Bronchiolitis
Pathologic Considerations

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Bronchiolitis represents a cellular and mesenchymal reaction involving bronchioles. The interplay between the cellular infiltrate and the mesenchymal reaction affects the lumen size, lamina propria, muscular layer, and bronchiolar adventitia. The result is a variety of clinical, radiologic, and functional patterns of bronchiolar disease. The anatomy of the small airways is discussed, and a pathologic classification applicable to the surgical pathology of bronchiolitis is presented. The classification is practical and includes asthma, chronic obstructive pulmonary disease, cellular bronchiolitis, respiratory bronchiolitis, respiratory bronchiolitis–associated interstitial lung disease, bronchiolitis obliterans (including bronchiolitis obliterans with intraluminal polyps and constrictive bronchiolitis), dust-related small airway fibrosis, and (postinflammatory) bronchiolar scarring and peribronchiolar fibrosis. (Key words: Asthma; Bronchiolitis; Bronchiolitis obliterans; Constrictive bronchiolitis; Follicular bronchiolitis; Obliterative bronchiolitis; Respiratory bronchiolitis; Small airway diseases) Am J Clin Pathol 1998;109:101–109.

THE BRONCHIOLES

Bronchiolitis = Inflammation of the Bronchioles

This definition is simplistic, but it reminds us that bronchiolitis is an inflammatory process. An inflammatory reaction is a response to injury and reflects an interplay of inflammatory cells and mesenchymal tissue (including fibrosis). The distribution and amounts of the cellular and mesenchymal components vary from case to case. Inflammation and fibrosis may be distributed in a nodular or a diffuse fashion along airways, may or may not involve the peribronchiolar alveoli, and may or may not be associated with luminal narrowing. The result is a diverse histologic picture of bronchiolitis and a variety of clinical, radiologic, and functional patterns. The inflammatory (cellular) and mesenchymal (granulation-type tissue and scarring) components often occur together but sometimes are separated in subclassification (see later).

The interplay between inflammatory cells and mesenchymal tissue seen histologically in bronchiolitis explains the various radiographic findings of bronchiolitis: nodules, branching lines, air trapping, mosaic perfusion, ground glass change, and mixtures of these.[1]

The Bronchioles Are the Bridge Between Bronchi and Alveoli

The bronchiole cannot be separated from the bronchus at one end and the alveoli at the other. In terms of pathologic reactions, it is not possible to define only one or two clinicopathologic patterns of bronchiolar disease. Cases of bronchiolitis may be associated with obstructive or restrictive pulmonary function; wheezing or crackles; radiographic nodules, infiltrates, or hyperinflation; and nodular and diffuse inflammation and scarring histopathologically. Bronchiectasis, chronic bronchitis, cystic fibrosis, and similar conditions of the bronchi typically include pathologic changes in the small airways that reflect the full spectrum of bronchiolar pathology described below. Conversely (but less well recognized), primary pathology in the small airways (eg, diffuse panbronchiolitis and transplant-associated constrictive bronchiolitis) frequently results in proximal bronchiectasis.[2–5] Similarly, inflammatory lesions of the bronchioles (especially respiratory bronchioles) commonly include involvement of the adjacent alveoli. Such cases illustrate that the separation of "parenchymal disease" from "airway disease" clinically or histologically becomes impossible.

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The bronchovascular bundles are a functional unit, as well as an anatomic unit, and lesions affecting one of these structures often affect the other. These interactions form the basis of ventilation and perfusion matching in the supplied lung tissue. Subtle changes in the small pulmonary arteries often accompany inflammatory and fibrotic changes in the adjacent bronchioles, and this may explain the mosaic perfusion pattern (thought to represent decreased perfusion to poorly ventilated regions involved by constrictive bronchiolitis) that is seen by high-resolution computed tomography (CT) in some cases of bronchiolitis.[1]

ANATOMIC CONSIDERATIONS

"Small airways" are those airways less than 2 or 3 mm in diameter.[1,4,6] This definition includes small bronchi, as well as bronchioles. Bronchioles usually are 1 mm in diameter or smaller. Respiratory bronchioles have alveoli in their walls, communicate directly with alveolar ducts, and are in the range of 0.5 mm (500 μm) or smaller in diameter.[6,7]

Histologically, from the lumen to the adventitia, bronchioles have a lining mucosa (including Clara, ciliated, and basal cells), a basement membrane region, a thin lamina propria, an elastic tissue membrane, a layer of smooth muscle, and an adventitial connective tissue layer that is attached to the surrounding alveolar and perivascular interstitium.[6]

Lymphoid tissue usually is not present in the normal adult lung. In chronic inflammatory conditions, however, lymphoid follicles along small airways form part of the mucosa-associated lymphoid tissue reaction. When germinal centers are present, the term "follicular bronchiolitis" is appropriate.[4] The epithelium overlying lymphoid follicles represents specialized "lymphoepithelium."

