PART

IV

Obstructive Lung Diseases

40
CHAPTER

Pathologic Features of Chronic Obstructive Pulmonary Disease: Diagnostic Criteria and Differential Diagnosis

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Chronic obstructive pulmonary disease (COPD) is a general name for the chronic airflow obstruction that develops most often as a result of chronic tobacco smoking. The pathology of COPD encompasses a variety of pathologic lesions in the airways, lung parenchyma, and pulmonary vasculature, and these lesions can be correlated, to a greater or lesser degree, with changes in pulmonary function tests and clinical appearances. In general, although the mechanisms involved are complex, airflow obstruction can be attributed largely to a marked increase in airways resistance secondary to a variable mix of structural abnormalities involving all or many of the compartments of the airway. However, in individual cases, it

may be difficult to prove associations between physiological abnormalities and pathologic changes. The recently developed Global Initiative on Obstructive Lung Disease (GOLD), classifies patients with COPD purely upon indices of airflow and thus far there is only limited integration with pathologic findings.

This chapter presents the pathologic features of COPD and how these findings can be differentiated from other lesions associated with airflow obstruction.

HISTORY OF PATHOLOGIC DESCRIPTIONS OF COPD

The word emphysema is derived from Greek and means "to blow into," hence "air-containing" or "inflated." Although "voluminous lungs" and lungs "turgid particularly from air" were described respectively by Bonet in 1679, and Morgagni in 1769, the first description of enlarged airspaces in emphysema in the human, together with illustrations, was furnished by Ruysh in 1721, followed by Matthew Baillie in 1807, who not only clearly recognized and illustrated emphysema, but also pointed out its essentially destructive character.

Laennec, writing in the early 1800s, made a number of seminal contributions to the basic descriptions of pathologic changes in COPD. He was the first to make a clear-cut distinction between interstitial emphysema and emphysema proper, and related the enlarged airspaces to the clinical syndrome of emphysema. He also recognized that air trapping and increased collateral ventilation were features of emphysematous lungs, and that the peripheral airways were the primary site of obstruction in emphysema. Furthermore, he noted that airspaces enlarged with increasing age, and he distinguished these changes from emphysema. He was the first to describe an association of emphysema with chronic bronchitis and to clearly describe the pathology of bronchiectasis.

Little of major importance was added to the gross descriptive morphology of emphysema for almost the next 150 years. The foundation of modern knowledge of the pathologic anatomy of pulmonary emphysema was laid by J. Gough in 1952 when he described centrilobular emphysema and distinguished it from panlobular emphysema. The paper section technique developed by Gough and Wentworth was largely responsible for this advance, as it made examinations of sections of entire inflated lungs possible and simple (Fig. 40-1). A comprehensive microscopic description of emphysema was then provided by McLean, who demonstrated the relationship of destruction to inflammatory alterations of the bronchioles, and also discussed alterations of the vasculature.

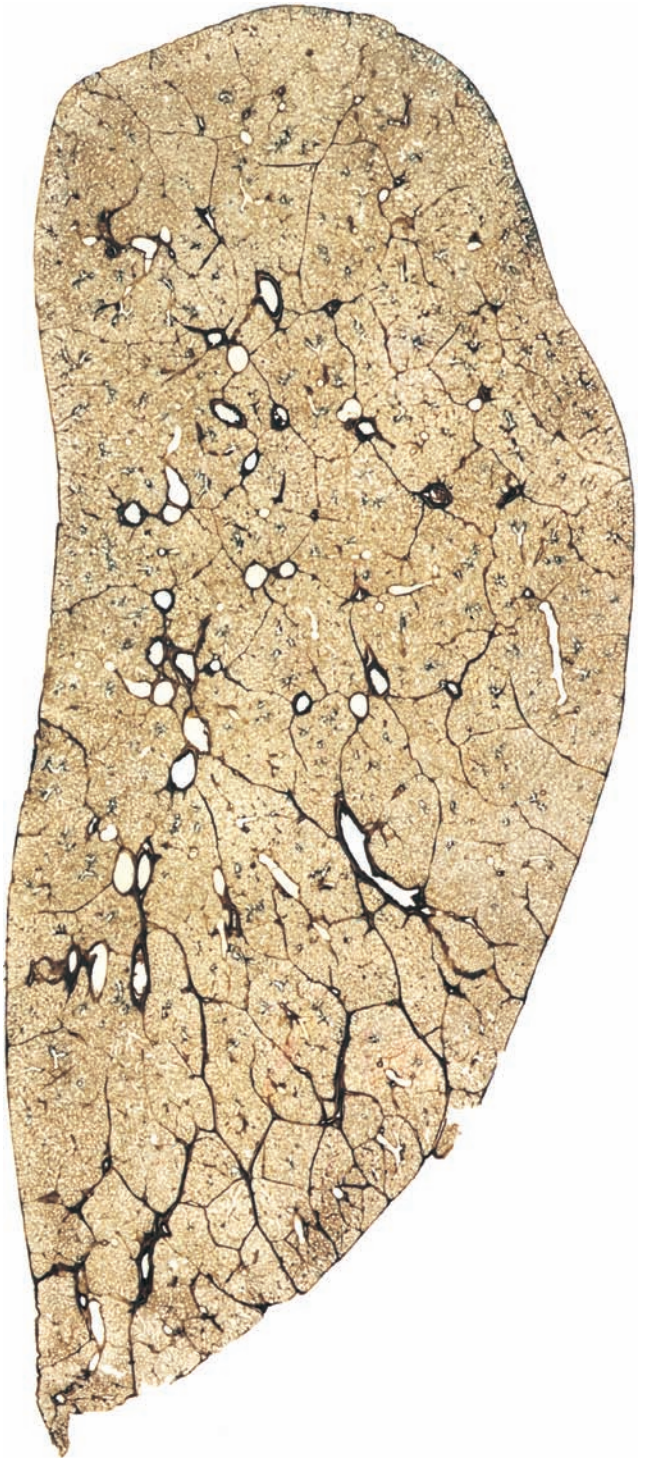


Figure 40-1 Gough sagittal section. Paper mount. Normal lung. *(This section and subsequent sagittal sections courtesy of Dr. S. Moolton.)*

LESIONS OF THE LUNG PARENCHYMA IN COPD: EMPHYSEMA

A major problem in describing the pathologic features of emphysema has been the lack of a generally accepted and easy to apply definition. In 1959, a Ciba Guest Symposium defined emphysema in anatomic terms as "a condition of the lung characterized by increase beyond the normal of airspaces, distal to the terminal bronchiole, either from dilatation or from destruction of their walls." Subsequent definitions differed in that destruction of respiratory tissue became a requirement: "Emphysema is a condition of the lung characterized by

