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REVIEW ARTICLE

Helmut H. Popper

Bronchiolitis, an update

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Abstract Besides the classical forms of acute and chronic bronchiolitis, different special forms, such as obliterative, respiratory, and follicular bronchiolitis are recognized. In addition, even new entities emerge, such as Sauropus-induced bronchiolitis. Despite this progress in pathology, pulmonologists still prefer the diagnostic term 'small airways disease', instead of the more specific and even etiology-directed diagnoses provided by the morphologic examination. In this overview, an updated classification will be presented, which includes all forms of bronchiolitis described so far. This classification is structured along morphologic features of bronchiolitis. Different forms of acute and chronic bronchiolitis are described, so that a given reaction pattern can be associated with specific causes, such as eosinophilic bronchiolitis in asthma, or necrotizing bronchiolitis in viral infection. However, there exist more than just one morphologic reaction for a given etiologic agent, resulting in an overlap of morphologic appearances for a given disease.

Keywords Bronchiolitis · Acute · Chronic · COPD bronchiolitis · Granulomatous · Obliterative · Constrictive · Respiratory · Follicular · Panbronchiolitis · BOOP · Respiratory bronchiolitis-ILD

Introduction

In the past, not much emphasis was attributed to the categorization of bronchiolitis by clinicians and pathologists. With the invention of high-resolution computed tomography and more sophisticated lung function tests, the classification of bronchiolitis has regained interest [15, 17, 51, 55]. However, a few special forms of bronchiolitis have always been recognized, such as bronchiolitis obliterans (BO) and respiratory bronchiolitis (RB) [10, 11, 13, 39]. The past decade has seen a reemerging interest in bronchiolitis in connection with interstitial lung disease and, since then, many different forms have been described [8, 37, 38]. Recently, a new form of bronchiolitis has been reported [6].

Helmut H. Popper (✉)
Institute of Pathology,
Lab. Environmental and Respiratory Pathology,
University of Graz, Medical School, Auenbruggerplatz 25,
Graz, A-8036, Austria
e-mail: popper@email.kfunigraz.ac.at
Tel.: +43-316-3804405

The anatomy

Bronchioles are characterized by a specialized bronchiolar epithelium, usually three to five layers of cells, a thin muscular coat, the absence of cartilage and glands, and a diameter of less than 1 mm [36]. These are usually airways of the 16th generation and higher. Bronchial and bronchiolar branching in primates and humans, in contrast to many other mammalians, is asymmetrical. In the next generation of bronchioles, the bronchiolar diameter is divided into two-thirds and one-third (Fig. 1a), whereas in other mammalians, bronchioles are divided symmetrically into two equally sized next generation bronchioles (Fig. 1b). This asymmetrical branching has major implication for airflow and particle impaction.

In humans and primates, airflow is not linear at the bifurcations, but induces turbulences. This in consequence causes particle impaction predominantly at these bifurcations. Therefore, impaction of foreign particulate matter (mean aerodynamic diameter >5 μm) in humans occur primarily at these bifurcations, and subsequent inflammation is most pronounced at the same site, unlike the situation in many laboratory animals.

As in the bronchi, cellular elements of bronchioles have secretary columnar, goblet, reserve, and basal cells (Fig. 2a, b), but ciliated cells are fewer and are becoming scarce in the respiratory bronchioles. Also, neuroendocrine cells are fewer in number than in the bronchi. In addition, there is a special epithelial cell, the Clara cell, which in humans and some other mammalians are exclusively seen in the bronchioles (Fig. 2c). This is in contrast to some mammalians, such as cats, where Clara

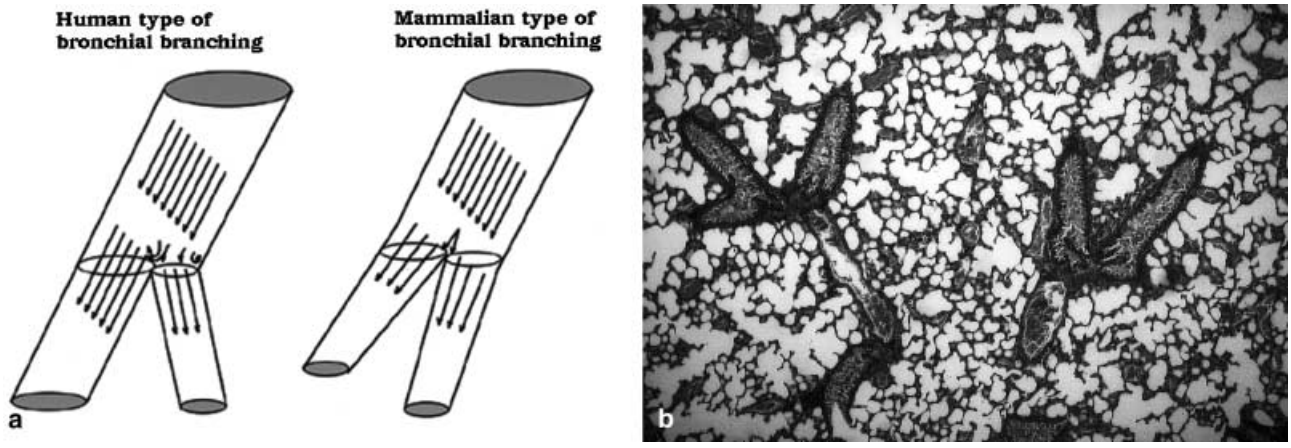

Fig. 1 **a** Schema showing the branching pattern of bronchioles in humans and most other mammalians. Note the different size of the bronchiolar diameters in two next generation bronchioles and the resulting consequences of air flow: turbulences at bifurcations in asymmetrical branching and a more laminar flow in dichotomous branching. This results in differences in particle impaction. **b** Micrograph of the dichotomous bronchial and bronchiolar branching pattern in a mole lung. Hematoxylin and eosin; original magnification ×60

