Review

Bronchiolitis Obliterans

Talmadge E. King, Jr.

National Jewish Center for Immunology and Respiratory Medicine, Denver, Colorado, USA

Abstract. Bronchiolitis obliterans in the adult patient is a relatively uncommon and vexing clinical entity. This confusion results because this pathologic finding occurs in a variety of diverse clinical settings. Bronchiolitis obliterans is a fibrotic process that primarily affects the small conducting airways. The lesion results from damage to the bronchiolar epithelium and the repair process leads to excessive proliferation of granulation tissue. The alveoli adjacent to the small airway are almost always involved; however, a considerable portion of the interstitium is usually spared. The findings in these patients may physiologically and radiographically mimic chronic obstructive pulmonary disease (COPD). On the other hand, some of the processes associated with bronchiolitis obliterans result in restrictive or mixed restrictive and obstructive ventilatory defects; consequently, they may be confused with other diffuse infiltrative lung disorders. This review will focus principally on bronchiolitis obliterans in adults, which, until recently, was considered rare. There has been heightened interest in this process in adults because of its association with the connective tissue diseases, its development following toxic fume exposure, its occurrence as a result of chronic graft versus host reactions, and the increasing recognition of patients with idiopathic forms of the disease that have an insidious onset often confused with more common problems such as COPD or idiopathic pulmonary fibrosis.

Key words: Bronchiolitis obliterans—Inhalation, toxic fumes—Bronchiolitis—Pneumonia, organizing—Connective tissue disease.

* Address offprint requests to Talmadge E. King, Jr., M.D., National Jewish Center for Immunology and Respiratory Medicine, 1400 Jackson Street, Denver, CO 80206, USA
Introduction

Bronchiolitis in the adult patient is a relatively uncommon and vexing clinical entity [67]. This confusion results because this pathologic finding occurs in a variety of diverse clinical settings. Furthermore, inflammatory processes involving the "small airways" may initially go "unnoticed" in the adult because the resistance of the peripheral airways falls considerably after approximately age 5 and thus leaves the small airways of the adult relatively silent, physiologically and symptomatically [57]. As the disease progresses and becomes clinically evident, many of the findings in these patients may physiologically and radiographically mimic chronic obstructive pulmonary disease. On the other hand, some of the processes associated with bronchiolitis result in restrictive or mixed restrictive/obstructive ventilatory defects and may be confused with other diffuse infiltrative lung disorders. In addition, different terms have been applied to these diseases, based mainly on the pathologic descriptions: bronchiolitis obliterans, bronchiolitis, bronchiolitis obliterans with organizing pneumonia, bronchiolitis fibrosa obliterans, bronchiolitis and diffuse interstitial pneumonia, follicular bronchitis/bronchiolitis, and small airway disease.

This review will focus principally on bronchiolitis obliterans in adults, which, until recently, was considered rare (Table I). There has been heightened interest in this process in adults because of its association with the connective tissue diseases, its development following toxic fume exposure, its occurrence as a result of chronic graft versus host reactions, and the increasing recognition of patients with idiopathic forms of the disease.

Bronchiolitis obliterans of known etiology

Bronchiolitis obliterans is a fibrotic lung disease that primarily affects the small conducting airways, often sparing a considerable portion of the interstitium. The lesion results from damage to the bronchiolar epithelium and the repair process leads to excessive proliferation of granulation tissue. The alveoli adjacent to the small airways are almost always involved [33]. Until recently there have been only case reports describing this lesion in various clinical settings. Consequently, any uncertainties regarding the epidemiology, pathophysiology, long-term sequelae, and therapy of bronchiolitis obliterans exist.

Toxic Fume Inhalation

Toxic fume exposure, especially to "nitrous fume," may cause acute respiratory failure as a result of pulmonary edema and the development of the adult respiratory distress syndrome (ARDS), leading in some cases to death (either acutely or after a 4–6 h latent period). It is now recognized that toxic fume exposures are a significant industrial and environmental hazard occurring in a number of settings, for example, among agricultural workers (silo filler's dis
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Table 1. Clinical classification of bronchiolitis obliterans

| Bronchiolitis obliterans of known etiology               |
|---------------------------------------------------------|
| Toxic fume inhalation                                   |
| Postinfectious bronchiolitis obliterans                 |
| Diffuse lesions                                         |
| Localized lesions                                       |
| Mineral dust exposure                                   |

| Bronchiolitis obliterans of unknown etiology             |
|---------------------------------------------------------|
| Bronchiolitis obliterans and organizing pneumonia        |
| Associated with connective tissue disease                |
| De novo process                                         |
| Drug reaction                                           |
| Associated with organ transplantation                    |
| Associated with other diseases                          |
| Idiopathic pulmonary fibrosis                            |
| Hypersensitivity pneumonitis                             |
| Malignant histiocytosis                                  |
| Chronic eosinophilic pneumonia                           |
| Panbronchiolitis                                         |
| Respiratory bronchiolitis                               |

ease), chemical workers, munition and missile industries, gold and coal mining, and arc welding in confined spaces [60, 98] (Table 2).