Direct communications occur between bronchioles and surrounding alveoli (Lambert's canals), and it is through these canals that bronchiolar epithelium may grow in the healing of bronchiolitis.[6] This has been called lambertosis, bronchiolarization of alveoli, and peribronchiolar metaplasia.

PATHOLOGIC CLASSIFICATION OF BRONCHIOLITIS

Pathologic changes in the bronchioles are tied to the clinical circumstances with which they are associated, and any discussion of these conditions requires clinicopathologic correlation.[8] In certain cases, a given pathologic finding is unique (or nearly so) to a specific condition, such as respiratory bronchiolitis (RB) in cigarette smokers. In most cases, however, pathologic changes in the bronchioles are associated with many conditions, and ascribing etiology and pathogenesis cannot be determined solely on the basis of the histologic features. As mentioned above, pathologic changes in the small airways are frequent in cases with primary pathology in the bronchi, such as cystic fibrosis, chronic bronchitis, and bronchiectasis; these conditions are conventionally classified by the bronchial changes and not included as part of primary bronchiolar pathology. The spectrum of bronchiolar pathology is shown in the Table.

SPECTRUM OF BRONCHIOLAR PATHOLOGY*

Asthmatic-type changes
Chronic bronchitis/emphysema–associated bronchiolar changes
Cellular bronchiolitis (acute, chronic, with or without fibrosis)
Subtypes: follicular bronchiolitis, diffuse panbronchiolitis
Respiratory bronchiolitis
Bronchiolitis obliterans with intraluminal polyps (synonym bronchiolitis obliterans)
Constrictive bronchiolitis (synonym bronchiolitis obliterans)
Mineral dust–associated airway disease
Peribronchiolar fibrosis and bronchiolar metaplasia

*Modified from Epler.[8]

Each group in the Table includes a spectrum of changes, and at the ends of the spectrum there is overlap among the groups; for example, cellular infiltrates involving bronchioles (cellular bronchiolitis) are seen in patients with asthma and chronic bronchitis or emphysema, and mucostasis is found in patients with asthma and chronic bronchitis or emphysema and in the airways of those with constrictive bronchiolitis. There also may be evolution from one group to another: Cellular bronchiolitis may be associated with, or show progression to, bronchiolitis obliterans with intraluminal polyps or constrictive bronchiolitis. The pathologic overlap and evolution from one condition to another, shown in the Table, reflects the complex interplay of inflammatory events affecting the bronchioles.

Asthma

The histologic changes of asthma are well described[8–10]: mucus stasis and plugging, bronchiolar epithelial sloughing, luminal and mural eosinophils, luminal eosinophil debris, submucosal edema, smooth muscle hypertrophy, goblet cell hyperplasia, bronchial gland hypertrophy, and hyaline thickening of the basement membrane region. Lymphocytes,

plasma cells, and neutrophils also are part of the cellular infiltrate. The net result of all these changes is luminal narrowing and airflow obstruction. The changes are most prominent in small bronchi, but bronchioles also are affected.

Between asthmatic attacks, the above changes may be muted or lacking.[8,11] Some patients with chronic asthma have bronchiolar and peribronchiolar scarring (constrictive bronchiolitis; see below), as well as bronchiectasis.

Bronchiolar Changes Associated With Chronic Obstructive Pulmonary Disease

The functional changes associated with chronic bronchitis and emphysema (chronic obstructive pulmonary disease [COPD]) are better known than the morphologic changes in the small airways.[8–12] The term "small airways disease" has been used for the functional changes ascribed to the lesions of the small bronchi and bronchioles in this setting. The morphologic changes in the bronchioles of patients with COPD can be grouped as follows[8]:

Inflammatory changes—This results in chronic inflammatory cells in the walls of bronchioles (cellular bronchiolitis); these changes also overlap with RB.

Smooth muscle hypertrophy—This affects bronchiolar smooth muscle.

Fibrotic narrowing and associated changes—Fibrosis of the bronchiolar wall may be quite subtle; it is partly responsible for the luminal changes and functional deficits.

Luminal changes—Small airways in patients with COPD frequently show mucus stasis and luminal distortion. They may be ectatic or narrowed; these changes overlap with constrictive bronchiolitis (see below).

Loss of radial attachments—This also causes luminal narrowing and partly explains why bronchioles may collapse during expiration.