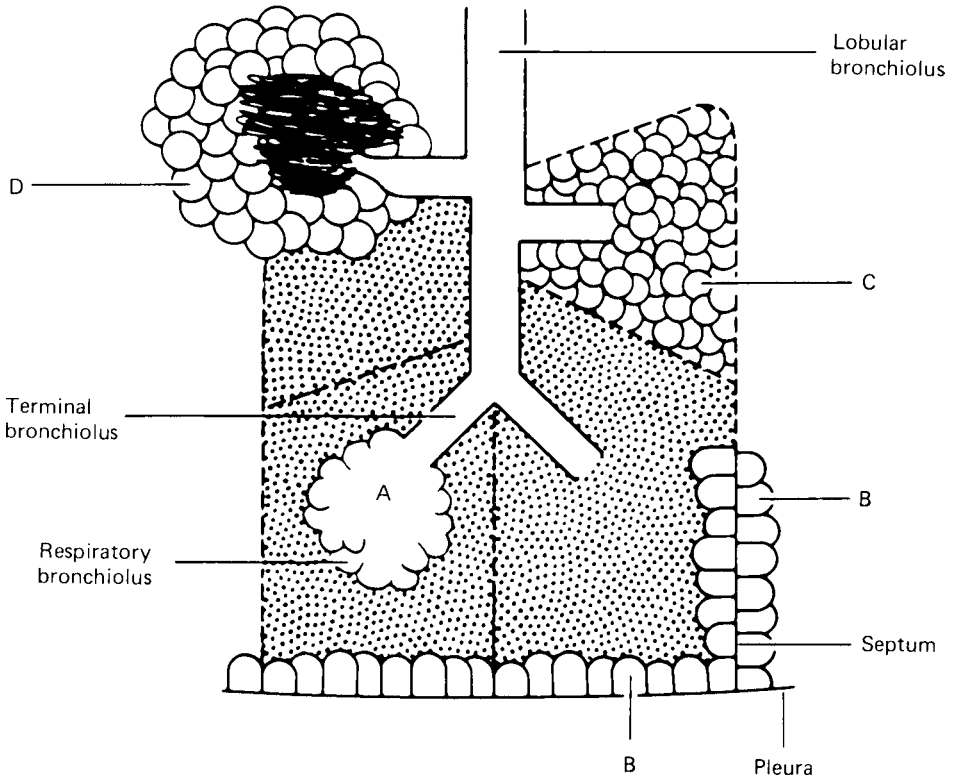


Figure 40-2 Anatomic varieties of emphysema. *A*. Centriacinar (centrilobular). *B*. Paraseptal (distal acinar). *C*. Panacinar (panlobular). *D*. Irregular (scar). The dashed lines mark the edge of the acinus. Only centriacinar and panacinar emphysema are commonly observed in COPD.

abnormal, permanent enlargement of the airspaces distal to the terminal bronchiole, accompanied by destruction of their walls." This requirement separates emphysema from enlargement of airspaces unaccompanied by destruction, the latter now being termed overinflation.

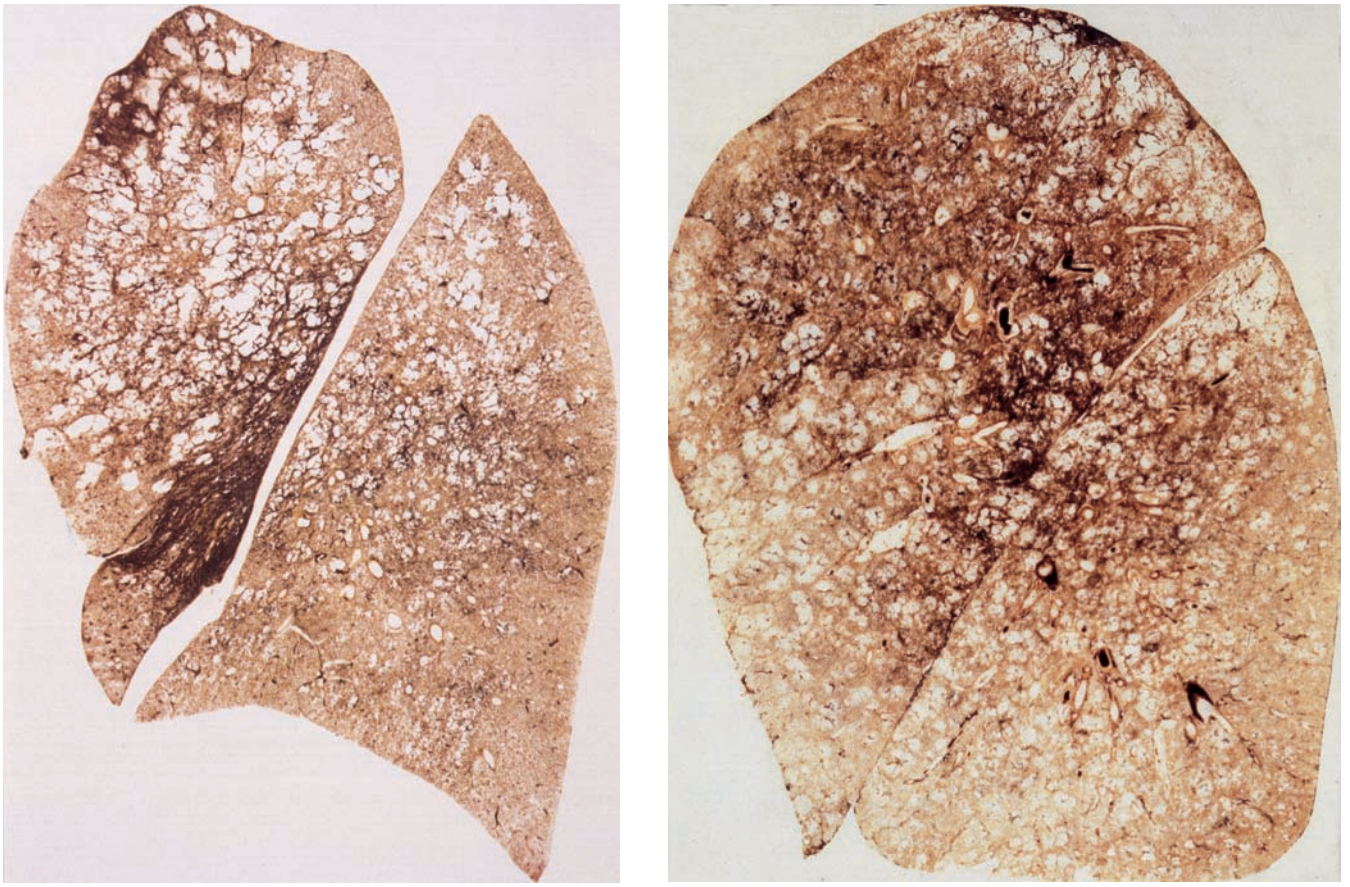
Destruction has been similarly difficult to define in an unambiguous way. A committee of the National Institutes of Health proposed that destruction was present when "there was nonuniformity in the pattern of respiratory airspace enlargement so that the orderly appearance of the acinus and its components is disturbed and may be lost." They recognized that emphysema was a subset of airspace enlargement defined as "an increase in airspace size as compared with the airspace of normal lungs. The term applies to all varieties of airspace enlargement distal to the terminal bronchioles, whether occurring with or without fibrosis or destruction." While these definitions, when strictly applied, would eliminate airspace enlargement due to overinflation or failure of septation, they would not eliminate airspace enlargement due to reorganization of the airspaces, such as is found in honeycomb lung.