Three clinical patterns may follow exposure to these toxic gases in those who survive the initial insult [59, 85, 97, 99, 126]. First, after mild exposure individuals may develop any of several findings: cough, dyspnea, fatigue, cyanosis, vomiting, hemoptysis, arterial hypoxemia, vertigo, somnolence, headache, emotional difficulties, and loss of consciousness. These usually resolve in hours but may persist for several weeks before complete recovery. Second, at higher concentrations of exposure, pulmonary edema frequently occurs. These patients may have mild or no symptoms at the time of exposure, only to develop a clinical picture of severe ARDS several hours later (3–30 h). Recovery is usual but death may occur at this stage. Finally, after recovery or in patients who had no initial illness following exposure, there may be a recurrence or onset of illness a few weeks later (2–6 weeks). This phase is characterized by the onset of a nonproductive cough, dyspnea, and an irreversible obstructive ventilatory defect (i.e. bronchiolitis obliterans) [25, 35, 85].

The roentgenographic pattern of bronchiolitis obliterans is variable. Most commonly a miliary or discretely nodular pattern occurs and is considered characteristic of this type of bronchiolitis obliterans [25, 59, 85, 91] (Fig. 1). Occasionally, only pulmonary hyperinflation is seen on chest x-ray. Rarely, the chest film may be normal [87, 133]. Histologically, the picture is of a pure bronchiolitis obliterans without organizing pneumonia or alveolar wall inflammation. The extent of the airway damage and functional impairment is related to the type and amount of fume inhalation.

Treatment of the late fibrotic stage of bronchiolitis obliterans may not be
helpful. Therefore, early recognition and treatment of these patients are important. Persons exposed acutely should be observed in the hospital for 48 hs, followed by weekly or biweekly evaluations for 6–8 weeks. Treatment with corticosteroids has been demonstrated to be useful in the management of both the acute phase (i.e., pulmonary edema) and the late phase illness (i.e., bronchiolitis obliterans) [59, 64, 85, 121]. Once instituted, therapy should be continued for a minimum of 8 weeks, since relapses have been reported with the premature cessation of therapy [64, 121]. Treatment may be required for several months to years. Bronchodilators are occasionallly helpful and probably should be given a trial in all symptomatic patients.

In general, the prognosis for survivors (one-third die acutely) of toxic fume inhalation is quite good [101]. Those who subsequently develop bronchiolitis obliterans may be permanently disabled and experience progressive disease and death over several months.

### Table 2. Setting of exposure to toxic gases, fumes, and mists associated with bronchiolitis obliterans

| Nitrogen dioxide ("nitrous fumes") |
|-----------------------------------|
| Spillage of nitric acid, component of jet and missile fuel; metal pickling; silo gas; chemical manufacturing; explosive, dyes, lacquers, celluloid; detonation of explosives; electric arc or acetylene gas welding; contamination of anesthetic gases (nitrous oxide gas cylinder); nitrocellulose combustion; tobacco smoke; astronauts, firemen, or others exposed to burning materials |

| Sulfur dioxide |
|----------------|
| Burning of sulfur-containing fossil fuels; bleaching of wool, straw, and wood pulp; sugar refining and fruit preserving; fungicide; refrigerant; ore smelting; acid production |

| Ammonia |
|---------|
| Fertilizer, refrigerator, explosives production |

| Chlorine |
|---------|
| Bleaching, disinfectant, plastic making |

| Phosgene |
|---------|
| Chemical industry, dye and insecticide making |

| Chloropicrin |
|-------------|
| Trichloroethylene |

| Ozone |
|-------|
| Arc welding, air, sewage, and water treatment |

| Cadmium oxide |
|--------------|
| Ore: smelting, alloying, welding |

| Methyl sulfate |
|---------------|
| Hydrogen sulfide |
| Natural gas making, paper pulp, sewage treatment, tannery work |

| Hydrogen fluoride |
|------------------|
| Etching, petroleum industry, silk-working |

| Talcum powder |
|---------------|
| Hydrous magnesium silicate |

| Oxygen toxicity |
|-----------------|
| Free-base cocaine |


Bronchiolitis obliterans is the second most common lower respiratory tract illness requiring hospitalization of infants and young children [113, 131]. It occurs primarily as a result of a viral infection, usually the respiratory syncytial virus (Table 3). Infectious bronchiolitis obliterans is rarely seen in children older than age 2 or in adults. When it occurs in older children and young adults,
Table 3. Infectious causes of bronchiolitis obliterans

| Category | Causes |
|----------|--------|
| Viral    | Respiratory syncytial virus; adenovirus (types 7, 3, 21, 1, 2, 5, 6); rhinovirus; parainfluenza; influenza; measles; mumps; varicella zoster; cytomegalovirus |
| Other infectious agents | Mycoplasma pneumoniae; Legionella pneumophilia; Serratia marcescens |

It has been associated primarily with *Mycoplasma pneumoniae*, but a number of other viral and bacterial agents have also been identified [23, 30, 43, 106]. The disease may also occur as a nonspecific localized process adjacent to a fungal or mycobacterial granuloma [65].