Cellular Bronchiolitis

Cellular bronchiolitis is used as a morphologic descriptor: inflammatory infiltrates of bronchioles (luminal, mural, or both). This term is useful in settings in which an etiologic diagnosis cannot be ascribed.[8,11] Other modifiers often are helpful: acute or chronic, depending on the cell type present; necrotizing; and follicular, if there is germinal center hyperplasia (Fig 1). Mural or peribronchiolar fibrosis is common in patients with cellular bronchiolitis, particularly in patients with chronic disease, such as bronchiolitis associated with bronchiectasis, and in those with constrictive bronchiolitis.

Conditions featuring a cellular bronchiolitis are many and varied (Figs 1–3). Most are considered airway diseases; some are considered interstitial. These conditions include the following: bacterial bronchopneumonia, viral infections, *Mycoplasma pneumoniae* pneumonia, fume or toxic exposures, transplant-associated airway injury (lymphocytic bronchiolitis, graft-*vs*-host disease), bronchiectasis (regardless of cause), connective tissue diseases (especially Sjögren's disease and rheumatoid arthritis), inflammatory bowel disease, extrinsic allergic alveolitis, RB (see below), aspiration, diffuse panbronchiolitis, disease distal to an obstructing lesion, asthma, COPD, Wegener's granulomatosis (rare), bronchiolocentric granulomatosis, and distal to any obstructing lesion.

Bronchiolar necrosis may be seen in suppurative bacterial infections, as well as in viral bronchiolitis, particularly that caused by herpes simplex or adenovirus. Bronchiolar mucosal necrosis also may be seen in acute fume or toxic exposures. In bronchocentric granulomatosis, the bronchiole is destroyed, and the wall is replaced by a palisaded histiocytic reaction; most patients have allergic bronchopulmonary aspergillosis. In Wegener's granulomatosis, bronchiolar necrosis may be seen to arise as collections of giant

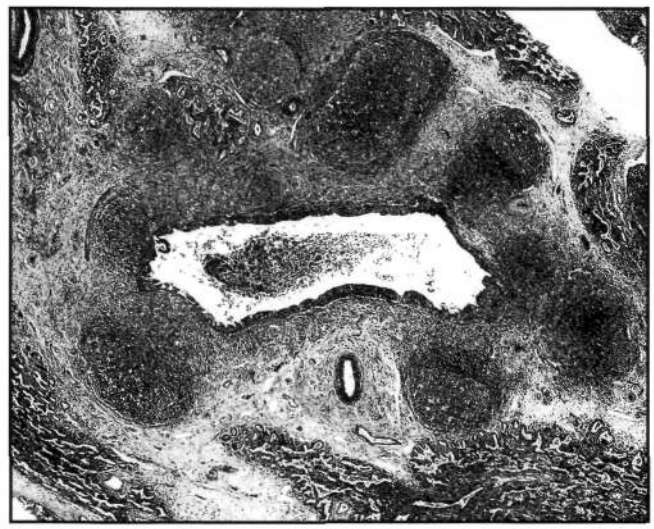

FIG 1. Follicular bronchiolitis from a child, aged 2 years. Germinal centers are seen in the wall of a bronchiole, the lumen of which contains acute inflammatory cells (hematoxylin-eosin).