Classification of Emphysema

Not only is emphysema defined in terms of lung structure, it is also classified in similar terms; therefore, several anatomic definitions are important. The part of the lung involved in emphysema is the acinus, which is defined as the unit of lung structure distal to the terminal bronchiole (final generation membranous bronchiole) and that consists of three orders of respiratory bronchioles: a single order of alveolar ducts, followed by the alveolar sacs, and finally the alveoli. Alveolar ducts are entirely alveolated and characteristically contain smooth muscle around the mouths of their alveoli. While the walls of alveolar sacs are also formed entirely by alveoli, muscle is absent. Alveolar pores of Kohn (also known as vents, stomata, or fenestrae) are normal components of adult alveoli, responsible for collateral ventilation. However, they may also be an initial site of destruction in the development of emphysema, particularly centriacinar emphysema.

The acinus is a three-dimensional anatomic structure, but it cannot be easily identified by gross examination. What can be seen instead on the surface of lung slices is the secondary lobule of Miller, defined as the tissue bounded on four sides by interlobular septa or pleura. Lobules vary tremendously in size, but are generally 2 to 4 cm on a side, and contain between three to five acini. The terminal bronchiole and subtending respiratory bronchioles tend to be situated in the center of the lobule. For this reason "centrilobular" emphysema and "panlobular" emphysema are reasonable and widely used approximations for the more accurate "centriacinar" and "panacinar" emphysema (see below) (Fig. 40-2).

The ways in which the acini are involved determine the classification of emphysema. There are four recognized patterns (Fig. 40-2). The acinus (and lobule) may be more or less uniformly involved; this is panacinar (panlobular) emphysema. The proximal portion of the acinus (center of the lobule) may be dominantly involved; the best term for this lesion is proximal acinar emphysema, although the usual term



A *B*

Figure 40-3 Pathologic subtypes of emphysema. *A*. Predominantly centriacinar emphysema. Emphysema is more severe in upper lobes. *B*. Predominant panacinar emphysema. Emphysema is more severe in the lower lobes.

is centrilobular or centriacinar emphysema. Alternately, the proximal portion of the acinus may be normal, and the distal part (alveolar sacs and ducts) may be dominantly involved. This is distal acinar emphysema, more commonly referred to as paraseptal emphysema since the lesion is accentuated along lobular septa where the peripheral parts of the acini lie. Finally, the acinus may be irregularly involved, producing irregular emphysema or paracicatricial emphysema, so called because it is usually associated with obvious scarring.

Morphology of Emphysema

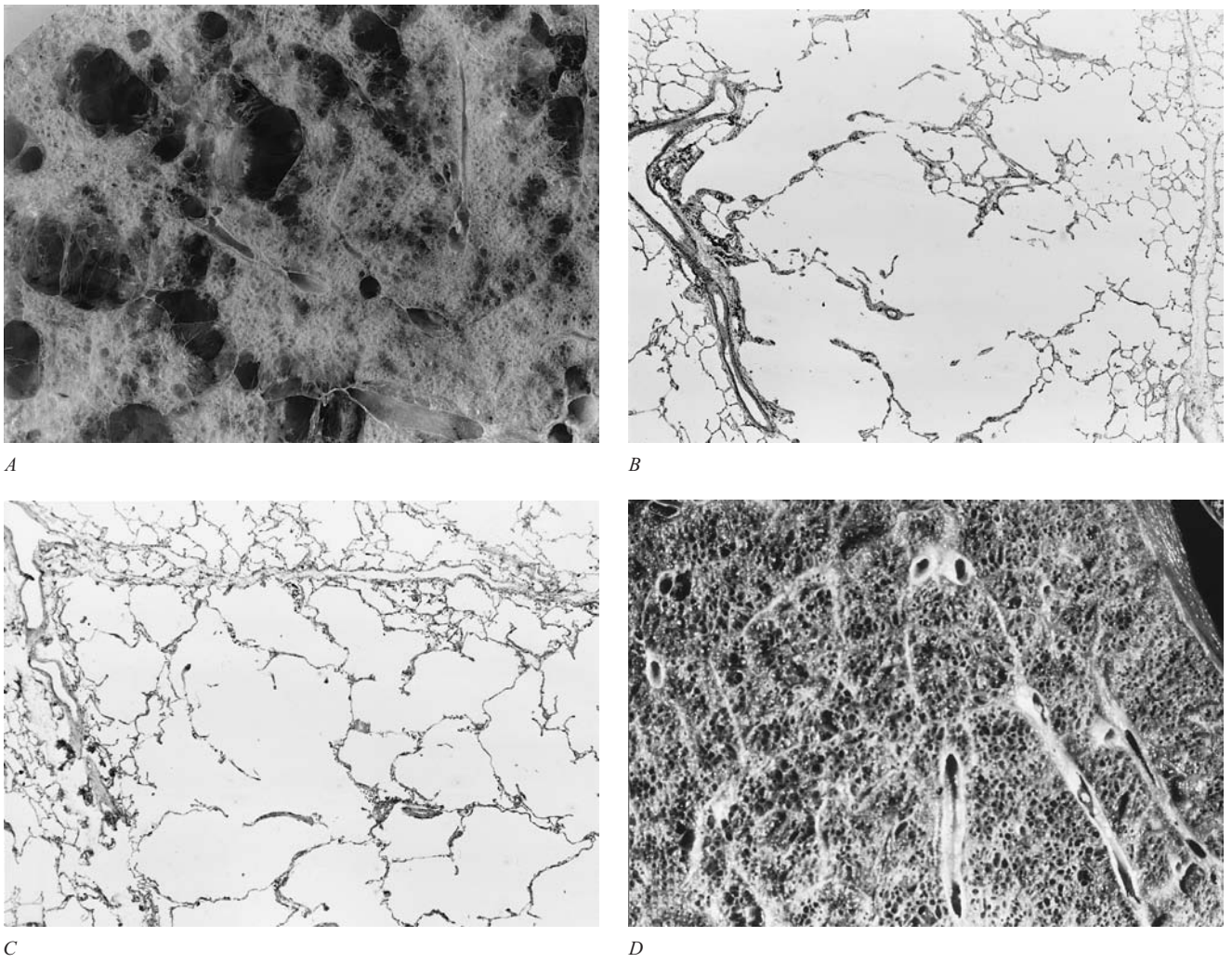
Centrilobular Emphysema

This destructive lesion of the respiratory bronchioles has a number of characteristic features on gross examination of the lung. In the *classical* lesion, the enlarged, destroyed respiratory bronchioles coalesce in series and in parallel to produce sharply demarcated emphysematous spaces, separated from the acinar periphery (the lobular septa), by intact alveolar ducts and sacs of normal size. The walls of the emphysematous spaces and adjacent tissue characteristically contain variable amounts of black pigment.