The children usually present with an acute illness that begins with mild coryza with sneezing. Several days later, cough, dyspnea, tachypnea, tachycardia, fever, chest wall retraction, sibilant and sonorous rales, expiratory wheezing, and, in the worst cases, cyanosis may develop. Prostration and respiratory failure are unusual. Recovery is usual and occurs in days or weeks [47, 113, 131]. The clinical presentation in adults has not been well characterized since no systematic study of infectious bronchiolitis obliterans in this group has been reported. Most patients have a history of an upper respiratory tract illness that precedes the onset of dyspnea with exertion, cough, tachypnea, fever, and wheezing [30, 53, 93]. A number of adults have developed an acute or subacute diffuse ventilatory obstruction that has occasionally been fatal.

The radiographic pattern of childhood bronchiolitis is variable. It may be normal or show hyperinflation with increased bronchial markings. Subsegmental consolidation and collapse may be seen [129]. A pattern similar to diffuse interstitial pneumonia often in association with hyperinflation is seen. Some patients demonstrate a diffuse nodular or reticulonodular pattern while others may have patchy alveolar or ground-glass opacities [10, 44]. Those with nodular pattern frequently have "pure" bronchiolitis obliterans on lung biopsy, whereas those with the reticulonodular pattern are likely to have more interstitial inflammation and scarring [10, 44, 131]. It is interesting that 1 of the long-term complications of this condition is the development of the Swyer-James-MacLeod syndrome, (i.e., unilateral hyperlucent lung) [24, 69].

Tests of lung function are usually normal, although increases in both end-expiratory lung volume and lung resistance have been reported. Dynamic compliance and arterial hypoxemia have been demonstrated [47, 130, 131]. It has been demonstrated that viral bronchitis may cause abnormalities in lung function that include "small airways dysfunction," reduced diffusing capacity, and frequency dependence of compliance [23]. Whether or not bronchiolitis in infancy predisposes to asthma or COPD in later life remains unproven but data suggesting such an association have appeared in the literature [47, 52, 78, 79, 128].
The pathologic features of acute viral bronchiolitis have been previously summarized [44, 82, 83, 133]. The earliest change is necrosis of the respiratory epithelium followed by proliferation. Dense plugs of alveolar debris and strands of fibrin are seen within small bronchi and bronchioles causing partial or complete obstruction. A lymphocytic infiltrate with germinal centers may be seen in the airway wall. Occasionally, severe and widespread destruction of the respiratory epithelium may cause denudation and a pronounced inflammatory response that may involve the adjacent peribronchial space and alveolar walls. The pathogenetic mechanisms involved in the development of obliterative bronchiolitis secondary to infections and the reason for the predilection in infants are unknown [84, 131].

Treatment is symptomatic, with oxygen therapy and adequate hydration being most important [31, 40, 84, 131]. Bronchodilators, antibiotics, and corticosteroids have no proven role in management. Mechanical ventilation is rarely required but may be necessary if progressive respiratory failure ensues.

Occasionally, localized areas of bronchiolitis obliterans are found at open lung biopsy performed to rule out carcinoma. These lesions present radiographically as an irregular nodule or irregular sublobar area of air-space consolidation. Surgical resection usually completely resolves this problem. The true origin of these lesions is unknown but it is very likely secondary to a resolving pneumonia.

**Bronchiolitis Obliterans of Unknown Etiology**

**Bronchiolitis Obliterans and Organizing Pneumonia**

The group of patients who are classified as having idiopathic bronchiolitis obliterans and organizing pneumonia (BOOP) may represent a subset of patients with unrecognized viral syndromes or toxic fume exposures [28, 34, 49, 66, 123]. The disease onset is usually in the fifth and sixth decade and affects men and women equally. A persistent and usually nonproductive cough (84% of patients) is the most common presenting symptom. Frequently, patients experience dyspnea with exertion (65% of patients) and two-thirds describe their onset as a flulike illness with fever, malaise, fatigue, and cough. Almost three-fourths of the patients have their symptoms for less than 2 months and less than one-fifth of the patients have symptoms for greater than 1 year. Cigarette smoking is not a precipitating factor. In three-fourths of the patients physical examination reveals crackles (Velcro rales). Wheezing has been found in 31% and is usually present with rales. Clubbing is not found and occasionally a normal physical examination is present.

Lung functional abnormalities are variable and there is relatively little correlation between histopathologic findings and function. Arterial hypoxemia is a universal finding in symptomatic patients. When the effect of smoking is considered, a higher percentage of patients have a restrictive ventilatory defect. Nineteen percent of patients have normal pulmonary function. Relatively few
studies of exercise gas exchange have been carried out since most of the studies have been retrospective reviews of pathologically defined cases. The diffusing capacity for carbon monoxide is abnormal in 72% of patients.