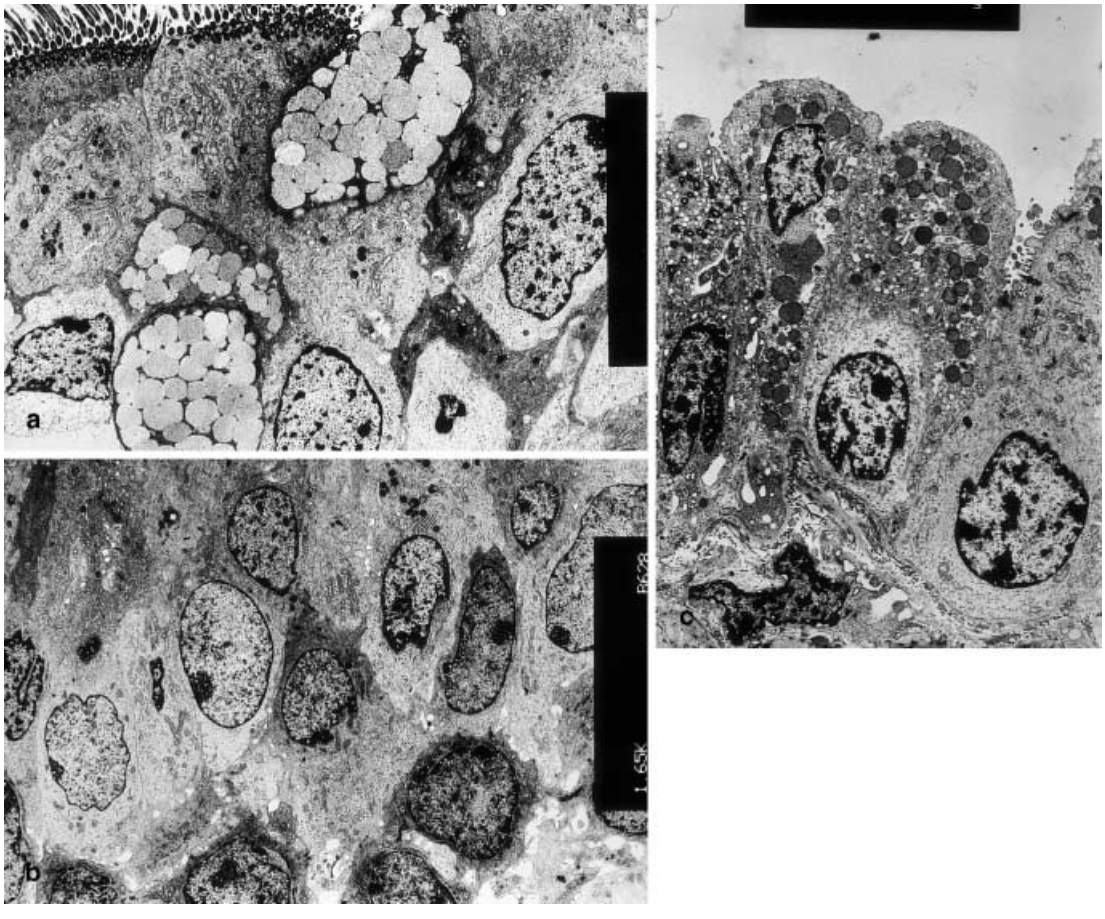

Fig. 2 Electron micrograph of a bronchiolar epithelium, original magnification ×3100. **a** Ciliated and goblet cells in a case of chronic bronchiolitis are shown. **b** Reserve and basal cells; the basal cells are often triangular in shape and have a darker cytoplasm, whereas reserve cells are less stained, have an irregular cell border, and possess more cytoplasmic organelles. **c** Clara and secretory columnar cells; Clara cells are characterized by their large apical situated electron-dense granules and their dome shaped apical cytoplasm; secretory columnar cells look similar to ciliated cells but, instead of cilia, possess small microvilli (*right side*)

cells can be found even in the trachea. The relative distribution of stromal cells, including fibrocytes, myocytes, endothelial cells and pericytes, resting macrophages, and antigen-presenting cells (dendritic, Langerhans) is similar to that found in the bronchi.

Aggregates of lymphoid cells or lymph follicles are not normally present in humans but, for example, are present in some wild living rodents, such as rats and rabbits. Homeostasis of cells and bronchiolar structure is maintained through cell communication facilitated by adhesion molecules and extracellular matrix proteins and by cell cycle mechanisms [3, 30]. This can change dramatically in inflammatory conditions, where cells up- and downregulate adhesion molecules to facilitate leukocyte movement, regeneration, etc. [18, 29, 46, 53, 54]. Some of these adhesion molecules are selectively expressed in certain inflammatory conditions, and others seem to be associated with selective docking of infectious organisms [4, 19, 21, 23, 26, 31, 46].

Respirotropic viruses, for example, preferentially dock to ciliated and Clara cells, whereas bacteria preferentially dock to ciliated and secretary columnar cells [26, 31, 32, 46]. Inorganic toxic substances show an order of susceptibility of ciliated > Clara > secretory cells [43, 53]. Therefore, if early stages of the inflammatory process are carefully examined, one can tell viral infection apart from bacterial infection and infection from toxic injury by analyzing the main targeted cells, the reaction of the cells and, very importantly, the types of leukocytes entering the inflammatory focus, i.e., lymphocytes in early viral and macrophages and neutrophils in early bacterial infection. Also, endogenous noxes can be separated in early stages, because those toxins enter the lungs via the blood stream and exert their primary effects on endothelial cells and the extracellular matrix before side effects on the epithelium start to happen [33]. Well-known examples are pancreatitis and sepsis or experimentally lipopolysaccharide (LPS)-induced lung injury. Due to their location and function being interspersed between bronchi and alveoli, respectively, bronchiolitis rarely is an isolated disease. Most often, it is associated with either pneumonia or with bronchitis. However, a few specific bronchiolitides do exist, not associated with alveolar or proximal airway disease.

