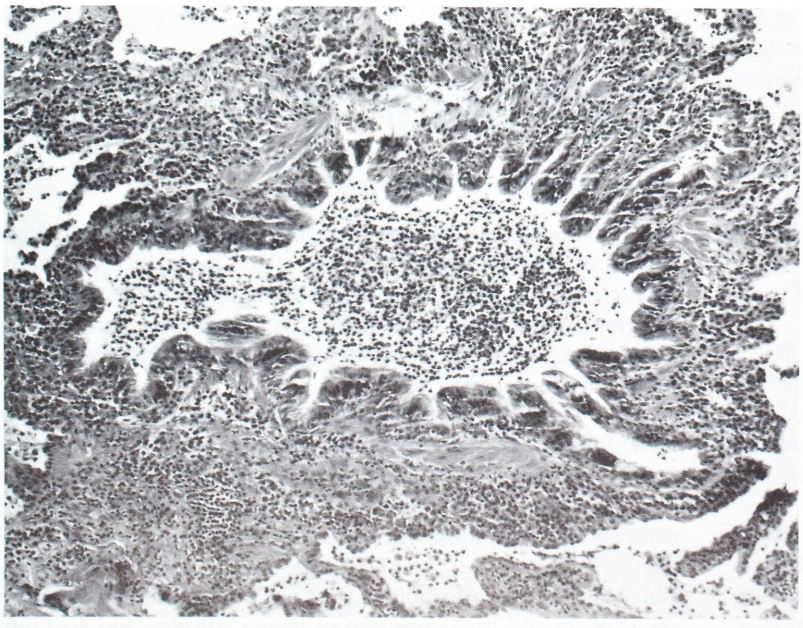

FIGURE 30-1. Acute bronchiolitis demonstrates a neutrophilic and lymphocytic exudate in the wall and lumen of a bronchiole. (H & E stain; low magnification.)

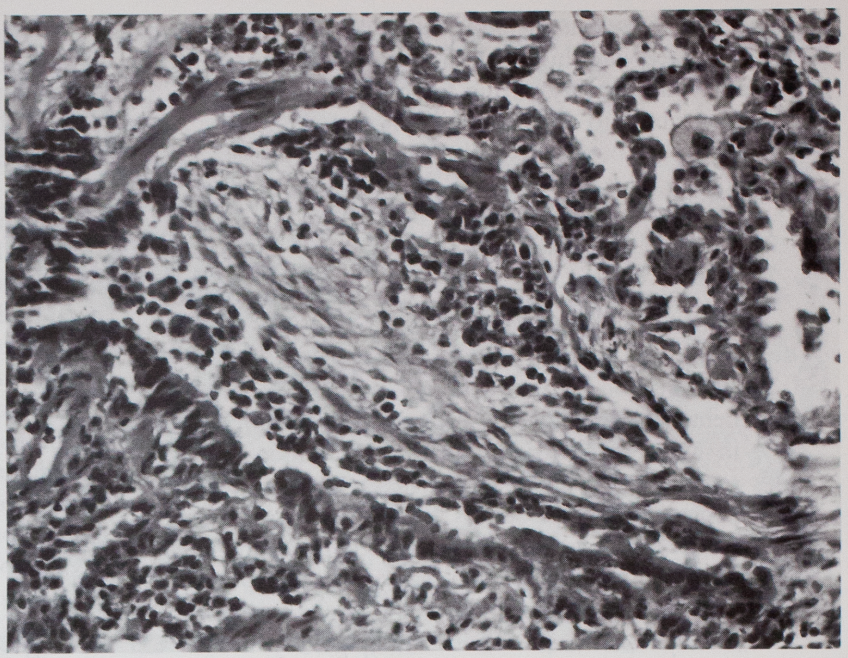

FIGURE 30-2. Proliferative phase of bronchiolitis obliterans. A polyp of fibromyxoid tissue fills the lumen of the small airway. (H & E stain; intermediate magnification.)

or *in situ* hybridization studies. Adenovirus in particular causes intranuclear amphophilic inclusions, which can be identified by light microscopy. Other causes include infection by *Haemophilus* sp., *Mycoplasma* sp., influenza, *Bordetella pertussis*, or *Chlamydia* sp.