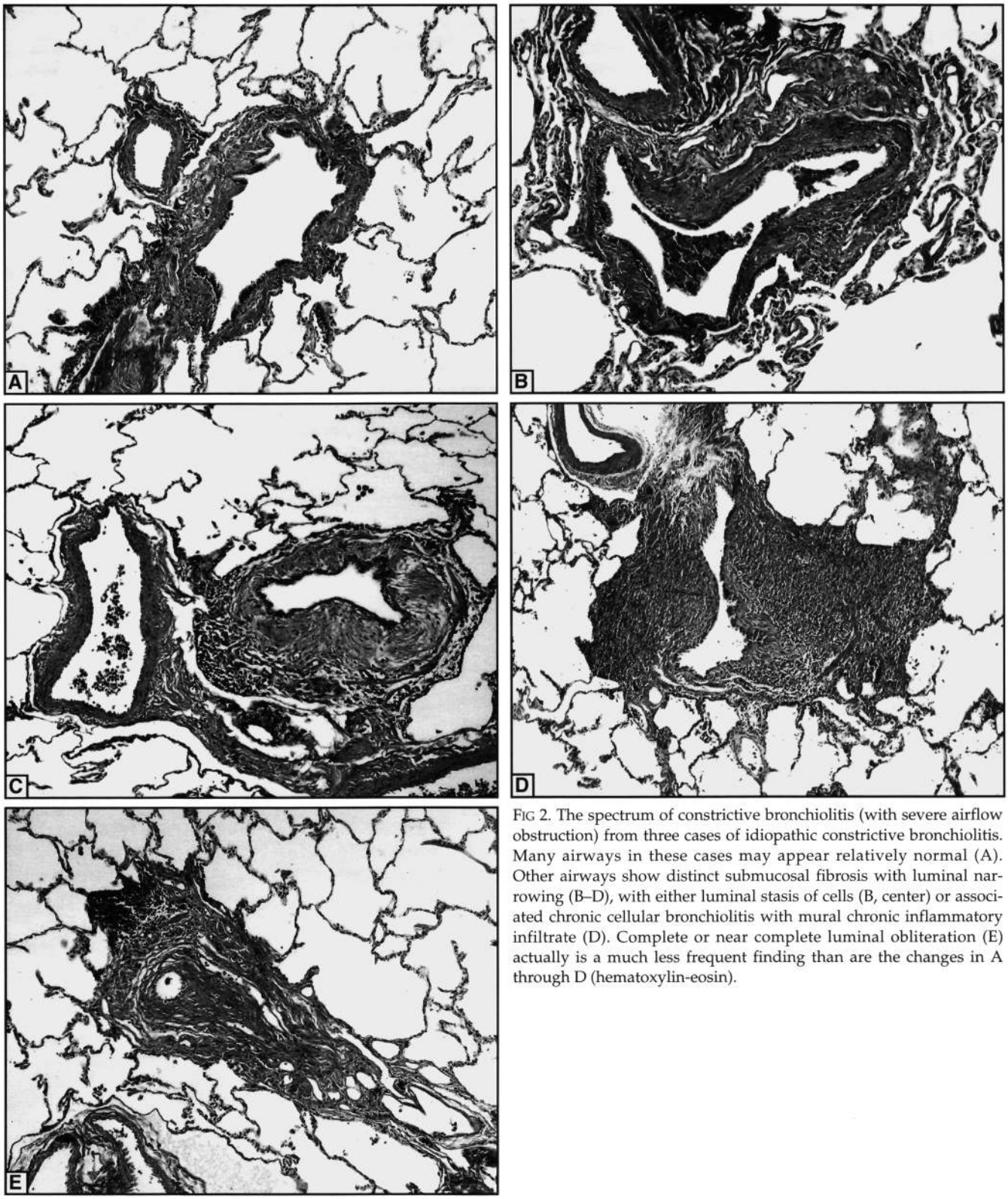

FIG 2. The spectrum of constrictive bronchiolitis (with severe airflow obstruction) from three cases of idiopathic constrictive bronchiolitis. Many airways in these cases may appear relatively normal (A). Other airways show distinct submucosal fibrosis with luminal narrowing (B–D), with either luminal stasis of cells (B, center) or associated chronic cellular bronchiolitis with mural chronic inflammatory infiltrate (D). Complete or near complete luminal obliteration (E) actually is a much less frequent finding than are the changes in A through D (hematoxylin-eosin).