The radiographic manifestations are also variable, but a characteristic pattern of bilateral, patchy, ground-glass, or alveolar opacities is seen in 72% of these cases (Fig. 2). A miliary pattern often confused with miliary tuberculosis has been reported in one-fourth of the patients. It has been proposed that the combination of radiographic and/or physiological evidence of hyperinflation and rales on physical examination is suggestive or bronchiolitis obliterans. This may be true of toxic fume exposure or viral-induced bronchiolitis obliterans, but it should be pointed out that radiographic evidence of hyperinflation is distinctly uncommon in BOOP. Very rarely (1%) is the x-ray appearance normal in patients with BOOP. In Epler and co-workers' [34] recent series, it was shown that the severity of the radiographic abnormalities was significantly correlated with the extent of histologic involvement of the respiratory bronchioles and alveolar ducts but not of the larger terminal bronchioles.

In BOOP the extent of involvement of the small airways is variable. The fibrotic process is patchy and usually involves the airspaces with a peribronchiolar distribution. In 1 series [34] 50% of the cases showed extensive involvement of the terminal and respiratory bronchioles and two-thirds had significant involvement of the alveolar ducts. The cellular infiltrate found in the bronchiolar walls is composed primarily of mononuclear cells, plasma cells, and histiocytes. Occasionally neutrophils are seen in the lumens of these airways. In some instances an acute inflammatory exudate is seen in neighboring alveoli. The fibrotic processes in these cases are interesting: the early lesions are characterized by organization of the inflammatory and fibrinous exudates with proliferating fibroblasts and little collagen deposition. As the lesions progress, well-formed plugs of edematous granulation tissue that involve terminal and respiratory bronchioles appear and are associated with an intense reaction that extends into the alveolar ducts (Fig. 3). Honeycombing is rarely, if ever, seen [34, 66]. "Cholesterol," "obstructive," or "endogenous lipid" pneumonia is occasionally seen but sometimes can be so marked as to cause confusion in the diagnosis of this process with pneumonias due to exogenous lipid. It is important that the histologic lesions of BOOP appear uniform in appearance. This contrasts with the usual interstitial pneumonia, in which there are areas of varying degrees of interstitial fibrosis with foci of honeycombing and mononuclear cell infiltration throughout the involved lung [34, 66]. Tables 4 and 5 outline the contrasting clinical and pathologic features of bronchiolitis obliterans and usual interstitial pneumonia, a process with which it is frequently confused [14, 66].

Corticosteroid therapy is effective and clinical improvement is very common, often occurring within days of initiation of therapy. As many as two-thirds of the patients demonstrate complete clinical and physiological recovery following corticosteroid therapy. Death from progressive disease occurs, but is infrequent [60]. Early cessation of corticosteroid therapy may be associated
Fig. 2. Bronchiolitis obliterans and organizing pneumonia. Appearance in a 38-year-old patient with 2-week history of progressive dyspnea with exertion and nonproductive cough. A Initial posteroanterior roentgenogram shows mixed alveolar and interstitial infiltrates throughout all lung zones but most prominently in both upper lung zones. B Follow-up posteroanterior roentgenogram, after corticosteroid therapy, documents marked improvement.
with a recurrence of both symptoms and/or radiographic and physiological abnormalities [27, 28, 34].

**Connective Tissue Diseases**

*Rheumatoid Arthritis.* Pleuropulmonary manifestations are frequently encountered in patients with rheumatoid arthritis (RA): (1) pleural lesions with and without pleurisy; (2) interstitial lung disease; (3) parenchymal rheumatoid nodules; (4) Caplan’s syndrome; (5) arteritis; and (6) gold-induced interstitial lung disease. An increased prevalence of obstructive pulmonary disease has been noted [4, 20, 26, 39, 95, 108]. Several studies have demonstrated that factors other than tobacco smoking are involved [20, 42, 125, 127] and bronchiolitis obliterans has recently been recognized as a cause of the airway obstruction in many of these patients [4, 20, 21, 32, 41, 48, 56, 61, 62, 70, 77, 88, 137]. The clinical manifestations of bronchiolitis obliterans associated with RA help to differentiate it from other pulmonary processes associated with RA. There is an abrupt onset of dyspnea and dry cough often associated with inspiratory rales and a midinspiratory squeak. The majority of patients are middle-aged women with seropositive RA, often associated with Sjogren’s syn-

**Fig. 3.** Bronchiolitis obliterans and organizing pneumonia. Polypoid masses of granulation tissue fill the lumens of respiratory bronchioles and alveolar ducts (top and right). Adjacent alveolar interstices are broadened by a lymphoplasmacytic inflammatory infiltrate, and prominent type II pneumocyte hyperplasia is present (H & E, × 50).
Table 4. Clinical features of bronchiolitis obliterans with organizing pneumonia (BOOP) and idiopathic pulmonary fibrosis