The lesions vary qualitatively as well as quantitatively even within the same lung. There is striking irregularity of involvement of lobules, and even within the same lobule. The lesions are usually more common and become more severe in the upper than in the lower zones of the lung (Fig. 40-3*A*, Fig. 40-4*A,B*). Most affected are the upper lobe, particularly the posterior and apical segments, and the superior segment of the lower lobe. In cases of severe CLE, the destruction proceeds toward the periphery of the lobule, and the distinction between CLE and PLE becomes blurred.

In CLE, alveolar pores are abnormal in size and shape, and occasionally contain epithelial debris and macrophages. Although there are numerous pores of variable size in the emphysematous areas, there are also increased numbers of pores in the grossly normal areas, and accentuation of these changes in the center of the lobule. Thus, it appears that in CLE the pores of Kohn are possibly the initial site of destruction.

There is increased cellularity in the alveolar walls of cigarette smokers, and when this has been quantified, the parenchyma in severe emphysema has increased numbers of neutrophils, macrophages, eosinophils, and both CD4 and CD8 T lymphocytes. There is also a significant inflammatory cell infiltrate in the airspaces in severe emphysema, with the same cells types increased. Although not readily apparent grossly or on standard histological stains, use of histochemical stains or biochemical analysis demonstrates that collagen is increased in both centrilobular and panlobular emphysema.



A *B* *C* *D*

Figure 40-4 *A,B*. Gross and histologic sections illustrating centriacinar; and (*C,D*) panacinar emphysema. *A*. Cut surface from a lung with centriacinar emphysema showing holes in the center of lobules surrounded by relatively normal parenchyma. The severity varies among lobules. *B*. Microscopic section showing that the airspace enlargement in centriacinar emphysema is most marked adjacent to the abnormal respiratory bronchiole, corresponding to the center of the lobule. Also, some of the alveolar walls of the abnormal airspaces are thickened and fibrotic (H&E × 16). *C*. Cut surface of a lung slice showing how the entire lobule is uniformly affected in panacinar emphysema. *D*. Microscopic section demonstrating that in panacinar emphysema, the airspaces adjacent to the lobular septa are enlarged to the same degree as those in the center of the lobule (H&E × 16).

Panlobular Emphysema

The recognition of mild panlobular emphysema is very difficult. The normal lung has a very characteristic appearance when seen through a dissecting microscope: The multifaceted alveoli form a contrast to the larger, cylindrical conducting structures that are alveolar ducts and respiratory bronchioles. In panlobular emphysema the distinction between alveolar ducts and alveoli becomes lost as alveoli lose their sharp angles, enlarge, and then lose their contrast in size and shape with the ducts, resulting in simplification of the lung architecture, with formation of small box-like structures. As the process becomes worse, the architectural derangement becomes more obvious, with progressive effacement and loss of the orderly arrangement of the lung until little remains other than the supporting framework of vessels, septa, and bronchi. The best way to see panlobular emphysema grossly is to examine lung slices immersed in a water or fixative bath and then immediately after removal from the bath. The immersed specimen shows enlarged airspaces and, when the slices are lifted from the bath, panlobular emphysema can be suspected because the lung parenchyma "falls away" from the supporting structures and protrudes slightly above them. In contrast to centrilobular emphysema, panlobular emphysema is usually worse in the lower lobes (Fig. 40-3*B*).

Histological examination is a sensitive method of recognizing panlobular emphysema. The pattern is again one of simplification with diminishing contrast between alveoli and alveolar ducts (Fig. 40-4*C,D*). Despite the greater extent of tissue destruction, in panlobular emphysema the pores of Kohn are more uniform and inconspicuous than those found in centrilobular emphysema.

Panlobular emphysema is the characteristic lung lesion seen in α-1-antitrypsin deficiency. Panlobular emphysema may also occur as a consequence of permanent obliteration of airways (obliterative bronchiolitis, constrictive bronchiolitis). Most often, obliteration of airways results in collapse of the distal lung parenchyma and dilatation of the bronchi proximal to the obliterated airways. This is the sequence of events in postinfective bronchiectasis. In some instances, however, the lung parenchyma does not collapse, but remains fully expanded or becomes emphysematous. The parenchymal sequel to bronchial and bronchiolar obliteration depends on the extent of the obliteration and the amount of collateral ventilation between adjacent airspaces distal to unobstructed airways. If collateral ventilation is present, then the units distal to the obliterated airways will remain expanded by virtue of the air reaching them by collateral ventilation, producing overexpansion and destruction of lung parenchyma beyond the obliterated airways. The terms Swyer-James or MacLeod's syndrome are applied when this process affects most of one lung but spares the other.

Distal Acinar Emphysema: Paraseptal Emphysema

The original description of distal acinar emphysema is generally credited to Loeschcke, who described collections of subpleural bullae. It was Heard, however, who first noted that the lesions could extend into the substance of the lung, where they lay along the septa, and coined the term "paraseptal" emphysema. Since the distal part of the acinus (alveolar sacs and ducts) is dominantly involved, emphysema is most striking adjacent to the pleura (superficial emphysema or mantel emphysema), along lobular septa (paraseptal emphysema), at the margins of lobules and acini (periacinar emphysema), and along vessels and airways, which, when cut longitudinally, display a linear pattern. The characteristic morphology is that of multiple contiguous, enlarged airspaces, varying from <0.5 mm to >2 cm in diameter.

Paraseptal emphysema is usually limited in extent, and is found most commonly along the anterior and posterior parts of the upper lobe and along the posterior surface of the lower lobe. When extensive, it is usually more severe in the upper half of the lung. Gough has stressed that it is associated with fibrosis of the tissue between the enlarged airspaces, and this is certainly a common finding.

Irregular Emphysema

Irregular emphysema is logically named, because the acinus is indeed irregularly involved in it. Irregular emphysema is almost invariably adjacent to a scar, giving name to the synonyms scar or paracicatricial emphysema. Most scars within the lung are usually small and the emphysema is limited in extent. The severity of irregular emphysema depends on the extent of damage to lung tissue, and multiple scars through the lung may lead to multiple foci of irregular emphysema.

Differential Diagnosis of Emphysema (Table 40-1)

Gas Trapping

The lungs of an asthmatic who has succumbed during an attack are usually characterized by gas trapping, and thus

Table 40-1

Differential Diagnosis of Airspace Enlargement

	Distribution	Enlarged Structure
Centrilobular emphysema	Upper lobes, center of lobule	Alveolar ducts, alveoli
Panlobular emphysema	Lower lobe, uniform in lobule	Alveoli
Paraseptal emphysema	Apical, adjacent to septum	Alveoli
Irregular emphysema	No typical site, adjacent to scars	Alveoli
Aging	Uniform in lung	Alveolar ducts
Compensatory alterations	Uniform in lung	Alveoli
Obstructive alterations	Affected area	Alveoli
Genetic alterations	Uniform in lung	Lack of septuation
Asthma	During acute attack	Alveoli
Honeycomb lung	Variable—often subpleural	Total remodeling

remain inflated, with focal areas of atelectasis. In a patient with longstanding asthma who has died from other causes, or has had a lung resection, there may still be areas of atelectasis. Focal bronchiectasis can be found also, particularly in the anterior segment of the upper lobe. However, parenchymal destruction is not a feature of asthma, and thus gross, microscopic, and morphometric analyses will all be normal in the chronic asthmatic.