How to interpret architectural and cellular patterns in bronchiolitis and relate it to etiology

The reaction pattern of bronchiolitis can, with some certainty, be attributed to groups of causing agents. For example, particulate matter between 200 µm and 5 µm of aerodynamic diameter will primarily cause bronchitis and bronchiolitis but rarely inflammation in the alveolar region. Gases, aerosols, or particulate matter <5 µm will easily pass the larger airways, causing either no or only mild inflammatory reactions, whereas the major inflammatory reaction will be seen in the bronchioles and the alveoli [43, 44]. Viral infection in an otherwise immunocompetent patient will present as a lymphocytic inflammation in the bronchi, bronchioles, and alveoli, whereas bacteria early on causes a granulocytic inflammatory response. Epithelial damage can aid to our knowledge: respirotropic viruses show a preferential docking to ciliated, secretory columnar, Clara cells, and pneumocytes. Later on, viruses very often induce a reactive cell proliferation with virus-associated changes of nuclei and inclusion bodies. Acid gases or nebulized acids (at higher concentration) cause cell death of all epithelial cells in bronchioles and alveoli (Fig. 3). In addition, these acidic compounds characteristically cause constriction of smooth muscle cells [43]. Endogenous noxes primarily act on endothelial cells and cause interstitial edema and leakage of capillaries. At later stages, hypoxia, as a consequence, act on the epithelial compartment and, by the end, different types of lesions coalesce into an undifferentiated inflammatory interstitial pneumonia and bronchiolitis.

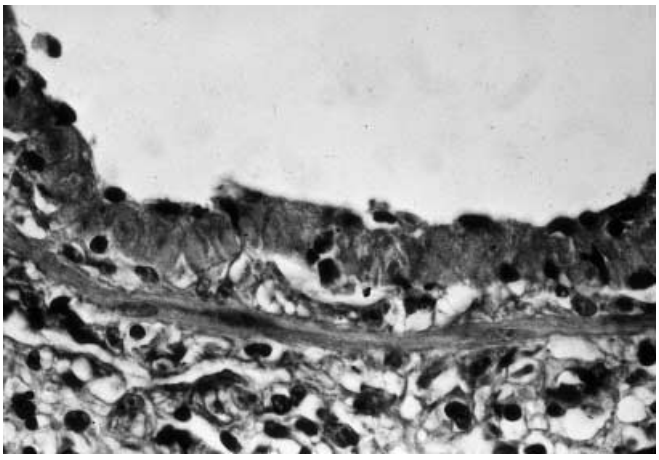

Fig. 3 Necrosis of bronchiolar epithelium in experimental gastric juice aspiration syndrome (Mendelsson syndrome); hematoxylin and eosin; original magnification ×250

The classification

At present, we best classify bronchiolitis into

1. Acute bronchiolitis
2. Chronic bronchiolitis
3. Chronic obstructive pulmonary disease (COPD)-associated bronchiolitis
4. Distinct forms of bronchiolitis

Acute bronchiolitis

The term cellular bronchiolitis is sometimes used. However, chronic bronchiolitis can also be cellular, Therefore, this term will not be used throughout this review. If no specific inflammatory pattern is recognized, an acute bronchiolitis NOS (not otherwise specified) can be diag-

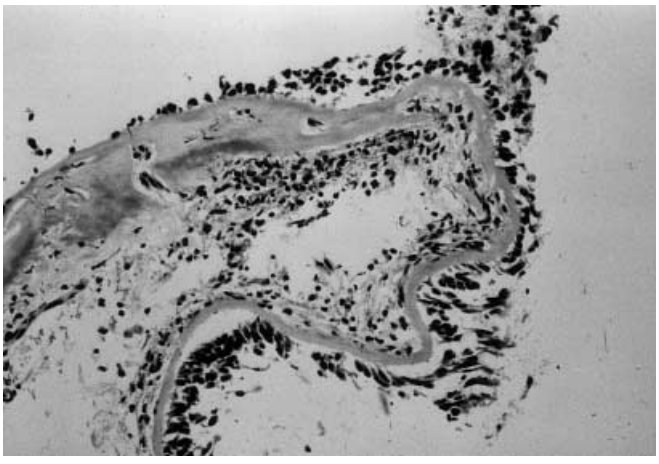

Fig. 4 Eosinophilic bronchitis and bronchiolitis in atopic asthma. Note prominent epithelial shedding and hyalinization of the basal lamina; hematoxylin and eosin; original magnification ×160

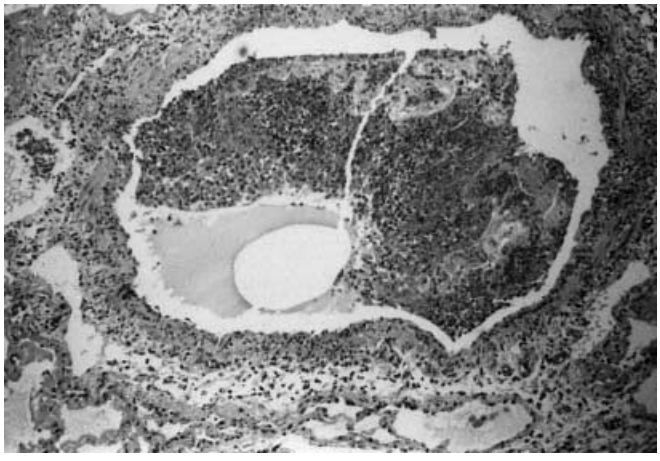

Fig. 5 Acute necrotizing bronchiolitis in influenza A infection; hematoxylin and eosin; original magnification ×60

nosed. This is characterized by a dense granulocytic and/or lymphocytic infiltrate within the epithelium, the subepithelial, and the muscular layers. The epithelium can show different degrees of degenerative and reactive changes, but there should be no metaplasia or hyperplasia. Usually, the lumen is filled with a mixture of granulocytes and cellular debris. Acute bronchiolitis can be caused by a variety of infectious organisms, such as respirotropic viruses, bacteria, and inhaled toxic substances. Within this group, specific entities can be separated:

1. Eosinophilic or asthmatic bronchiolitis
2. Pseudomembranous and necrotizing bronchiolitis
3. Granulomatous bronchiolitis

Eosinophilic or asthmatic bronchiolitis

Eosinophilic or asthmatic bronchiolitis is characterized by a mixed infiltration of eosinophils, mast cells, plasma cells, and lymphocytes within the bronchiolar wall. The most characteristic feature is numerous eosinophils, which can be highlighted with a Congo red stain, picking up the basic cytotoxic proteins of eosinophilic granules. With this stain, even degranulation and extracellular granules can be seen. Other diagnostic features of asthma bronchiolitis are mucus plugs in the lumen containing cellular debris, eosinophils, Curshman spirales, and Charcot Leyden crystals, a prominent thickening and even hyalinization of the basal lamina, and a shedding of the columnar cells (Fig. 4). Immunohistochemically, there is an upregulation of vascular cell adhesion molecule (VCAM)-1 on the endothelial cells of small blood vessels and a disease-specific upregulation of very late activation antigen (VLA) 4 and intercellular adhesion molecule (ICAM)-3 on lymphocytes and eosinophils [42]. The shedding of columnar cells might be due to a loss of intercellular adhesion molecules, such as VLA 1, 2, 3, 5, and 6 and an upregulation of ICAM-1 on these cells, by which they lose contact, especially to the triangular-shaped basal cells [42]. The muscular coat can either show hyperplasia or atrophy, probably related to the duration of the disease.

Acute necrotizing and pseudomembranous bronchiolitis

Acute necrotizing and pseudomembranous bronchiolitis are characterized by necrosis of the epithelial layer with or without disruption of the basal lamina. Cellular infiltrates may be predominantly neutrophils or lymphocytes or a mixture of both. The cellular composition reflects, most often, the specific response to the causing agent, such as lymphocytic infiltration, early on in viral infection. The necrotic debris is mixed with fibrin leaking out from the capillaries beneath the basal lamina. In the case of pseudomembranous bronchiolitis, this fibrin, together with debris, forms the pseudomembrane on the bronchiolar surface. There are certain organisms, such as influenza, parainfluenza, and herpes viruses, which can cause this condition [5]. A classical example of pseudomembranous bronchiolitis caused by a bacterium is *Bordetella pertussis* bronchiolitis.

Pseudomembranous bronchiolitis can progress into BO with complete or incomplete occlusion of the bronchiolar lumen. The same kind of viruses can also cause necrotizing bronchiolitis. These viruses probably belong to more virulent strains (Fig. 5). At higher than ambient air concentrations, necrotizing bronchiolitis can be caused by some inhaled toxins, such as SO_x, NO_x, and O_3 [1, 50]. Some acidic aerosols can cause this bronchiolitis. This is the case in Mendelson's syndrome, where hydrochloric acid together with pepsin are the actors [43]. Due to the fact that the basal lamina is destroyed or at least interrupted, this kind of bronchiolitis will never heal 'ad integrum' and can progress into BO-organizing pneumonia (BOOP) [43].

Granulomatous bronchiolitis/bronchitis

Granulomatous bronchiolitis/bronchitis is a condition often seen in sarcoidosis and tuberculosis. However, other kinds of granulomatoses should be kept in mind [40]. Granulomatous bronchiolitis may show the classic sarcoid granuloma with or without necrosis or a mixture of sarcoid and pallisading histiocytic granulomas. In the first case, tuberculosis, mycobacteriosis, or sarcoidosis are the major differential diagnoses to be considered [40]. In rare cases, occupational exposure to beryllium or zirconium oxides may mimic sarcoidosis. If mixtures of histiocytic and epithelioid cell granulomas together with infiltrating granulocytes are seen, a diagnosis of broncho- and bronchiolocentric granulomatosis can be made. If there is substantial eosinophilic infiltration, an allergic bronchopulmonary mycosis [aspergillosis, allergic bronchopulmonary aspergillosis (ABPA)] might be the underlying disease. However, parasitic infection must be ruled out [40]. If a neutrophilic infiltration predominates, bacterial infection is the most likely cause, very often mycobacterial infection. If there is a pure histiocytic granulomatous bronchiolitis, rare infectious diseases and occupational lung disease have to be considered [38]. Granulomatous leprosy very rarely involves the lungs. More often, *Mycobacteria avium* and other slow growing mycobacteria in the setting of immunocompromized patients might induce a pure histiocytic granulomatous bronchiolitis. Other rare examples of infectious histiocytic granulomatous bronchiolitis are involvement of the lung in Whipples disease and infections with *Listeria monocytogenes*.

Histiocytic granulomatous bronchiolitis is seen in occupational lung disease [7]. It can be found in silicosis, silicatosis, coal workers pneumoconiosis, and in asbestosis. However, granulomas are usually an early lesion, more related to exposure, and not encountered or obscured in full-blown disease. In most instances, the etiologic diagnosis can be made easily by means of polarized microscopy or by the evidence of asbestos bodies.

Pallisading histiocytic granulomatous bronchiolitis can rarely be seen in autoimmune disorders. Especially rheumatoid arthritis with lung involvement can show this reaction pattern, whereas most other collagen vascular diseases do not induce granuloma formation [14].