|                          | BOOP                                      | Idiopathic pulmonary fibrosis |
|--------------------------|-------------------------------------------|------------------------------|
| Duration of symptoms (range) | 3 months (several days–6 months)  | 2 yr (2 months–5 yr)         |
| Symptoms (%)              |                                           |                              |
| Cough                    | 67                                        | 67                           |
| Fever                    | 58                                        | 13                           |
| Dyspnea                  | 50                                        | 100                          |
| Upper respiratory infection | 21                                      | 0                            |
| Associated connective tissue disease | 29                                      | 19                           |
| Associated occupation exposure | 0                                       | 31                           |
| Pulmonary function tests (%) |                                         |                              |
| Restriction              | 40                                        | 85                           |
| Obstruction              | 20                                        | 21                           |
| Decreased diffusing capacity of CO | 50                                      | 100                          |
| Radiographic manifestations (%) |                                         |                              |
| Airspace opacities       | 50                                        | 0                            |
| Lobar                    | 46                                        | 0                            |
| Bibasilar                | 4                                         | 0                            |
| Interstitial opacities   |                                           |                              |
| Reticular                | 42                                        | 94                           |
| Reticulonodular          | 42                                        | 63                           |
| Honeycomb                | 0                                         | 13                           |
| Mixed alveolar and interstitial opacities | 0                                         | 19                           |
| Lung volume              |                                           |                              |
| Decreased                | 25                                        | 75                           |
| Normal                   | 75                                        | 25                           |

Adopted from refs 14 and 66

Table 5. Contrasting pathologic features of bronchiolitis obliterans with organizing pneumonia and idiopathic pulmonary fibrosis

|                          | BOOP                                      | Idiopathic pulmonary fibrosis |
|--------------------------|-------------------------------------------|------------------------------|
| Distribution of lesions  | Patchy, peribronchiolar                   | Diffuse, random              |
| Location of lesions      | Predominantly airspace                     | Predominantly interstitial   |
| Temporal appearance of changes | Uniform, recent                           | Varying ages                 |
| Type of fibrosis         | Fibroblastic                               | Mainly mature (collagen)     |
| Honeycomb                | Unusual                                    | Common                       |
| Foamy macrophages        | Common                                     | Unusual                      |

After ref 66
drome [9, 76, 107]. The chest radiography is usually normal. Physiological
studies usually reveal airflow obstruction, mild to moderate arterial hypoxemia
and respiratory alkalosis, and normal pulmonary compliance. The rapid rate of
progression of the airflow obstruction is atypical of COPD.

Pathologically, there is a lymphoplasmocytic infiltration of small airway
walls. The lumens are gradually obliterated and bronchiolar wall is destroyed
by granulation tissue. The lesions are usually confined to the small bronchi and
bronchioles but occasionally there is patchy organizing pneumonia with granu-
lation tissue plugs extending into the alveolar ducts. Parenchymal involvement
is generally localized to the area surrounding the bronchiolitis. The lesions may
be at different stage of development or appear quite uniform [4, 137]. Immuno-
fluorescence studies show granular IgM or linear IgG depositions along the
alveolar septa, suggesting a possible direct immune-mediated lung injury [56,
62].

The prognosis for these patients is poor, with a number of early deaths [41].
Treatment with antibiotics and bronchodilators has been ineffective. Cortico-
steroid therapy with or without cyclophosphamide appears to be effective in
some patients [139].

Penicillamine-Associated Bronchiolitis Obliterans in RA. Penicillamine ther-
apy has been implicated in the pathogenesis of 4 diffuse lung processes: (1)
bronchiolitis obliterans; (2) interstitial infiltrates, (3) Goodpasture’s syndrome,
and (4) bronchospasm [4, 13, 15, 16, 32, 62, 88, 96, 115, 116, 122, 132, 139]. The
overwhelming majority of the patients with presumed penicillamine-associated
bronchiolitis obliterans are women who never smoked. There is a sense that
this form of bronchiolitis obliterans is characterized by a rapidly deteriorating
course characterized by pulmonary insufficiency [139]. Breathlessness and
cough begin within 3–14 months after initiation of penicillamine therapy. In
one-third of the cases in which the outcome is known, death from progressive
respiratory failure occurs. Radiographic abnormalities are unusual except for
mild hyperinflation. Pulmonary function abnormalities are characteristically
those of airflow obstruction. The histologic appearance is thought by some to
be distinct from that of other causes of bronchiolitis obliterans because the
penicillamine-associated cases usually show a concentric, constrictive form of
bronchiolar obstruction [32, 41, 62, 88, 96, 139]. Although conclusive proof of
association between bronchiolitis obliterans and penicillamine therapy is lack-
ing, when confronted with a dyspneic patient with RA being treated with peni-
cillamine, one should stop use of the drug, consider open lung biopsy, and then
administer corticosteroids to prevent disease progression [32, 117].

Other Connective Tissue Diseases

Obstructive airway disease has been reported in patients with Sjogren’s syn-
drome [90]. In fact, a number of these patients had bronchiolitis obliterans and
RA [4]. Pathologic studies are limited but in 2 instances lung biopsy revealed
mononuclear cell infiltration around narrowed small airways. A restrictive ventilatory defect is frequently found in Sjogren's syndrome. This defect probably results from the underlying interstitial lung disease associated with the particular connective tissue disease and is not due to the sicca complex.