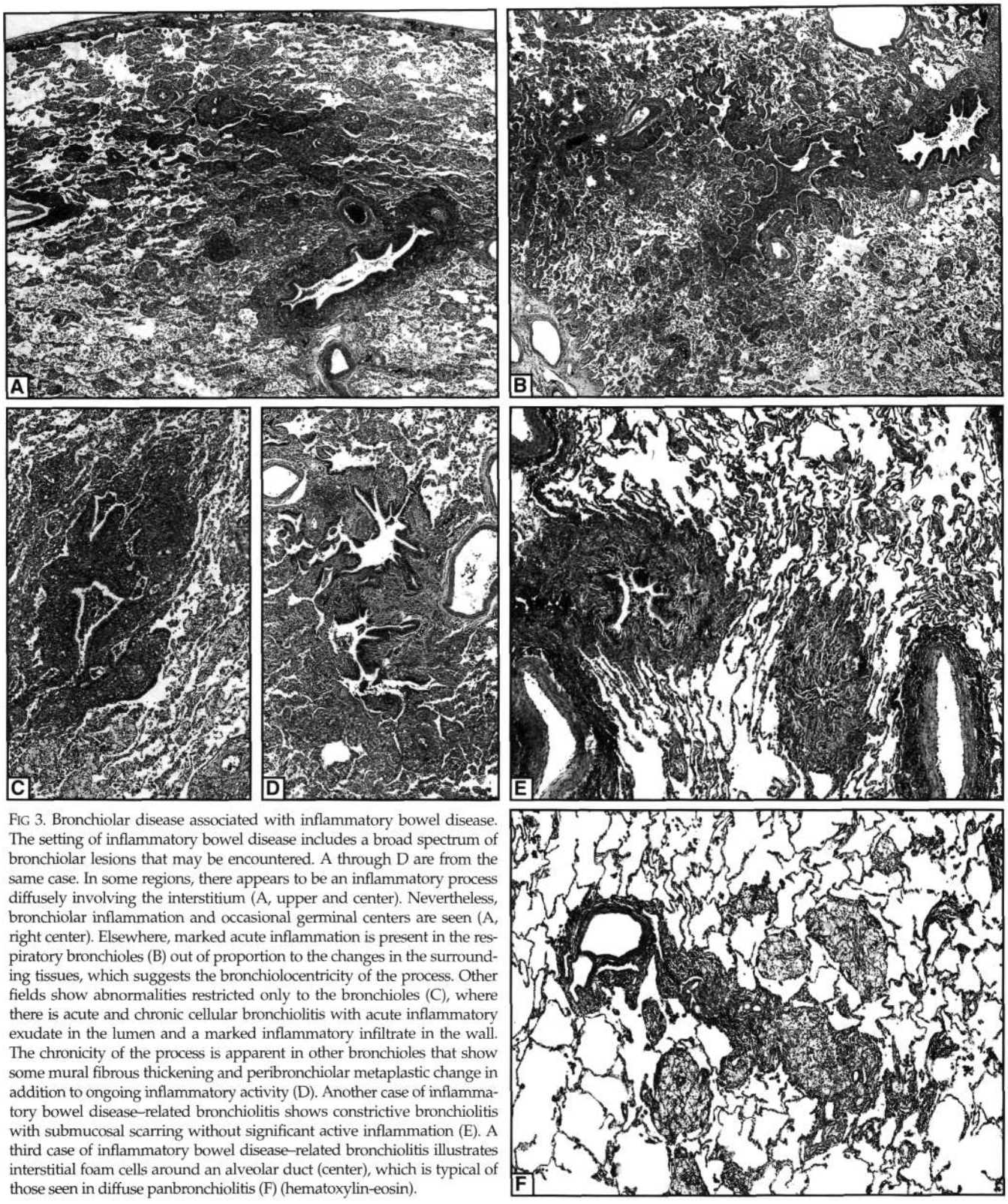

FIG 3. Bronchiolar disease associated with inflammatory bowel disease. The setting of inflammatory bowel disease includes a broad spectrum of bronchiolar lesions that may be encountered. A through D are from the same case. In some regions, there appears to be an inflammatory process diffusely involving the interstitium (A, upper and center). Nevertheless, bronchiolar inflammation and occasional germinal centers are seen (A, right center). Elsewhere, marked acute inflammation is present in the respiratory bronchioles (B) out of proportion to the changes in the surrounding tissues, which suggests the bronchiolocentricity of the process. Other fields show abnormalities restricted only to the bronchioles (C), where there is acute and chronic cellular bronchiolitis with acute inflammatory exudate in the lumen and a marked inflammatory infiltrate in the wall. The chronicity of the process is apparent in other bronchioles that show some mural fibrous thickening and peribronchiolar metaplastic change in addition to ongoing inflammatory activity (D). Another case of inflammatory bowel disease–related bronchiolitis shows constrictive bronchiolitis with submucosal scarring without significant active inflammation (E). A third case of inflammatory bowel disease–related bronchiolitis illustrates interstitial foam cells around an alveolar duct (center), which is typical of those seen in diffuse panbronchiolitis (F) (hematoxylin-eosin).

cells and neutrophil microabscesses in the bronchiolar submucosa. Diffuse panbronchiolitis is a cellular bronchiolitis with a predilection for the respiratory bronchioles; interstitial accumulations of foamy macrophages are the most distinctive feature of diffuse panbronchiolitis.

Respiratory Bronchiolitis

Respiratory bronchiolitis (RB) was described by Niewoehner et al[13] as an incidental autopsy finding primarily in young male smokers. This disorder now is recognized as extremely common in cigarette smokers, and the term "smokers' bronchiolitis" is descriptively appropriate.

Respiratory bronchiolitis primarily affects respiratory bronchioles, but inflammatory changes also may be seen in terminal bronchioles. Mild chronic inflammation is found in the wall of the respiratory bronchioles, associated with slight fibrosis, smooth muscle hypertrophy, and thickening of the adjacent alveolar walls, which also may show mild chronic inflammation. The most characteristic feature of RB is the accumulation of tan-brown macrophages in the lumens of respiratory bronchioles and the adjacent alveoli. The alveolar macrophages stain positively with digested periodic acid-Schiff (PASd) and iron stains. They typically contain dark flecks of dark particulate material.