Chronic bronchiolitis

Chronic bronchiolitis can be defined by a predominant lymphoplasmocytic infiltrate, a goblet cell, and a smooth muscle hyperplasia [49]. Goblet cell hyperplasia is defined by a change of the ciliated to goblet cell ratio in favor of goblet cells (normal 6–8:1). Since there is an individual variation of this ratio in humans, a clear cut off point is a ratio of 4:1. Muscle cell hyperplasia is not always present. In long-standing chronic bronchiolitis, and in some special forms (concentric bronchiolitis), the muscle layer may be replaced by fibrous tissue. Other features seen sometimes in chronic bronchiolitis but more often in bronchitis are nodular thickening of nerves and fibrosis of the basal lamina. The later one never reaches that extent seen in asthma bronchiolitis. Eosinophils may be present in chronic bronchiolitis, especially in bronchiolectasis. However, they do not stain with VLA 4 and ICAM-3 antibodies, as is the case in asthma [42].

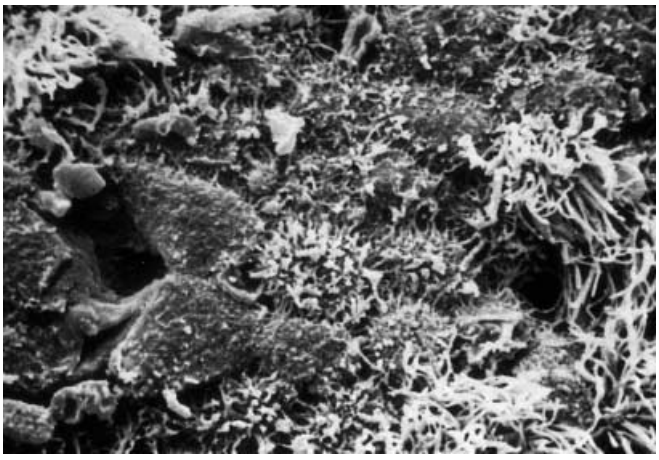

Fig. 6 Chronic bronchitis/bronchiolitis in immotile cilia syndrome; scanning electron micrograph showing loss of cilia and disorientation of remaining cilia; original magnification ×1600

In the etiology of chronic bronchiolitis, the same causes as in acute forms are encountered. These include infections with respirotropic viruses, bacteria, fungi, allergic reactions, autoimmune diseases, graft versus host disease (GVHD), inhalation of toxic substances, and airborne dust. Over all, in the majority of patients, chronic bronchiolitis is induced by continuous tobacco smoke inhalation [16]. In some cases a causative agent cannot be identified and therefore the etiology remains unknown (clinically referred to as cryptogenic bronchiolitis).

In young-aged patients with recurrent bronchitis/bronchiolitis and combined rhinosinusitis, an immotile cilia syndrome (ICS) might be suspected. This disease is characterized by a partial or total loss of the inner and/or outer dynein arms of the cilia axonemata [2]. This results in uncoordinated cilia beats and, subsequently, loss of ciliated cells due to recurrent infection (Fig. 6). One of the clearance mechanisms of the lung, the mucus escalator system, does not function properly. There may be inflammation-related features, such as giant cilia, loss of one layer of cilia membranes, loss of spikes, and axonemata [41].

Chronic bronchiolitis combined with COPD

Chronic bronchiolitis combined with COPD should be defined by a combination of pathologic and clinical features [49]. In my own experience, these cases cannot be distinguished from chronic bronchiolitis. However, in some cases, an open-lung biopsy specimen can be as-

sessed (due to pneumothorax or volume reduction surgery) and many bronchiolectases and a centrolobular emphysema can be evaluated and graded. If there is chronic bronchiolitis with narrowed and/or ectatic bronchioli and a centrolobular emphysema, the pathologist's report may suggest COPD, which then should be confirmed by clinical assessment, including lung function studies.

Special variants of bronchiolitis

All these variants either arise from an acute bronchiolitis or have a distinctive acute phase. Our knowledge, why and how these variants develop, is still limited. Some of these forms have a narrow spectrum of etiologic causes, such as RB, whereas others are seen in a variety of infectious and non-infectious conditions, such as BOOP. However, they all have in common some unique features, by which they can be differentiated from ordinary bronchiolitis and, due to their special etiologic background, must be sorted out. These different variants have to be considered:

1. BO
2. BO combined organizing pneumonia
3. Constrictive bronchiolitis (CB)
4. RB
5. RB combined interstitial lung disease
6. Follicular bronchiolitis
7. Diffuse panbronchiolitis

It might be considered to include histiocytosis X, which is also in this spectrum of bronchiolitis, because bronchioles are also involved. However, since histiocytosis X does involve bronchi and, in the majority of cases alveolar tissues, I have excluded this entity. In addition, a reactive from a tumor-like form has to be separated in histiocytosis X (Langerhans' cell granulomatosis).

Bronchiolitis obliterans

BO can arise from some forms of acute bronchiolitis, such as necrotizing bronchiolitis or starts as a focal necrosis of the epithelial layer and submucosal tissue, with disruption of the basal lamina. This defect is subsequently organized by an inflammatory granulation tissue, growing into the bronchial lumen like an inflammatory polyp. The cellular infiltrates are composed of macrophages, lymphocytes, fibroblasts, and myofibroblasts. The granulation tissue can either completely occlude the bronchiolar lumen or leave a narrow slit-like space. When the granulation tissue matures, more matrix proteins are deposited, and fewer inflammatory cells are seen. There may be an epithelial regeneration overgrowing the polyp. The endstage is partial or complete obliteration of the lumen. From a functional aspect, airflow is impaired in either case. The etiologic background in BO includes chronic rejection of lung and lung/heart transplants [57], graft versus host reaction in bone marrow transplants, collagen vascular diseases (lung involvement in rheumatoid arthritis or polymyositis) [48, 52], and idiopathic BO.

Bronchiolitis obliterans-organizing pneumonia

BOOP is characterized by BO as described above and, in addition, by inflammatory granulation tissue within alveoli. As in the bronchioles, OP can be preceded by alveolar cell damage, including disruption of the basal lamina. However, there are also cases where this granulation tissue extends along terminal bronchioles and alveolar ducts into alveoli, and no primary defect can be seen in the alveolar wall (Fig. 7). From a functional standpoint, this organizing alveolar process results in gas exchange and diffusion abnormalities. BOOP is a classical reaction pattern of non-resolved acute bronchiolitis combined with interstitial or alveolar pneumonia. For a long time, it was known in the German pathologic literature as 'carnification', although it should be mentioned that other types of interstitial pneumonia were also included in that entity.