Connective tissue diseases induce small airway injury as one manifestation of their autoimmune damage.[3] This bronchiolar damage may be the result of deposits of immunoglobulins within the basement membrane or to abnormal epithelial cell–lymphocyte interactions. This phenomenon is particularly seen in rheumatoid arthritis, ulcerative colitis, Sjögren syndrome, systemic lupus erythematosus, progressive systemic sclerosis, and eosinophilic fasciitis.[9] Penicillamine has been recommended for the treatment of rheumatoid arthritis; however, airway injury has also been associated with the use of this drug, among others.[9,10] Finally, a lymphocytic bronchiolitis with BO has been noted in the setting of organ transplantation. This alloreactive rejection of airway epithelium occurs in both lung and bone marrow transplantation and is a significant cause of mortality in both populations (see Chap. 71).[11–13]

The clinical course of patients with idiopathic BO is variable. It has been noted that patients may have mild or rapidly progressive disease; however, there appears to be a mortality rate of at least 50% at 12 years of clinical follow-up.[4,14] Treatment with corticosteroids has provided a variable response. Patients usually die of superimposed pulmonary infections.

Follicular Bronchitis and Bronchiolitis

Follicular bronchitis and bronchiolitis (FBB) represents an inflammatory reaction that occurs around the small airways and is characterized by prominent peribronchiolar germinal centers.[15] It represents a hyperplasia of the bronchial-associated lymphoid

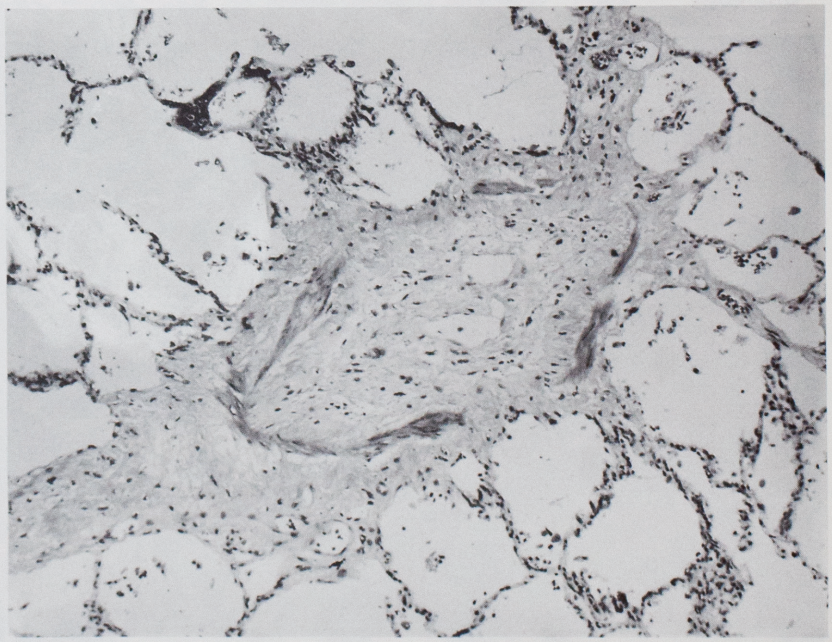

FIGURE 30-3. Cicatricial phase of bronchiolitis obliterans. The lumen of a small airway is completely obliterated by dense fibrous scar tissue (see Color Fig. 30-1). (H & E stain; intermediate magnification.)

tissue normally present in the bronchovascular bundles (Color Fig. 30-2). Associated with this inflammation is fibrosis and epithelial hyperplasia with papillary tufting and goblet cell metaplasia that can also contribute to the airway obstruction (Fig. 30-4).

When groups of patients with FBB have been analyzed, four major etiologies emerge.

1. FBB may be the result of infection.[16] *Mycoplasma pneumoniae, Chlamydia* sp., and *Brahamella catarrhalis* have been associated with reactive follicles in the epithelium. Therefore, culture studies are warranted in this histopathologic subgroup.
2. FBB may be a manifestation of altered immunity in patients with immunodeficiency syndromes. It may be seen in AIDS and in patients with the common variable or severe combined immunodeficiency, or patients with leukocyte chemotactic deficits. It also may be a manifestation of cystic fibrosis in which inspissated mucus and its ensuing inflammatory reaction induce follicle hyperplasia.
3. FBB may be associated with connective tissue diseases, usually rheumatoid arthritis and Sjögren syndrome.[15–17] Sjögren syndrome presumably is caused by desiccation of airways and an inflammatory reaction, in addition to the generalized lymphoid hyperplasia.
4. FBB may be associated with local or systemic hypersensitivity reactions. This is particularly seen in individuals older than 50 years of age, characteristically with peripheral blood eosinophilia.