Respiratory bronchiolitis most commonly is seen as an incidental finding in lobectomy specimens for carcinoma and as an incidental finding in lung tissue from smokers. It rarely may be sufficiently extensive in its involvement of lung tissue to cause mild interstitial lung disease, or RB-associated interstitial lung disease .[11,14,15]

Respiratory bronchiolitis–associated interstitial lung disease is a mild interstitial lung disease seen in cigarette smokers, most of whom are aged 25 to 55 years (7–75 pack/y). Symptoms include cough and sputum production; two thirds of patients have crackles on auscultation. Chest radiographs show reticulonodular infiltrates; approximately 20% have normal chest radiographs. High-resolution CT scans show patchy ground glass or vague nodular densities.

Respiratory bronchiolitis–associated interstitial lung disease is thought to be an exaggeration of the RB reaction, sufficient to cause clinical disease. The treatment is smoking cessation; the lesion appears either to stabilize or to resolve slowly and does not show progression to fibrotic lung disease.

Desquamative interstitial pneumonia, in theory, should be a diffuse uniform process, and RB-associated interstitial lung disease a lesion that is restricted to the regions around respiratory bronchioles. Although the distinction is straightforward conceptually, considerable overlap does exist.[15]

Bronchiolitis Obliterans

Bronchiolitis obliterans has been the one term describing bronchiolar pathology that has been associated with the most confusion.[11,12,16–18] This is because this term has been used to describe a clinical syndrome, as well as two subsets of histologic findings herein described as bronchiolitis obliterans with intraluminal polyps and constrictive bronchiolitis.[11,12,16]

Clinically speaking, bronchiolitis obliterans refers to a syndrome of chronic airflow obstruction with radiographic hyperinflation caused by pathologic changes in the small airways.[16] Pathologically, bronchiolitis obliterans has been used to refer to two groups of lesions,[16] and it was thought that the two might be temporally related, ie, one leads to the other. These two groups show little clinical overlap, however, and rarely are temporally related histologically; rather, they represent two clinicopathologic groups.

Bronchiolitis obliterans with intraluminal polyps—Bronchiolitis obliterans with intraluminal polyps is a common reparative reaction that occurs in a number of settings. It usually is associated with patchy organizing pneumonia in the more distal lung tissue; the two terms are combined in the name "bronchiolitis obliterans organizing pneumonia" (BOOP).

Bronchiolitis obliterans with intraluminal polyps histologically shows polypoid endobronchial connective tissue masses composed of myxoid fibroblastic tissue (resembling granulation tissue); central clusters of mononuclear inflammatory cells may be found in them. The polyps appear to float freely within a bronchiole or be only focally attached to the wall. The fibroblastic proliferation is continuous with a similar process in the more distal airspaces: the organizing pneumonia. The adjacent alveolar walls show a mild chronic inflammatory infiltrate with reactive type II cells. Foamy macrophages often are increased in the alveoli. This constellation of findings can be called the BOOP pattern.

A BOOP pattern may be a component of other pathologic changes and, as such, may be seen in many conditions, such as with Wegener's granulomatosis, around neoplasms, or in the wall of abscesses. A BOOP pattern also may be the only histologic change present. In either setting, many conditions are included in the differential diagnosis, and only a minority of cases showing a BOOP pattern represent

the idiopathic syndrome (idiopathic BOOP) described by Epler et al[17] and Davison et al[19] as cryptogenic organizing pneumonitis (COP). Settings in which a BOOP pattern may be encountered include the following: organizing diffuse alveolar damage (more diffuse than patchy); organizing infections, eg, viral, mycoplasma, bacterial, fungal, pneumocystic, and those associated with chronic bronchitis, bronchiectasis, and cystic fibrosis; organizing pneumonia distal to obstruction; organizing aspiration pneumonia; drug, fume, or toxic exposure (organizing phase); connective tissue diseases; extrinsic allergic alveolitis; eosinophilic pneumonia; secondary reaction associated with diffuse panbronchiolitis; idiopathic BOOP/COP; and as part of a localized process (focal organizing pneumonia) or associated with other lesions, such as tumors or abscesses.