Less than 5% of patients with systemic lupus erythematosus (SLE) have airflow obstruction. Kinney and Angelillo [68] have recently reported a patient with SLE who developed rapidly progressive airway obstruction and had early obliterative bronchiolitis on open lung biopsy. This suggested that this lesion may account for the obstructive dysfunction occasionally seen in SLE.

Small airways disease is not frequently found in nonsmokers with scleroderma even in the presence of interstitial pulmonary involvement [6, 50]. A single case of rapidly fatal bronchiolitis obliterans has been reported in a 57-year-old woman with circulating antinuclear and rheumatoid factors without evidence of a defined connective tissue disease [61]. These authors suggested that the serologic abnormalities could be secondary to the inflammation of the bronchioles. No data exist to support this hypothesis.

Schwarz et al. [109] were among the first specifically to distinguish bronchiolitis obliterans as a de novo process in patients with polymyositis and dermatomyositis. They also suggested that this lesion was corticosteroid responsive.

Small airways disease has been detected in a relatively high percentage of patients with essential mixed cryoglobulinemia, especially if signs of exposure to hepatitis B virus are present [8]. Most of these patients had overall normal lung function, that is, no evidence of airway obstruction or restriction. On the other hand, frequent, although moderate, pulmonary interstitial involvement was present on the chest film in most of these otherwise asymptomatic patients.

Recently, a follicular bronchitis/bronchiolitis has been described in patients with rheumatoid arthritis, Sjogren's syndrome, juvenile rheumatoid arthritis, immunodeficiency syndromes, familial lung disorders, chronic infection, and a heterogeneous group of patients with a hypersensitivity-type reaction [2, 36, 37, 112, 138]. Pathologically, there is a follicular bronchitis/bronchiolitis with abundant germinal centers in the peribronchiolar regions, characterized by hyperplastic follicles located between bronchioles and pulmonary arteries and often compressing the bronchiolar lumen into a slitlike or fish-mouth shape. In almost all cases, a concentric inflammatory infiltrate of lymphocytes and plasma cells surrounded the bronchiole. Patients with rheumatoid arthritis usually presented with dyspnea (100%); fever and cough occasionally occurred. All have positive rheumatoid factor, often at high levels (1:640–1:2560). The chest film was consistently abnormal with bilateral reticulonodular shadows. Pulmonary function tests revealed arterial hypoxemia and hypocapnia, with a widened alveolar–arterial pO₂ difference. Both obstructive and restrictive patterns were identified by spirometry, but the restrictive pattern was more common. It has been suggested that this lesion may be the precursor of an interstitial lymphoid pneumonia or pseudolymphoma. It appears to be distinct from bronchiolitis obliterans, since the lesions of follicular bronchiolitis obstruct by external compression of the bronchioles rather than the direct luminal occlu-
sion characteristic of bronchiolitis obliterans. Treatment with corticosteroids has yielded variable results.

Organ Transplantation

Bone Marrow Transplantation. Acute or chronic graft versus host disease (GVHD) frequently complicates the course of patients undergoing allogeneic bone marrow transplantation [3, 120]. The acute disease involves the skin, liver, and gut. Ninety percent of patients with this complication survive. The syndrome of chronic GVHD occurs in 33% of long-term survivors of allogeneic transplantation. The protean manifestations of this disorder include scleroderma-like skin lesions, sicca syndrome, oral and esophageal mucositis, malabsorption, chronic liver disease, generalized wasting, infections, and disorders of immune regulation [3, 26, 111, 118, 120]. Pulmonary disease is uncommon and is usually the result of an infectious pneumonia (bacterial, fungal, or viral) or idiopathic interstitial pneumonitis. In addition, there are reports of lymphocytic bronchitis and lymphoplasmacytic infiltrate of the trachea and large bronchi [5].

Recently, several cases of rapidly progressive airflow obstruction due to bronchiolitis obliterans complicating bone marrow transplantation have been found [51, 63, 73–75, 94, 98, 102–105, 114, 134, 135]. These cases have appeared in the setting of chronic GVHD and this entity has been postulated to play a role in the development of this lung disease. It has been estimated that approximately 10% of long-term survivors with chronic GVHD develop the complication of severe obstructive pulmonary disease [98].

Patients usually present with symptoms of dry, nonproductive cough, dyspnea with exertion, bibasilar rales, and scattered wheezing. Hypoxemia is common. The chest roentgenogram may show diffuse interstitial infiltrates, but most often in those cases with obstructive lung function the lung fields are normal or hyperinflated. It is important to note that abnormal pulmonary function has been found in a high percentage of patients following bone marrow transplantation, especially in the presence of GVHD. There can be restrictive and/or obstructive ventilatory dysfunction associated with impairment in gas exchange. Bronchial hyperreactivity was also identified in some patients after undergoing transplantation.

An open lung biopsy is usually necessary to diagnose these cases. Since infections are frequent, they should be diagnosed and treated promptly. Bronchoalveolar lavage has not been a useful procedure in these cases [22, 71, 103].