Respiratory Bronchiolitis

Respiratory bronchiolitis is a ubiquitous finding in the small airways of symptomatic and asymptomatic cigarette smokers and may be a precursor to centrilobular emphysema.[18–20] It is manifested by lymphocytes and plasma cells present within the terminal and respiratory bronchioles (Fig. 30-5). Goblet cell metaplasia and mucus inspissation may also be seen. Fibrous bands radiate from these small airways into the adjacent peribronchiolar alveolar septa, and bronchiolar metaplasia may be noted there.

The hallmark of respiratory bronchiolitis is the presence of numerous finely pigmented brown macrophages within the lumens of the small airways as well as peribronchiolar air spaces (Fig. 30-6). These are present in a patchy distribution and are confined to the centrilobular zones. The brown pigmentation of the macrophages corresponds to abundant secondary phagolysosomes, which contain crystalline material characterized as kaolinite, an aluminum silicate.[18]

Patients with respiratory bronchiolitis may present with clinical findings resembling interstitial lung disease, typically a chest radiograph showing a diffuse bilateral, finely reticular infiltrate with basilar predominance.[19] All patients have a history of cigarette smoking. No patient has developed a diffuse interstitial fibrosis in follow-up studies, as could be expected given the histologic similarity of respiratory bronchiolitis to desquamative interstitial pneumonia (see Chap. 32).[19] Symptoms resolve with cessation of cigarette smoking and steroid therapy for acute exacerbations.

Diffuse Panbronchiolitis

Homma and colleagues described a lesion that has a peculiar predilection for Oriental men and occurs within a wide age range.[21,22] Patients present with chronic cough, sputum, and dyspnea and frequently have associated chronic sinusitis. Chest radiographs show bilateral small nodular densities associated with pulmonary overinflation. These patients frequently have chronic colonization of their sputum by *Pseudomonas* species and die of infectious complications.

Diffuse panbronchiolitis shows extensive acute and chronic inflammation of the terminal and respiratory bronchioles, which may extend into the peribronchiolar air spaces (Fig. 30-7). The infiltrate is characterized by abundant lymphocytes, plasma cells, and interstitial aggregates of foam cells. With time, these patients progress from small airway involvement to large airway involvement, dilatation, and inflammation of the more proximal airways (*i.e.*, bronchiectasis). Only rare cases have been reported in Caucasians.[23] In one instance, association with ulcerative colitis as well as certain HLA phenotypes was noted.[21,24]

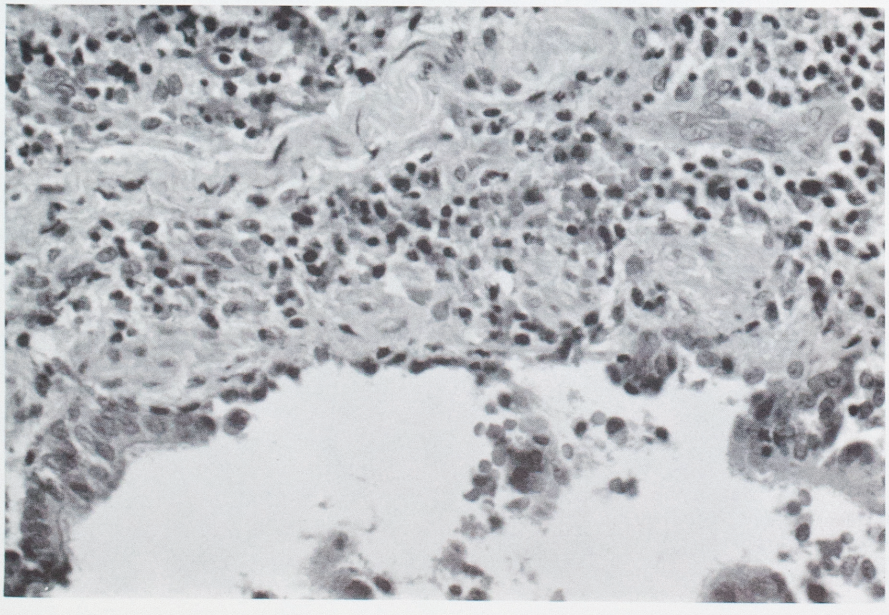

FIGURE 30-4. Infiltration of bronchiole by lymphoid cells produces ulceration of the epithelium in a case of follicular bronchitis and bronchiolitis. (H & E stain; intermediate magnification; contributed by the editor.)