Nonemphysematous Airspace Enlargement

Although not part of the differential diagnosis of COPD, nonemphysematous airspace enlargement also occurs in infancy. In congenital lobar hyperinflation (emphysema), the lobes are overinflated rather than emphysematous, but in some instances they may be polyalveolar. Some other genetic abnormalities will also give enlarged airspaces, but this is due to failure of septation with a simplified rather than a destroyed alveolar framework.

At the other side of the age spectrum, the term senile emphysema was once used to describe the enlarged airspaces found in the aged. On gross examination, lungs round out with increasing age. An analysis of Gough sections showed increases in anteroposterior distance, height, perimeter, and area of the lung up to the age of 59 years. After this age, only the anteroposterior diameter continued to increase significantly, thus "rounding" the lung dimensions. This change is due to an increase in the volume proportion of alveolar duct air, with shallower and flatter alveoli, a process termed ductectasia. There is no evidence of lung destruction; thus, the condition does not fulfil the criteria for emphysema.

If a part of the lung collapses or is removed, the remaining lung can expand to fill the increased amount of space available, a process known as compensatory overinflation. The exact way that this happens and the limits of the process are unknown. However, no tissue destruction has occurred and, by definition, this is not emphysema. It is not clear how much larger the overinflated lung can become, or how it expands to reach the new and larger volume. It is generally thought that the possible extent of overinflation is modest and that all the parts of the acinus are equally expanded.

Obstructive overinflation can occur in adults, and two mechanisms may be involved. In one, the obstruction in the bronchus may act as a ball valve, so that air enters on inspiration but does not leave on expiration. Alternatively, the bronchus may be completely obstructed and air may be trapped behind channels of collateral ventilation. Whatever the mechanism, the affected part of the lung can expand considerably. Obstructive overinflation differs in a number of ways from compensatory overinflation, although, in both, the lung contains too much air per unit of lung and lung tissue.

Honeycomb Lung

The airspace enlargement that occurs in cryptogenic fibrosing alveolitis (usual interstitial pneumonia) and other fibrotic lungs diseases could possibly be confused with emphysema. While honeycomb spaces are enlarged airspaces, they are the result of parenchymal remodeling with formation of new airspaces, rather than destruction of normal airspaces, and thus have thickened and irregular walls with none of the structure of an acinus. They are lined by bronchiolar epithelium, and often contain mucus; the walls have abundant and well collagenized connective tissue, which may also contain impressive amounts of muscle and sometimes fat. There is usually interstitial inflammation in the form of varying degrees of lymphocytic and plasma cell infiltration.

LESIONS OF THE LARGE AIRWAYS IN COPD

The majority of studies in this area have focused upon the lesions present when the clinical signs and symptoms of chronic bronchitis are also present.

Gross Findings

Gross lesions in the large airways are few and subtle. Bronchial pits are the dilated openings of one or more mucous glands into the epithelium. They are most often found along the margins of the cartilaginous rings and at the bifurcations of the airways. In nonbronchitis the pits can be seen using a hand lens or a dissecting microscope, but in chronic bronchitis, the ducts may be distended with mucus and the mucus may protrude into the lumen of the bronchus and be visible grossly. It is not correct to refer to these as diverticula. First, these are protrusions of normal ducts; and second, they do not extend through all of the muscle coats of the bronchial wall.

While enlarged bronchial pits are the most obvious gross lesions in COPD, careful examination of lung specimens will show that the bronchi do not taper progressively as they approach the pleura, and they also display prominent circular ridges, probably due to bands of hypertrophic smooth muscle. Mucus may be present in the airway lumen, particularly in subjects with chronic bronchitis.

Microscopic Findings

The intraluminal mucus found in the airways of subjects with COPD contains a mixed population of epithelial cells and acute and chronic inflammatory cells; large numbers of neutrophils can be found during an exacerbation.

Detailed microscopic analysis of the large airways in COPD reveals alterations in the entire airway wall (Fig. 40-5). Epithelial changes are mild in degree and are not necessarily consistent from patient to patient. Epithelial sloughing can occur, but in most instances the epithelium is generally intact and shows only mild goblet cell or squamous cell metaplasia, both of which appear to be more marked if the subject has symptoms of chronic bronchitis. The reticular basement membrane thickness is within the normal range.

The thickness or area of mucous glands in subjects with COPD in general, or chronic bronchitis in particular, is increased over a population mean, but has a distribution that extensively overlaps that of normals and asthmatics.

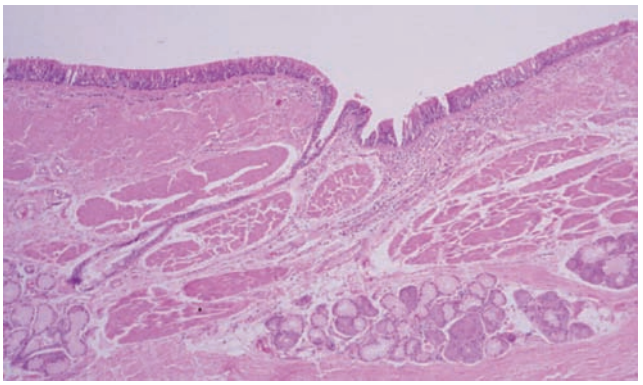


Figure 40-5 Large airway from a subject with chronic bronchitis. The overall wall is thickened with inflammation and fibrosis, and there is prominence of the smooth muscle in addition to the bronchial mucous glands.

Interestingly, there appears to be a decreased percentage of serous acini in these glands, a feature that apparently does not occur in asthma.

Thickening of the inner wall (area internal to the muscular layer) appears to be the most consistent component of airway wall thickening in the large airways of subjects with COPD, and appears to be generalized. This increase in thickness can be partially attributed to edema and hyperemia of the bronchi, but is also due to an increase in fibrous tissue or other matrix proteins.

In the large airways of subjects with COPD, increases in the thickness of the muscular layer have not been consistently identified. Although some studies have found that the average proportion of muscle in main, lobar, and segmental bronchi was approximately doubled in patients with chronic bronchitis and airflow obstruction, others have found that a substantial number of patients fell within the normal range.

Alteration in the amount of cartilage in COPD does not appear to be a consistent finding. While some studies described cartilage atrophy in chronic bronchitis and/or emphysema, or circumferentially arranged cartilage that extended farther distally in nonbronchitis than bronchitis, this was not supported by other reports. However, histological signs of cartilage damage, as judged by loss of cellular or pericellular metachromasia and vacuolated or empty lacunae can be consistently identified.