The pathogenesis of the obstructive ventilatory defect is unknown. Several mechanisms have been postulated. Shulman et al. [111] described ectasia and a lymphoplasmacytic infiltration of the tracheal submucosal glands and ducts resembling those described in Sjogren's syndrome. In addition, a dense peribronchial lymphoplasmacytic infiltrate was occasionally seen. Other investigators [5] have found a lymphocytic bronchitis, characterized by lymphocyte-associated necrosis of the bronchial mucosa and submucosal glands. This was
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often associated with an increased incidence of bronchopneumonia and acute bronchitis with mucous plugging. Bronchiolitis obliterans was not noted in this study. Lymphocytic bronchitis is thought to represent a pulmonary manifestation of GVHD. However, others have questioned its association with acute GVHD [51, 75]. Most patients with rapidly progressive airflow obstruction in whom lung biopsy has been obtained revealed marked lymphocytic or plasma cell and neutrophilic infiltration of the walls of the terminal respiratory bronchioles and obliteration of the bronchiolar lumina with fibrous tissue and surrounding interstitial fibrosis, that is, “pure” bronchiolitis obliterans [94, 98, 102, 105, 134]. Since chronic GVHD is associated with a fibrosing process in other organs, it is not surprising that bronchiolar fibrosis may be an additional manifestation of the chronic GVHD. Chronic GVHD is associated with esophageal and sinus disease that may result in recurrent esophageal aspiration and thus could contribute to the lung injury [111].

The treatment and prognosis of bronchiolitis obliterans associated with bone marrow transplantation are unclear. Bronchodilators and corticosteroids, in the majority of cases, have not improved the airflow limitation. Furthermore, the use of immunosuppressive agents for the treatment of chronic GVHD has had no consistent beneficial effect on pulmonary function. Consequently, it would appear that early recognition and management of this process are required if successful treatment is to be attained. The prognosis is quite variable. A significant number of the patients reported had progressive or persistent disease and many died as a result of respiratory failure.

Heart–Lung Transplantation. Heart–lung transplantation is being utilized increasingly for the management chronic lung and/or heart disease: end-stage pulmonary vascular disease, idiopathic cardiomyopathy, coronary artery disease, congenital heart disease, terminal pulmonary lymphangiomyomatosis, cystic fibrosis, and end-stage Eizenmenger’s syndrome. Recently it has been noted that obliterative bronchiolitis is a major complication in long-term survivors of heart–lung transplantation [1, 11, 12, 29, 45, 80, 119, 136]. The clinical presentation occurs several months to several years following transplantation. Cough productive of mucopurulent sputum followed by progressive dyspnea is common. The chest examination revealed diffuse coarse crepitations and expiratory rhonchi.

Chest radiographs reveal diffuse peribronchial and interstitial infiltrates with variable pleural thickening and bronchography revealed cylindrical bronchiectasis in those examined. Arterial hypoxemia and hypocapnia are universally present. Pulmonary function tests demonstrate irreversible airflow obstruction, often with an associated reduction in total lung capacity. The diffusing capacity of carbon monoxide is moderately depressed. Spontaneous improvement does not occur often.

On pathologic examination, patients have evidence of bronchiolitis obliterans with patchy involvement throughout all areas of the lung [136]. Mucus inspissation and distal obstructive changes were frequently associated. Diffuse increases in peribronchial and interstitial fibrosis were present in all biopsy
specimens. Pleural, venous, and arteriosclerotic vascular changes were common. These changes are different from those of the acute pulmonary rejection, which is characterized by perivascular lymphocytic cuffing and diffuse alveolar damage.

Yousem and co-investigators [136] have suggested the following as possible causes of bronchiolitis obliterans in patients who have undergone heart-lung transplantation: (1) recurrent or persistent bacterial or viral infections; (2) immune reaction to transplanted lung, for example, GVHD or transplant rejection; (3) altered mucociliary clearance as a result of impaired ciliary function caused by injury to the pulmonary nerve supply or abnormal mucus chemistry and viscosity; (4) bronchial artery ligation leading to alteration in the repair process of injured bronchi and bronchioles; (5) reaction to immunosuppressive drugs, especially cyclosporine, which has been shown to have fibroproliferative properties that could cause progressive narrowing and obliteration of the affected bronchioles; and (5) loss of cough reflex and aspiration leading to the establishment of a milieu necessary to encourage the continued and persistent growth of infectious agents.

No clearly useful treatment protocol has been found. Corticosteroids, bronchodilators, and antibiotics have been used without any documented stabilization or reversal of disease in the majority of patients. Recently, an immunosuppressive regimen of cyclosporine, prednisone, and azathioprine has been suggested as effective in treating bronchiolitis obliterans. A prospective study utilizing this regimen is required to determine its efficacy [1, 45]. Retransplantation has been a successful alternative in patients with progressive disease.