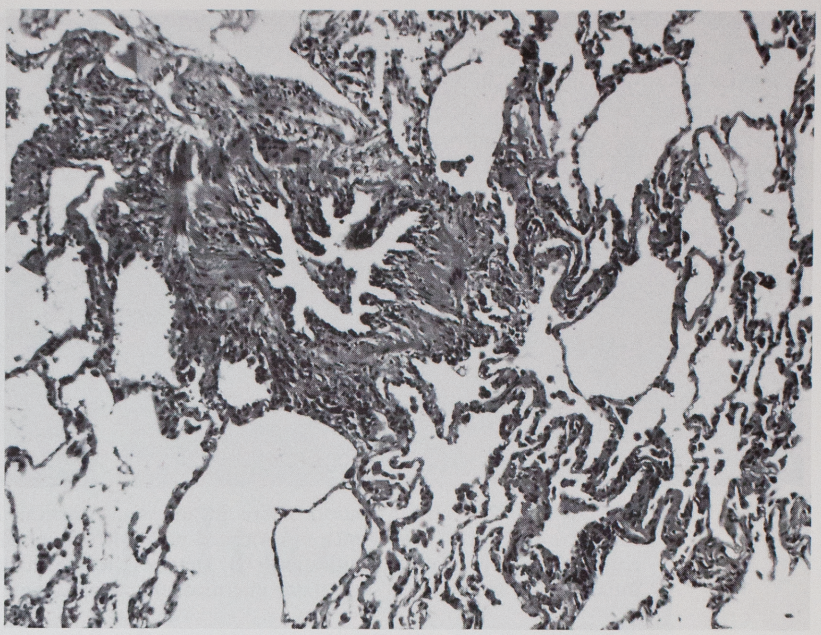

FIGURE 30-5. A chronic respiratory bronchiolitis is seen associated with mucus inspissation and intraluminal collections of smokers' macrophages. (H & E stain; low magnification.)

Mineral Dust-Associated Small Airway Disease

Small airway fibrosis can occur as a result of mineral dust exposure. The histologic features are similar to those of BO; however, there is a clinical history of excessive dust exposure. This problem is especially evident in studies of asbestos-induced lung disease (see Chap. 36).[25,26] The controversial entity of asbestos airway disease reveals small airway fibrosis with ferruginous bodies of the asbestos type within the lumens and peribronchiolar air spaces of these individuals. Ascribing causality to asbestos in these cases may be difficult because many of these patients are also cigarette smokers.

CONCLUSION

Diseases of the small airways (*i.e.*, airways <2 mm in diameter) are frequently seen in classic chronic obstructive pulmonary disease, such as emphysema, chronic bronchitis, bronchiectasis, and asthma, and represent a main cause of chronic airway obstruction in such conditions. Comparatively much rarer is the situation of SAD, largely unassociated with the above conditions yet severe enough to produce chronic irreversible airway obstruction. SAD represents a nonspecific reaction to a variety of injurious agents. In some cases, this injury may be transient and associated with an inflammatory reaction. In other instances, however, the injury can result in obstruction and fibrosis of the small airways, with irreversible