Idiopathic BOOP/COP is the best known member in this group (Fig 4), and it is the lesion for which the term *BOOP* was coined. Idiopathic BOOP has been put near the bottom of the list to emphasize that many conditions may show a BOOP pattern; therefore, idiopathic BOOP should be considered a diagnosis of exclusion.[16,18]

Constrictive bronchiolitis—This is a much less common pattern than a BOOP pattern. Complete luminal obliteration in constrictive bronchiolitis is relatively uncommon when compared with the wide spectrum of less than completely obliterative changes, which may be very subtle. Constrictive bronchiolitis usually is a pure lesion of the bronchioles, with few changes in the distal parenchyma (ie, organizing pneumonia usually is lacking). Constrictive bronchiolitis refers to luminal narrowing by scarring rather than to smooth muscle contraction.

The histologic features of constrictive bronchiolitis include a broad spectrum, from very subtle abnormalities to complete luminal obliteration. There is mural thickening of the bronchioles caused by submucosal collagenization. Progressive concentric narrowing is associated with distortion of the lumen, mucostasis, and chronic inflammation (cellular bronchiolitis). Bronchiolectasis with mucus stasis also may be seen, as may bronchiolar smooth muscle hypertrophy. Subtle changes can be best appreciated with an elastic tissue stain, which highlights the submucosal scarring. Adventitial scarring may be a finding in some cases of constrictive bronchiolitis.

Constrictive bronchiolitis is the usual histologic finding in patients with the clinical syndrome of bronchiolitis obliterans. Sometimes the term "obliterative bronchiolitis" is used for this group. Conditions in which constrictive bronchiolitis may be seen include the following: healed infections (especially viral and mycoplasma), healed toxin or fume exposure; chronic bronchitis or emphysema, cystic fibrosis, and bronchiectasis; connective tissue disease; bone marrow or heart-lung transplantation; inflammatory bowel disease; drug reactions, eg, penicillamine, *Sauropus androgynus*[20];

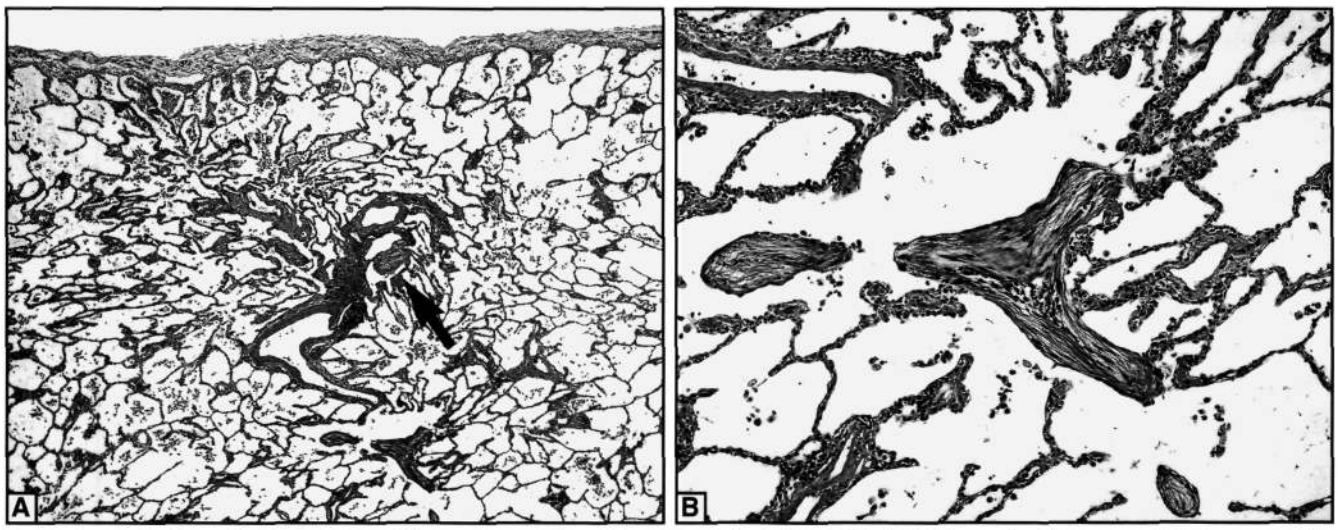

FIG 4. A case of idiopathic bronchiolitis obliterans organizing pneumonia (idiopathic BOOP/COP) is used to illustrate a BOOP pattern. The lung architecture is maintained in this well-inflated biopsy specimen with the pleura at the top (A). Airspace organization is seen within bronchioles (arrow), as well as in alveolar ducts immediately below where branched intraluminal polypoid lesions composed of spindled fibroblastic cells are seen (A, lower center; B, center). Airspace organization in the BOOP pattern typically is much more prominent in alveolar ducts than in bronchioles (hematoxylin-eosin).

bronchiolar neuroendocrine cell hyperplasia; healed bronchopulmonary dysplasia; aspiration; idiopathic.