A wide variety of diseases can progress along a BOOP morphology: non-resolved infectious diseases, either viral, bacterial, fungal, or parasitic. Other causes are inhaled toxic gases, such as SO_x and NO_x [12, 25] and gastric juice aspiration syndrome (Mendelson disease) which, in the organizing phase, may progress into BOOP [43]. In most of these cases, focal remnants of the acute phase can persist, i.e., a necrotizing bronchiolitis combined with an acute interstitial pneumonia and diffuse alveolar damage in viral infection. This preceding viral infection might also be suspected, because of virus-induced proliferations of type II pneumocytes and bronchiolar epithelial cells which can persist for some time. This can be proven using immunohistochemical or in situ hybridization analysis [12, 25]. Autoimmune diseases, such as rheumatoid arthritis, polymyositis, and systemic lupus

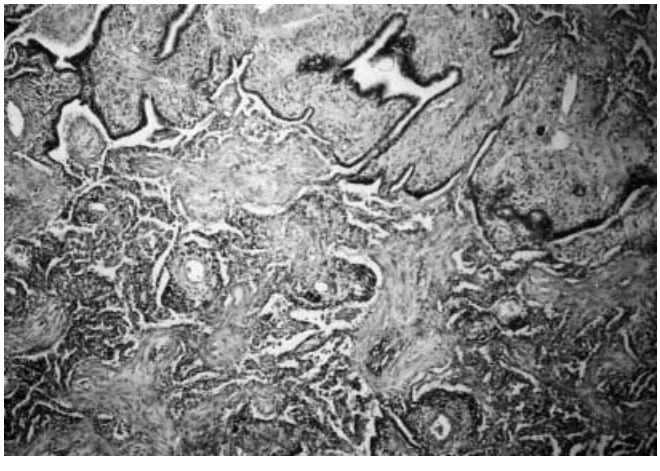

Fig. 7 Bronchiolitis obliterans-organizing pneumonia. Granulation tissue is replacing most of the bronchioles and also the alveoli; hematoxylin and eosin; original magnification ×40

erythematodes very often affect lungs by a BOOP pattern. In rare cases, Wegener's granulomatosis can present with a BOOP morphology [45, 56]. In addition, hemophagocytic syndrome, either acquired or inborn, in late stages shows a BOOP morphology [59].

A wide variety of drugs can induce BOOP. Among them are many cytotoxic drugs, such as cyclophosphamide, mitomycin, metothrexate, chlorozotocin, and bleomycin. Noncytotoxic drugs, such as gold salts, sulfasalazine, penicillamine, amiodarone, tocainide, hexamethonium, phenitoin, and 'street drugs', such as cocaine, can also induce BOOP [35]. Having excluded all of these causes, there remains idiopathic BOOP, which clinically behaves less aggressive and responds better to corticosteroid treatment than the above secondary forms of BOOP [9].

Constrictive bronchiolitis

CB is a recently reinvented entity; in the old German pathologic literature, it was called fibrosing bronchiolitis. It involves preferentially membranous bronchioles and is characterized by a lymphoplasmocytic infiltrate within the bronchiolar wall, mural thickening, and fibrosis of the stroma, narrowing the lumen in a concentric fashion. The muscle layer may be hypertrophic in early lesions but atrophic in late stages, and finally is replaced by fibrotic tissue (Fig. 8). This is in contrast to BO, where remnants of the muscular layer are usually found even in late stages of the disease. In the lumen, there is considerable mucostasis. In end stages, the bronchiolar lumen might be completely occluded.

The early stage of CB is not well defined. We have seen few cases at an early stage; there is a dense neutrophilic infiltration in the mucosa increasing towards the muscular layer, but surprisingly, the epithelium is spared. Only mild degenerative changes are found in the epithelium, and very few neutrophils are found in the lumen, but a dense infiltration is found in the subepithelial and muscular layers. There is a muscular destruction (Fig. 9). CB has been described in cases of chronic rejection of lung and heart–lung transplants, GVHD in bone marrow recipients, in collagen vascular diseases, mainly rheumatoid arthritis, and in drug reactions (gold salts) [8]. However, we still have to await further reports, before coming up with an established list of possible causes of CB. In addition, the pathogenesis of this form of bronchiolitis awaits further clarification.

Recently, cases of Sauropsus androgynus juice-induced bronchiolitis, which closely mimic CB, were reported [6]. Bronchiolitis starts with myxoid degeneration

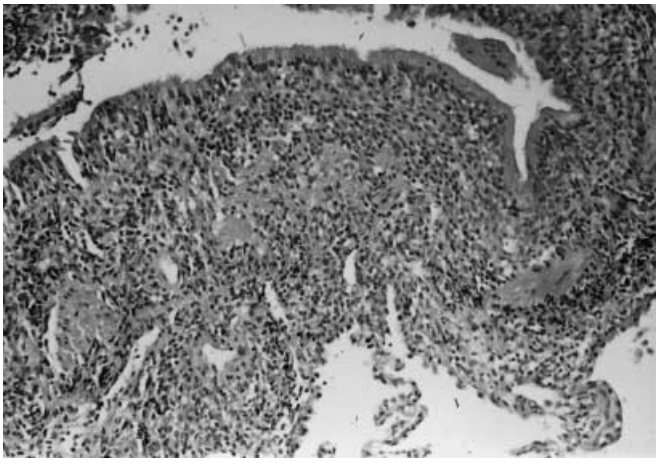

Fig. 9 Early constrictive bronchiolitis. The mucosa is heavily infiltrated by neutrophils. However, the epithelium is not destroyed and is much less infiltrated than the deeper layers of the mucosa. Note the dense infiltration and destruction of the smooth muscles; hematoxylin and eosin; original magnification ×140