The large airways in COPD show a mild, usually mixed, inflammatory infiltrate. Bronchus-associated lymphoid tissues (BALT) is not consistently found, but its frequency appears to be considerably higher (82 percent) in smokers than nonsmokers (14 percent). Bronchial biopsy analysis consistently shows an increase in CD8 T cells, with eosinophils and neutrophils found during exacerbations. Chronic inflammation can also be found around the bronchial glands, particularly in subjects with chronic bronchitis.

Differential Diagnosis (Table 40-2)

Asthma

In asthma the large airways are not dilated, but mucus plugs are classically identified in the large airways of subjects with fatal or near-fatal asthma, and the mucus may be continuous with that present in the ducts of the mucus glands. Visible bronchial pits are not a standard feature of asthma, and although the airway wall may be thickened, this is usually not apparent grossly.

In the large airways of subjects with asthma, desquamation of the epithelium is a common feature, and this may be worse in people who have persistent rather than intermittent activity. Sloughing of cohesive epithelial clusters produces the Creola bodies found in cytology specimens. Goblet cell metaplasia can be marked in both asthma and bronchiectasis, but there is a considerable degree of variability, so that this feature cannot be used in isolation to distinguish among the airways of subjects with COPD, asthma, and bronchiectasis. These epithelial cell changes result in an overall thickening of the epithelium in asthma, but not in COPD. In asthma, the reticular basement membrane (lamina reticularis) is characteristically thickened. This alteration occurs early in the course of disease, and remains even when the asthma is mild or well controlled.

The airways of asthmatics demonstrate a greater severity of inner wall thickening, with values double those found in patients with COPD. The increase in thickness is due to variable increases in fibrous tissue, inflammatory cells, edema fluid, and vascular prominence. Analysis of the muscular wall in subjects with severe or fatal asthma compared with normals or those with COPD shows a marked increase in amount of muscle, with a lesser increase in asthmatics who died *with* rather than *from* their asthma There has also been a suggestion that the increase in muscle mass may occur relatively early during childhood.

Neutrophils are the predominant cell present in the mucus of patients with bronchiectasis, while eosinophils and accompanying Charcot Leyden crystals are the hallmark of asthmatic mucus. As noted, the cartilaginous destruction present in polychondritis is severe and associated with chronic inflammation, thus easily distinguishing the two processes. Depending upon the severity of the inflammation in bronchiectasis, there may be significant cartilaginous destruction.

Airways from fatal and near-fatal asthma also contain isolated aggregates of lymphoid cells, roughly in the same proportion as that present in COPD. However, in asthma, by contrast to COPD, there is an inflammatory infiltrate consisting of activated eosinophils, and activated CD4 T cells in the submucosa, and both mast cells and neutrophils within the glands. There is little in the literature regarding the inflammatory cell infiltrates present in the airway walls in bronchiectasis. Compared with asthma, there appear to be fewer eosinophils, but a similar population of CD 45 (as opposed to any specific subtype) lymphocytes, with both cell types having a greater density in the inner, as opposed to the outer aspect of the airway.

Bronchiectasis

In bronchiectasis, there is by definition an abnormal and permanent dilatation of the bronchi, and this is usually present to a much greater degree than is found in COPD, and is often

Table 40-2

Pathologic Differential Diagnosis of Large Airway Lesions in COPD

	Dilatation	Structural Distortion	Pits	Glands	Submucosal Fibrosis	Basement Membrane	Epithelium	Lumenal Mucus	Cartilage	Muscles
Chronic bronchitis	√	Fibrosis and inflammation	√	√	√	X	Goblet cell metaplasia	√	√	√/X
Asthma	Focal	Focal	X	√	√	√	Goblet cell metaplasia	√	X	√
Bronchiectasis	√	Fibrosis and inflammation	√	√/X	√	X	Focal goblet cell metaplasia	√	√	X
Tracheobronchiopathia osteoplastica	√	Bony nodules	X	X	X	X	X	X	√	X
Tracheomegaly	√	X	Diverticula	X	X	X	X	X	X	X
Relapsing polychondritis	√	√	X	X	X	X	X	X	√	X

Check mark indicates that the feature is present; X indicates that the feature is absent.

accompanied by airway distortion. There is exaggeration of the muscular ridges and the presence of multiple bronchial gland–based pits. The large airway walls can be thickened and/or irregularly thinned as a result of inflammation and fibrosis, and there is often inspissated mucus or actual purulent material.

Miscellaneous Conditions

Tracheobronchomegaly (Mounier-Kuhn syndrome) is characterized by a marked dilatation of the trachea and major bronchi, with diameters 5 to 10 cm above normal values. In this condition there are multiple true diverticula, with outpouchings formed of membranous tracheal tissue between the cartilaginous rings, with atrophy or absence of elastic fibers.

Patients with tracheobronchopathia osteoplastica have an obstructive pulmonary function pattern; however, unlike the trachea and large airways in COPD, cartilaginous and bony nodules are present in the subepithelial space (submucosa). Relapsing polychondritis shows variable dynamic expiratory and/or inspiratory obstruction depending on the size and location of the airways involved. In this disease, however, the obstruction is due to impaired airway clearance of inflammatory debris, and an ineffective cough because of dynamic upper airway collapse. The airways are dilated and the walls are thickened because of the extensive fibrosis and chronic inflammation due to the immunological nature of this condition. In particular, the cartilaginous plates show extensive destruction.

LESION OF THE SMALL AIRWAYS IN COPD

In the context of COPD, small airways refer to airways with an internal diameter of 2 mm or less. In COPD, intraluminal mucus can be found in the small airways, and there appears to be an overall relationship between the degree to which the airways are occluded by mucus and the FEV_1. Goblet cells are rare in normal small airways, but goblet cell metaplasia is a frequent finding in the airways of patients with COPD.

Similar to the large airways, there is alteration of the all of the small airway wall compartments in patients with COPD (Fig. 40-6). These changes result in an overall decrease in the internal bronchiolar diameter and, as assessed by a conformity index, produce significant deformity. Similar results are obtained from three-dimensional reconstructions. Detailed measurements of the airway walls show that the increased wall thickness is due to increases in the epithelium, subepithelial fibrous tissue compartment (submucosa, lamina propria), smooth muscle, and adventitia. Although the adventitia is thickened, there is a loss of alveolar attachments to the airway wall, an important process because it allows early airway collapse on expiration.

One of the earliest histological abnormalities that can be detected in cigarette smokers is the presence of macrophages in the lumen of the respiratory bronchioles. However, an inflammatory infiltrate can also be identified within the walls of both membranous and respiratory bronchioles in subjects with COPD. When examined in conjunction with the GOLD (Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease) stage, the proportion of airways which had measurable neutrophils appear to be increased in GOLD stages 2 to 4, and airways with measurable macrophages show a progressive increase from GOLD stage 0 to 4, while there does not seem to be any alteration in the percentage of airways that contain eosinophils among the GOLD stages. The percentage of airways with CD4, CD8, and B cells also increase with GOLD stage, but when these data are expressed as total accumulated volume, only the B cells and CD8 cells show progressive increases. The presence of lymphoid follicles is markedly increased in GOLD stages 3 and 4.