Although many of the causes of a BOOP pattern are similar to those of constrictive bronchiolitis, one rarely can document the former evolving into the latter, re-emphasizing the fact that they represent separate and distinct clinicopathologic groups as they present to the surgical pathologist.

Dust-Associated Bronchiolar Pathology

Inhalation of dusts may result in their deposition around small airways, with some associated fibrosis, or mineral dust airways disease.[11,12,15] Respiratory bronchioles and alveolar ducts primarily are affected with increased fibrous tissue associated with the dust. Chronic inflammation usually is minimal. A number of dusts have been implicated: asbestos, iron oxide, aluminum oxide, silica, silicate, and coal. Mineral dust airways disease is more akin to a pneumoconiosis than to bronchiolitis.

Peribronchiolar Fibrosis and Bronchiolar Metaplasia

There is a group of poorly understood cases that are associated with bronchiolar and peribronchiolar scarring and metaplastic changes (Fig 5): distorted bronchioles with thickened walls, smooth muscle hypertrophy, mild chronic inflammation, and metaplastic bronchiolar epithelium extending onto adjacent fibrotic alveolar walls (bronchiolarization).[11] There may be a history of a prior inflammatory event (eg, viral bronchiolitis or extrinsic allergic alveolitis), and some cases are associated with bronchiectasis. Clinically and radiographically, these cases often manifest as interstitial lung disease, which may be misinterpreted histologically as idiopathic pulmonary fibrosis.

The fact that fibrotic changes primarily involving the small airways produce evidence of restrictive or infiltrative lung disease is not surprising. Sufficient scarring and inflammation along the bronchovascular bundles can result in decreased compliance ("stiff lung") as well as radiographic evidence of infiltrates.

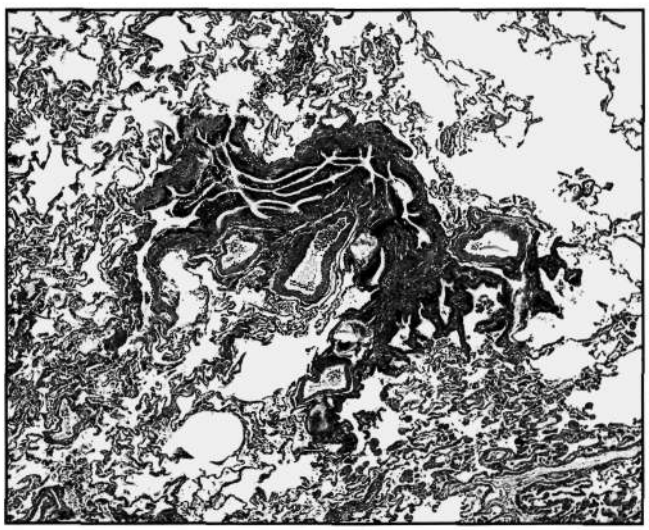

FIG 5. Bronchiolar fibrosis and peribronchiolar fibrosis and metaplasia. This patient had clinical and functional evidence of interstitial lung disease. The biopsy specimen shows a bronchiolocentric inflammatory lesion with bronchiolar and peribronchiolar scarring with associated metaplastic bronchiolar epithelium (center). This is presumably the result of a prior inflammatory process, but no specific diagnosis could be made (hematoxylin-eosin).

WHAT TO KEEP IN MIND

Know whether there is a localized or a diffuse process. For bronchiolar lesions associated with a localized process, think particularly of bronchiectasis and middle lobe syndrome (which may involve the right middle lobe and/or the lingula).

Are the bronchiolar lesions seen in the main lesion? Incidental airway changes in a smoker can be quite prominent.

Mild vascular thickening, raising the possibility of pulmonary hypertension, is particularly common in cases of chronic bronchiolitis.

Bronchiolitis may be associated with sufficient changes in the peribronchiolar lung parenchyma that the bronchiolocentricity of the process may be obscured.

Cases of chronic cellular bronchiolitis (regardless of cause) may be associated with an acute or organizing pneumonia, probably on the basis of secondary recurrent infections analogous to those complicating bronchiectasis.

If granulomas are present in a case of bronchiectasis, consider the possibility of atypical mycobacterial infection superimposed on underlying airway pathology; this may be seen in middle lobe syndrome and other cases of bronchiectasis. Bronchocentric granulomatosis should not be considered unless there is a necrotizing lesion involving bronchiolar walls.

Bronchiolar lesions may be very subtle in patients with airflow obstruction, even those with profound functional abnormalities. Bronchiolar lesions should be sought in the patient with lung disease who has a "normal" biopsy specimen.

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