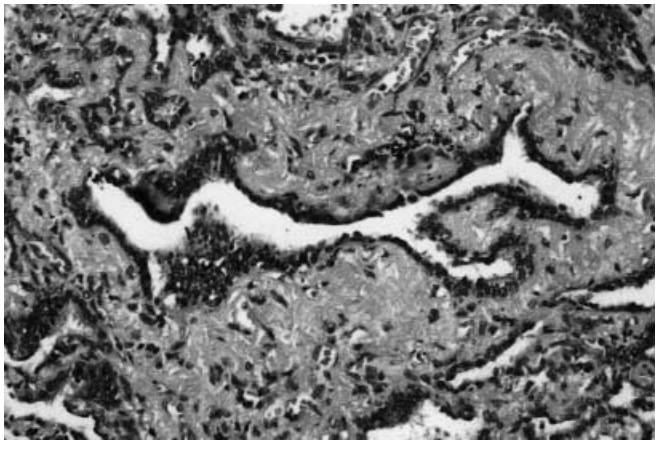

Fig. 8 Constrictive bronchiolitis. Note the loss of the muscular coat, which is replaced by fibrotic tissue. There is also a narrowing of the bronchiolar lumen; hematoxylin and eosin; original magnification ×200

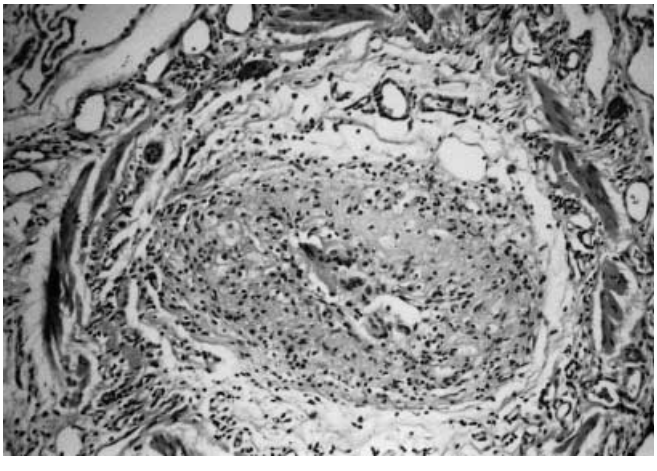

Fig. 10 Eccentric destructive bronchiolitis due to Sauropsus consumation; in this later stage, the bronchiolar epithelium but not the smooth muscles is replaced by a myxoid granulation tissue with scattered foreign body giant cells; hematoxylin and eosin; original magnification ×80

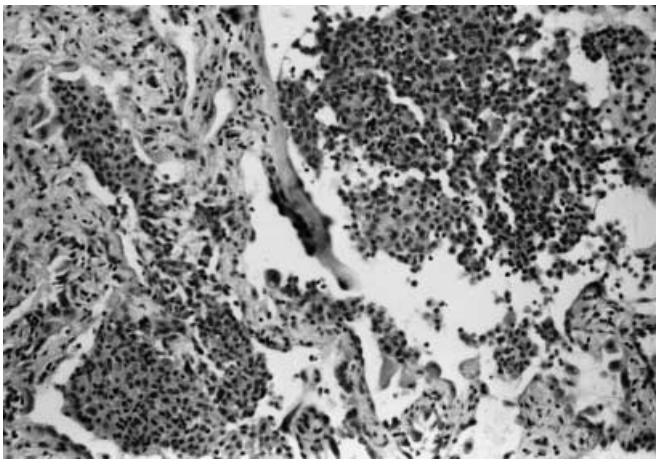

Fig. 11 Respiratory bronchiolitis in a young male heavy smoker; the lumima of the two respiratory bronchioles (*bottom left, upper right corner*) are completely filled with pigment-laden macrophages; hematoxylin and eosin; original magnification ×160

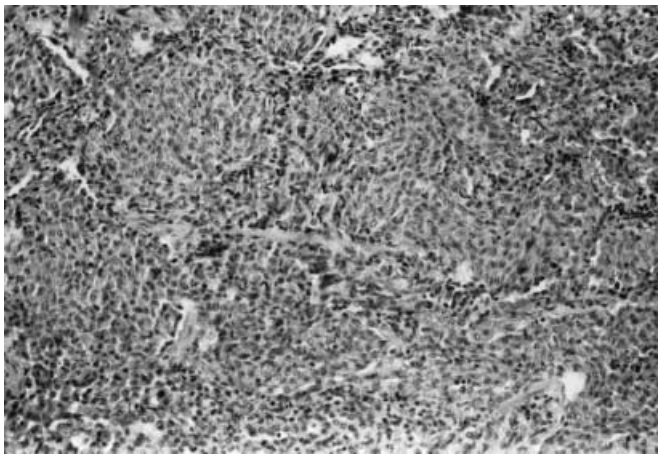

Fig. 12 Respiratory bronchiolitis-combined interstitial lung disease (desquamative interstitial pneumonia). Shown is the intraalveolar infiltration by macrophages, completely obscuring the alveolar lumina; hematoxylin and eosin; original magnification ×160

of matrix proteins, followed by a mixed infiltrate of eosinophils, histiocytes/macrophages and foam cells, occasional histiocytic giant cells, and few lymphocytes. This is followed by epithelial necrosis. The bronchioles are then replaced by granulation tissue and finally by a scar (Fig. 10). In contrast to concentric bronchiolitis, the muscular coat is retained in this form even in the occlusive stage. Bronchiolar lumen obstruction starts in an eccentric fashion. Therefore, eccentric destructive bronchiolitis would be an appropriate name for it. A similar process can be seen in larger bronchi and in blood vessel walls [6]. The mechanism by which the ingredients of Sauropsus juice interfere with the metabolism of matrix proteins is completely unclear. However, given the cellular infiltrate, a combined allergic/toxic reaction might be anticipated.