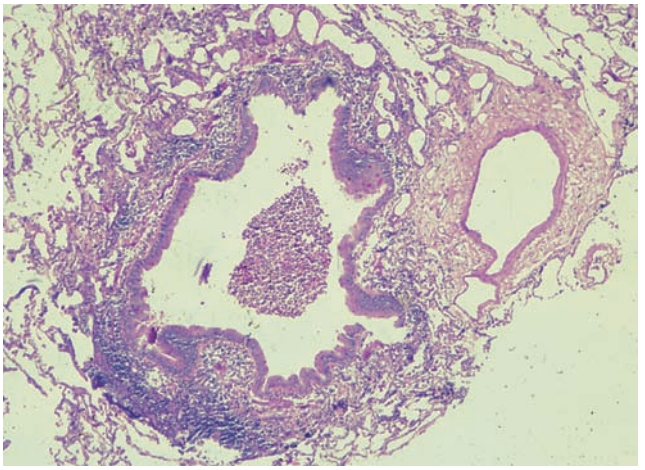


Figure 40-6 A small airway from a subject with COPD. The lumen contains mucus and inflammatory debris. There is goblet cell metaplasia of the epithelium. The subepithelial (submucosal) layer is increased in thickness due to an increase in fibrous tissue and inflammatory cells.

Differential Diagnosis

Asthma

Mucous plugs and goblet cell hyperplasia are markedly increased in the small airways of asthmatics and this increase is generally much greater than is seen in COPD. In addition, the basement membrane thickness is approximately 20 percent greater than that found in either normals or patients with COPD. The peripheral airways of asthmatics have an inflammatory infiltrate that features lymphocytes and eosinophils, with many of the inflammatory cells in the adventitial, as opposed to the submucosal compartment. The data regarding the vessels in the submucosa are controversial, with some studies suggesting that they are congested, but not increased in number, in asthmatics compared with COPD, and others demonstrating an increased number of vessels, but a lesser total area in asthma compared with COPD. Although smooth muscle is increased in asthmatics, the increase is not as great as that present in the large airways. Moreover, the distribution of smooth muscle increase in the bronchial tree may be quite different, with some patients displaying a generalized

increase, while in others the increase is restricted to the larger airways. Overall, the small airways in asthmatic subjects who have died because of their disease have a greater area of subepithelial fibrous tissue, smooth muscle, and adventitial fibrous tissue than do subjects who died with their disease, which in turn have a greater area than do the airways of subjects with COPD. Thus, although the same qualitative changes are present in both asthmatics and COPD, they are more severe in asthmatics and most severe in cases of fatal asthma. Interestingly, there appears to be a loss of alveolar attachments in cases of fatal asthma, although this is less than that present in the airways of patients with COPD.

Follicular Bronchiolitis

Follicular bronchiolitis is characterized by narrowing of the bronchioles due to adventitial and subepithelial lymphoid follicles, and accompanied by a lymphoplasmacytic inflammatory infiltrate. The condition is classically found in patients with rheumatoid arthritis or those with IgA deficiency. This process can mimic severe COPD small airways disease, but the inflammatory infiltrate is generally magnified compared to COPD, while there is little goblet cell metaplasia in the airway epithelium.

Panbronchiolitis

The presence of foamy macrophages in the airway wall and lumen and extending down into the alveolar ducts and alveoli is a feature of the condition known as panbronchiolitis, originally described in Japan but now known to occur worldwide. Follicular hyperplasia of the peribronchiolar lymphoid tissue is frequent, and bronchiolectasis is found in the more advanced lesions.

Constrictive Bronchiolitis

The term constrictive bronchiolitis appears to have been coined by Gosink et al. In constrictive bronchiolitis, the airway lumen is occluded by a progressive thickening of the subepithelial (submucosal) space. Both the membranous and respiratory bronchioles are involved, and show transmural inflammatory cell infiltrates, occasionally with epithelial necrosis. Mucous plugs can also be identified. As the process evolves, the inflammatory infiltrate wanes, and greater amounts of fibrous tissue can be demonstrated both in the peribronchial and subepithelial portions of the airway, acting to narrow or obliterate the airway lumen. Lesions of constrictive bronchiolitis, particularly in the organized phase, may be difficult to demonstrate, and may require elastic stains to outline the obliterated airway. Thus, the lesions in COPD differ from constrictive bronchiolitis only in degree.

Mineral dust–induced airways disease is a distinctive type of constrictive bronchiolitis, characterized by a stereotypic response of the small airways to high doses of particulate, regardless of the specific mineral dust involved. The lesions consist of fibrosis and thickening of the walls of both the membranous and respiratory bronchioles, sometimes extending down the alveolar ducts, the latter finding providing diagnostic discrimination from tobacco smoke–induced airways disease, which tends not to involve the alveolar ducts. Pigment deposition is highly variable, and is not a diagnostic feature.

Proliferative Bronchiolitis

The lesions of proliferative bronchiolitis have been elegantly described and illustrated. Within the lumens of the membranous and respiratory bronchioles are plugs of organizing fibroblastic (granulation) tissue. Occasionally, ulceration of the epithelium can be seen, and early lesions may have fibrin. The granulation tissue is formed of a pale matrix with proliferating spindle cells, accompanied by chronic inflammatory cells. As the lesions age, the granulation tissue usually shrinks and contracts. However, in a certain proportion of cases, the bronchiolar cells proliferate over the granulation tissue, and incorporate it into the subepithelial space, leaving an irregular airway lumen.

Although acute bronchiolitis, be it bacterial or viral in nature, is usually easily distinguished from the lesions of COPD by the presence of extensive epithelial damage, healed lesions may show nonspecific airway fibrosis and chronic inflammation, or the residua of proliferative bronchiolitis. Interestingly, latent adenoviral infection has been suggested as a contributor to airflow obstruction in adults by amplifying the inflammatory response in the bronchioles of cigarette smokers. Airway disease complicating other diseases may also need to be distinguished from that of COPD. For example, post-transplant bronchiolitis or airways disease in patients with inflammatory bowel disease (both Crohn's disease and ulcerative colitis) include both proliferative and constrictive bronchiolitis. Inflammatory bowel disease may also have large airway involvement.

LESIONS OF THE VESSELS IN COPD

There are no consistent alterations in the large elastic pulmonary arteries of subjects with COPD. Atheromata can be found, but unless there is pulmonary hypertension, the incidence is probably not greater than that found in a carefully matched population.

Cigarette smokers, with or without pulmonary hypertension, have an increase in arterial muscle media thickness as well as intimal fibrosis in the muscular arteries, and progressive muscularization of the small arterioles. Increases in intimal thickness with longitudinal muscle formation are a common feature in lungs of patients with COPD (Fig. 40-7). There appears to be a progressive increase in the numbers of smaller muscularized arteries, percent medial thickness, and percent intimal thickness of muscularized arteries from nonsmokers, to smokers without obstruction, to smokers with airflow obstruction.