Miscellaneous Processes

Idiopathic Pulmonary Fibrosis

Hamman and Rich [54] mentioned small airway narrowing in their original cases of rapidly progressive idiopathic pulmonary fibrosis. Liebow and Carrington [72] described this lesion superimposed on a background of usual interstitial pneumonia. Some cases of bronchiolitis obliterans and organizing pneumonia have a rapidly progressive course resulting in death that is very similar to the Hamman-Rich syndrome. Since this lesion is frequently confused with IPF, one wonders if many of these cases of Hamman-Rich syndrome are not examples of BOOP.

Hypersensitivity Pneumonitis

Interstitial pneumonitis (100%) and granulomas (70%) are the most common pathologic abnormalities identified in patients with hypersensitivity pneumonitis. However, bronchiolar lesions (bronchiolitis obliterans) are seen in 50% or more of the patients [100, 110] (Fig. 4). A reversible restrictive process is the most common physiological abnormality in chronic hypersensitivity pneumoni-
Hypersensitivity pneumonitis. Narrowing of airway lumen and marked inflammation (bronchiolitis). Multinucleate giant cells are seen in the wall of the airway; a lymphoid aggregate is also present. The surrounding parenchyma is minimally involved.

Small airway dysfunction may be present in patients with early hypersensitivity pneumonitis. As the disease progresses, it may cause both an obstructive or restrictive process depending on the predominant histopathologic process present.

Malignant Histocytosis

Colby and co-workers [19] described the clinicopathologic spectrum of pulmonary involvement in malignant histiocytosis. The tumor is systemic and com-
posed of malignant cells with morphologic and functional characteristics of histiocytes. The clinical presentation is variable. Fever, cough, lymphadenopathy, hepatosplenomegaly, and pancytopenia are common. The chest x-ray is frequently abnormal and reveals diffuse bilateral infiltrates (reticular, reticulonodular) or discrete nodules, with or without pleural effusions. Three of 5 patients died within 10 months of presentation. The predominant histologic feature is a nondestructive nodular infiltrate within pulmonary lymphatics and a tendency to invade adjacent structures. Invasion and occlusion of small airways, as well as bronchiolitis obliterans were identified in 3 of the 5 cases reported.

**Chronic Eosinophilic Pneumonia**

Eosinophilic pneumonia is a nonspecific term that refers to several entities that have in common pulmonary infiltration with lung and/or blood eosinophilia. The syndrome of chronic eosinophilic pneumonia is characterized by fever, cough, dyspnea, weight loss, and malaise. The disease often waxes and wanes. Physical examination reveals wheezes in some patients. The chest x-ray "typically" shows dense, progressive consolidation that frequently appears in the periphery of the lungs without a clear relationship to segmental and lobar anatomy. The histopathologic features are primarily characterized by infiltration of many mature eosinophils and a small number of lymphocytes and plasma cells. Multinucleated giant cells, Charcot-Leyden crystals, sarcoidlike granulomata, mild angiitis, edema, and proteinaceous exudates also occur. Bronchiolitis obliterans is a rare abnormality in the process [38, 86].

**Diffuse Panbronchiolitis**

Homma and co-workers [58] recently described their experience with 82 histologically confirmed cases collected through a nationwide survey in Japan. The disease is most prevalent in men. The age of onset is variable. Chronic cough, exertional dyspnea, wheezing, and chronic parasinusitis are the common clinical manifestations of this disease. Pulmonary function tests reveal marked obstructive ventilatory defect and hypoxemia. The chest roentgenogram often reveals small nodular shadows (up to 2 mm in diameter) diffusely throughout both lung fields. Hyperinflation may also be present. On pathologic examination the lesions are characterized by thickening of the walls of respiratory bronchioles with infiltration of lymphocytes, plasma cells, and histiocytes, and extension of the inflammatory changes toward peribronchiolar tissue. Advanced disease is manifested by secondary ectasia of proximal bronchioi. The prognosis is often poor with rapid progress and a fatal outcome.
Respiratory bronchiolitis is a distinct pathologic lesion commonly found in cigarette smokers [58]. It is characterized by the accumulation of pigmented alveolar macrophages within respiratory bronchioles and adjacent air spaces, often associated with mild thickening of the peribronchiolar interstitium (Fig. 5). It is occasionally seen in nonsmokers and thus may be associated with other environmental or occupational insults. Recognized primarily in autopsy specimens from victims of sudden death or in lungs excised for unrelated solitary nodule, it has generally been considered of little clinical consequence. Recently, it has been recognized that respiratory bronchiolitis is an uncommon cause of chronic lung disease, primarily in heavy cigarette smokers [7, 92]. It is often confused with idiopathic pulmonary fibrosis because the patients present with cough, dyspnea, and have crackles on physical examination. Diffuse interstitial infiltrates are present on the chest radiograph and pulmonary function tests reveals mild to moderate restriction and reduced diffusing capacity.

Respiratory bronchiolitis also occurs in patients with mineral dust exposure, such as asbestos. This is thought to be an early tissue reaction, with
scarring and inflammation in the membranous bronchioles; commonly these lesions contain a large amount of pigment [17, 18].

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