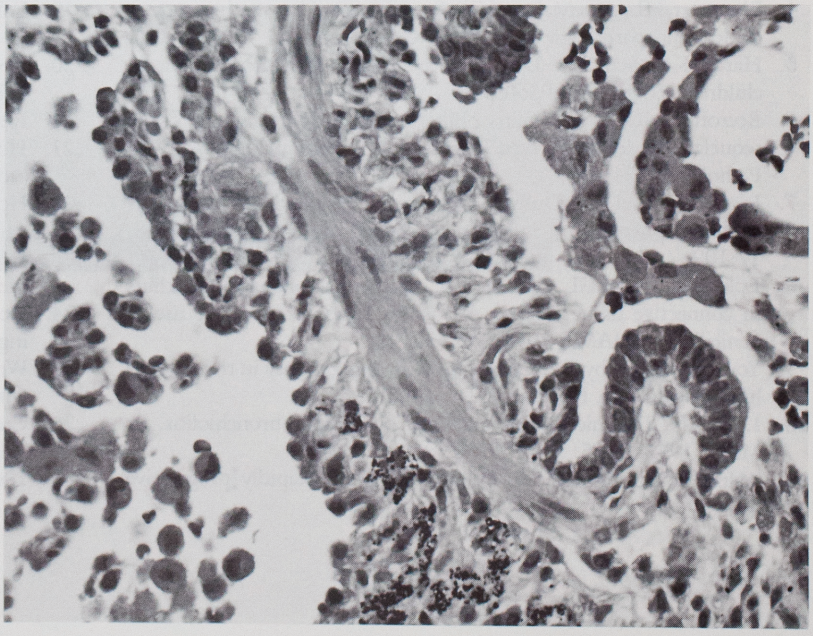

FIGURE 30-6. In respiratory bronchiolitis, finely pigmented macrophages fill the airways and air spaces of the lung. (H & E stain; intermediate magnification.)

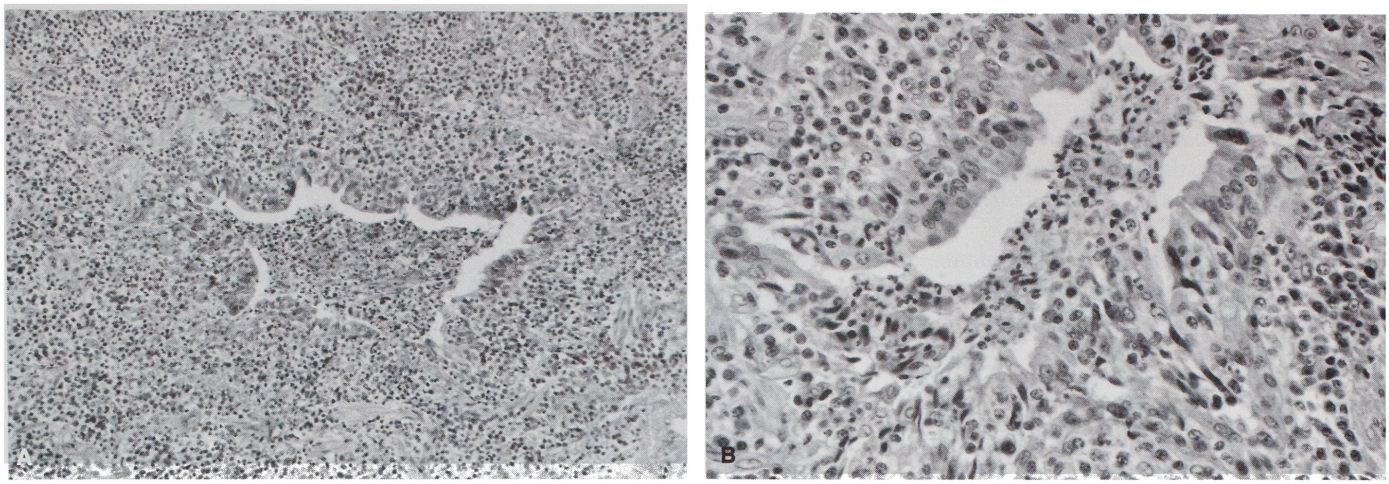

FIGURE 30-7. Diffuse panbriochiolitis in an Asian-American man. (**A**) Intense suppurative inflammatory exudate in the bronchiolar lumen is associated with a lymphoplasmacytic infiltrate extending to peribronchiolar tissue. (H & E stain; low magnification.) (**B**) Detail of the bronchiolar lumen shows extensive ulceration and severe inflammatory changes. (H & E stain; intermediate magnification; contributed by the editor.)

pulmonary function abnormalities. The severity and cause of SAD are to some extent reflected in the histologic pattern, with respiratory bronchiolitis of the smoker representing a relatively low-grade injury, and BO with fibroobliterative transluminal scars representing a lethal condition. The clinical picture, distinctive pulmonary function abnormality, and histopathology are helpful in making the diagnosis of SAD.

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