The lesions of primary pulmonary hypertension and hypertension secondary to vascular shunting also include intimal fibrosis and increased muscular media thickness. Intimal fibrosis is often cellular in its early phases, but progresses to concentric laminar fibrosis, which can almost totally obliterate the vessel lumen. These changes are of much greater

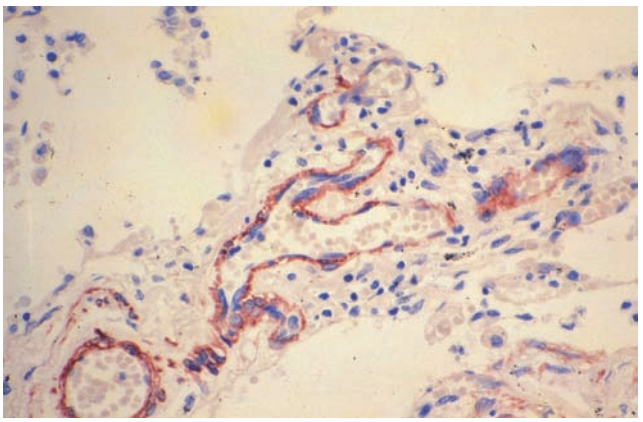


Figure 40-7 A small pulmonary artery from a subject with COPD. These vessels, situated adjacent to the alveolar ducts, are normally poorly muscularized, but in this case, the vessel has a distinct circumferential muscular layer.

severity than those identified secondary to COPD. Vasculitis, fibrinoid necrosis, and plexiform lesions are never found in COPD. Lesions of chronic thromboembolic disease include eccentric intimal thickening, and the occasional formation of webs due to recanalization of the thrombi.

SUMMARY

There are a number of pathological alterations of the lung in COPD. These involve almost all of the lung compartments, including the parenchyma, vasculature, and large and small airways. These changes can overlap the pathologic findings present in other diseases associated with airflow obstruction, or other diseases that are manifested in the lung. It is important to be able to make the distinction among these diseases. Although the pathologic alterations roughly correlate to alterations in pulmonary function, it is important to remember that their individual contributions are not well worked out. Thus, it may be difficult on an individual patient basis to proceed from a clinical classification such as the GOLD classification to a mechanistic/pathologic explanation of the airflow obstruction.

SUGGESTED READING

Aikawa T, Shimura S, Sasaki H, et al.: Morphometric analysis of intraluminal mucus in airways in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 140:477–482, 1989.

Cardoso WV, Sekhon HS, Hyde DM, et al.: Collagen and elastin in human pulmonary emphysema. *Am Rev Respir Dis* 147:975–981, 1993.

Carroll NG, Mutavdzic S, James AL, et al.: Increased mast cells and neutrophils in submucosal mucous glands and mucus plugging in patients with asthma. *Thorax* 57:677–682, 2002.

Ebina M, Yaegashi H, Chiba R, et al.: Hyperreactive site in the airway tree of asthmatic patients revealed by thickening of bronchial muscles. *Am Rev Respir Dis* 141:1327–1332, 1990.

Elliot JG, Jensen CM, Mutavdzic S, et al.: Aggregations of lymphoid cells in the airways of nonsmokers, smokers, and subjects with asthma. *Am J Respir Crit Care Med* 169:712–718, 2004.

Haraguchi M, Shimura S, Shirato K: Morphologic aspects of airways of patients with pulmonary emphysema followed by bronchial asthma-like attack. *Am J Respir Crit Care Med* 153:638–643, 1996.

Haraguchi M, Shimura S, Shirato K: Morphometric analysis of bronchial cartilage in chronic obstructive pulmonary disease and bronchial asthma. *Am J Respir Crit Care Med* 159:1005–1013, 1999.

Heard BE: A pathological study of emphysema of the lungs with chronic bronchitis. *Thorax* 13:136–149, 1958.

Hogg JC, Chu F, Utokaparch S, et al.: The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med* 350:2645–2653, 2004.

Jeffery P, Wardlaw AJ, Nelson FC, et al.: Bronchial biopsies in asthma. *Am Rev Respir Dis* 140:1745–1753, 1989.

Jeffery PK: Comparison of the structural and inflammatory features of COPD and asthma. *Chest* 117:251S–260S, 2000.

Jeffery PK: Remodeling in asthma and chronic obstructive lung disease. *Am J Respir Crit Care Med* 164:528–538, 2001.

Laurell CB, Eriksson S: The electrophoretica1-globulin pattern of serum in a1-antitrypsin deficiency. *Scand J Clin Lab Invest* 15:132–140, 1963.

Nagai A, Inano H, Matsuba K, et al.: Scanning electron microscopic morphometry of emphysema in humans. *Am J Respir Crit Care Med* 150:1411–1415, 1994.

Niewoehner DE, Kleinerman J, Rice DB: Pathologic changes in the peripheral airways of young cigarette smokers. *N Engl J Med* 291:755–758, 1974.

Pare PD, Wiggs BR, James A, et al.: The comparative mechanics and morphology of airways in asthma and in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 143:1189–1193, 1991.

Pauwels RA, Buist AS, Ma P, et al.: Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: National Heart, Lung, and Blood Institute and World Health Organization Global Initiative for Chronic Obstructive Lung Disease (GOLD): Executive summary. *Respir Care* 46:798–825, 2001.

Retamales I, Elliott WM, Meshi B, et al.: Amplification of inflammation in emphysema and its association with latent adenoviral infection. *Am Rev Respir Dis* 164:469–473, 2001.

Richmond I, Pritchard GE, Ashcroft T, et al.: Bronchus associated lymphoid tissue (BALT) in human lung: Its

distribution in smokers and non smokers. *Thorax* 48:1130–1134, 1993.

Ryan SF, Vincent TN: Ductectasia: an asymptomatic pulmonary change related to age. *Med Thorac* 22:181–187, 1965.

Saetta M, Turato G, Baraldo S, et al.: Goblet cell hyperplasia and epithelial inflammation in peripheral airways of smokers with both symptoms of chronic bronchitis and chronic airflow limitation. *Am J Respir Crit Care Med* 161:1016–1021, 2000.

Snider GL, Thurlbeck WM, Bengali ZH: The definition of emphysema. Report of a national heart lung and blood institute division of lung diseases workshop. *Am Rev Respir Dis* 132:182–185, 1985.

Thurlbeck WM, Wright JL: *Thurlbeck's Chronic Airflow Obstruction*, 2nd ed. Hamilton, Ont, BC Dekker, 1998.

Wang NS, Ying W-L: Morphogenesis of human bronchial diverticulum. A scanning electron microscopic study. *Chest* 69:201–204, 1976.

Wright JL, Levy RD, Churg A: Pulmonary hypertension in chronic obstructive pulmonary disease: current theories of pathogenesis and their implications for treatment. *Thorax* 60:605–609, 2005.