Respiratory bronchiolitis

RB is characterized by a predominantly intraluminal infiltration of pigment-laden macrophages at the bronchiolo–alveolar border with extension into the central alveolar region (Fig. 11). There is no necrosis of the epithelial layer, but there is an infiltration of the mucosa by histiocytes, macrophages, and few lymphocytes. Mild degenerative and reactive changes of epithelial cells can be seen. The pigment in alveolar macrophages is finely granular, and of light olive to yellow color. By means of electron microscopy, thin needles can be found within the macrophages. It is well established that this pigment represents metabolites and waste from tobacco smoke-related compounds. RB is usually found in smokers less than 35 years of age [38]. In some cases, the lymphocytic infiltrate may increase, forming lymph follicles with activated germinal centers, which then points to an additional chronic allergic reaction for some of the tobacco products.

RB-interstitial lung disease

Closely related to RB is RB-interstitial lung disease or RB with desquamative interstitial pneumonia (RB-ILD or RB-DIP), which has all the features of RB plus a DIP (Fig. 12). These infiltrates in the alveoli are entirely formed by alveolar macrophages and, as in RB, also contain tobacco smoke-related pigments. As in RB, RB-ILD is seen in young-aged heavy smokers [34, 38]. As yet, it is possible but not clear that RB is just the early stage and will progress into RB-ILD if smoking is not stopped. Heavy smokers were seen some decades before when RB and RB-ILD were considered rare diseases. Therefore, both entities might, in our experience, be related to the earlier onset of smoking, which was not seen in the 1940s to 1960s but was quite common in the 1980s to the 1990s up to our present time. In RB and RB-ILD, patients might be treated with corticosteroids, which can reduce inflammation, However, the only effective treatment is smoking cessation.

Follicular bronchiolitis

Follicular bronchiolitis is characterized by a hyperplasia of lymphoid tissue along the airways (including the large bronchi) and by the development of follicles and follicular centers. The lymphocytes are polyclonal upon immunohistochemical analysis. The follicles usually obstruct the bronchiolar lumen and, when this happens, secondary infection and peribronchiolar pneumonia may result (Fig. 13 and Fig. 14). It should be pointed out that in follicular bronchitis/bronchiolitis, no other component of the other special bronchiolitis variants is allowed, whereas the reverse might happen in other variants; follicular bronchiolitis can be present in the other forms of bronchiolitis without altering the diagnostic label [58].

Fig. 13 Follicular bronchiolitis. The distribution pattern can be seen at this low magnification; hematoxylin and eosin; original magnification ×10

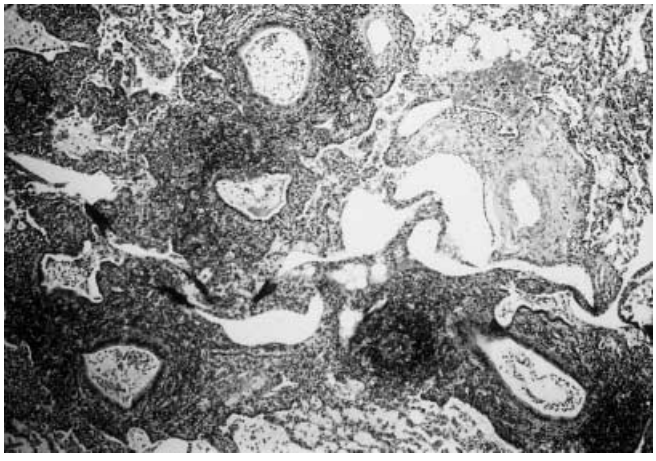

Fig. 14 Follicular bronchiolitis at a higher magnification shows lymphollicle formation one with germinal center around bronchioles; hematoxylin and eosin; original magnification ×80

Follicular bronchiolitis as an entity is seen in recurrent viral infections, in different types of immunodeficiency syndromes, and in collagen vascular diseases [20, 52]. Follicular bronchiolitis, together with lymphocytic interstitial pneumonia and epitheloid cell granulomas, is part of the morphologic reaction spectrum of extrinsic allergic alveolitis. This is important to know when one is dealing with bronchial biopsies. If follicular bronchiolitis is also encountered, the differential diagnosis of bronchial-associated lymphoid tissue (BALT) lymphoma should come into ones mind. Differentiation is facilitated by the presence of lymphoepithelial lesions and monoclonality of lymphocytes found in BALT lymphoma.

In childhood, the etiologic background of follicular bronchiolitis is of prognostic importance. In cases of recurrent viral infections, the prognosis is usually a good one. If maintained under good anti-infectious prevention, the children grow older, the immune system matures, and they develop normally. In cases of an inborn or acquired immunodeficiency, the prognosis is worse and, in idiopathic follicular bronchiolitis, the prognosis is even worse [27, 28]. In these cases, usually no therapy can stop the process and most children die within a few years from the onset of the disease.

Diffuse panbronchiolitis

Diffuse panbronchiolitis is confined to the respiratory bronchioles and shows scattered irregular lesions in both lungs. The bronchioles are infiltrated by lymphocytes, plasma cells, and monocytes/macrophages with abundant foam cell formation. Bacteria can usually be identified within the macrophages. Follicular hyperplasia and follicular bronchiolitis are regularly seen in diffuse panbronchiolitis. Healing occurs by the formation of intrabronchial granulation tissue, similar to early BO. The disease predominantly occurs in patients of Asian descent with an impaired immune reaction, associated with human leukocyte antigen (HLA)-BW54 or other HLA genes residing on chromosome 6 [22, 47]. A bacterial infection can usually be found in these patients. However, these most probably represent an epiphenomenon and not the cause of the disease. It seems that these patients are unable to completely clear their lungs from this bacterial burden and therefore develop a persisting chronic infectious bronchiolitis [24].

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