

# Chronic Obstructive Pulmonary Disease: Radiology-Pathology Correlation

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**Abstract:** Chronic obstructive pulmonary disease is defined as a preventable and treatable disease state characterized by airflow limitation that is not fully reversible. This review will discuss the relevant anatomy of the secondary pulmonary lobule, the subtypes of emphysema, and their imaging appearances and corresponding pathologic findings.

**Key Words:** emphysema, high-resolution computed tomography, bronchitis, secondary pulmonary lobule

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The introduction of high-resolution computed tomography (HRCT) of the lung in the early 1980s<sup>1–3</sup> opened a new era in radiologic-pathologic correlation. Before CT and HRCT, the detection of the structural abnormalities of COPD (ie, emphysema) by ordinary chest radiograph was not possible until disease had reached an advanced stage.

An HRCT image can be compared with a gray-scale macroscopic low-field histologic view. It is able to diagnose early and even preclinical emphysema with a high degree of pathologic correlation and locate the exact site of irreversible structural change in its centrilobular,<sup>4</sup> panlobular, paraseptal, or paracatricial location. This review will discuss the relevant anatomy of the secondary pulmonary lobule, the subtypes of emphysema, and their imaging appearances and corresponding pathologic findings.

## ANATOMY OF THE SECONDARY PULMONARY LOBULE

The secondary pulmonary lobule (Fig. 1) is the smallest unit of lung margined by connective tissue.<sup>5</sup> It is polyhedral and it contains pulmonary arteries, veins, lymphatics, airways, alveoli, and interstitium. It is supplied by a small bronchiole and a pulmonary arterial branch and is margined by connective tissue—the interlobular septa, containing pulmonary venules and lymphatics. The airway supplying the secondary pulmonary lobule is the preterminal or simply “lobular bronchiole,” which gives rise to several terminal bronchioles. The terminal bronchioles end in respiratory bronchioles. Respiratory bronchioles end

in alveolar ducts, sacs, and alveoli in succession. The respiratory bronchiole serves both for conduction and for gas exchange. The acinus is defined as the unit of lung that is distal to the terminal bronchiole, which is succeeded by 3 orders of respiratory bronchioles. The acinus typically measures about 7 mm in diameter.

All the acini arising from a terminal bronchiole comprise a primary lobule; a secondary lobule usually contains about 6 primary lobules with the center of each primary lobule being located about halfway between the center and periphery of a secondary lobule. The connective tissue septations that surround secondary lobules are not well defined everywhere in the human lung.

## EMPHYSEMA

Chronic obstructive pulmonary disease (COPD) is defined as a preventable and treatable disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking.<sup>6</sup> Emphysema is one of its components, along with asthma and chronic bronchitis. Emphysema is defined pathologically as permanent enlargement of the

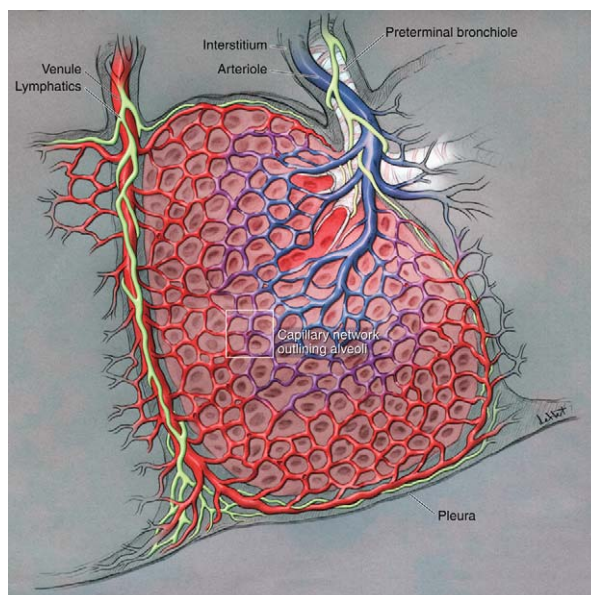
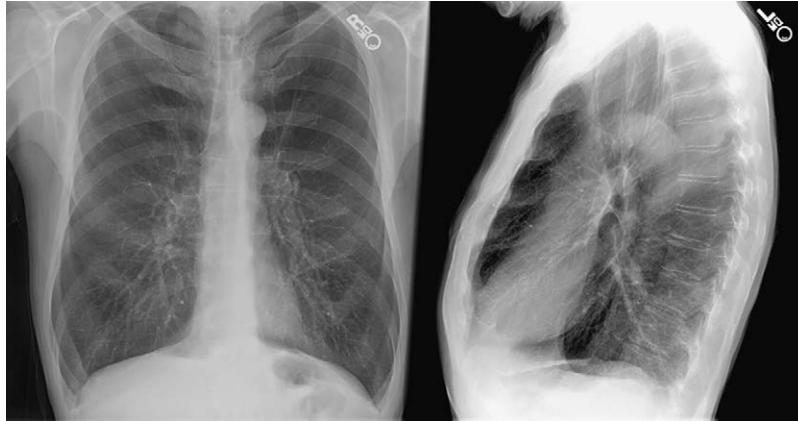


FIGURE 1. Anatomy of the secondary pulmonary lobule.

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**FIGURE 2.** Emphysema: chest radiographs, postero-anterior and lateral views, show hyperinflation of the lungs (flattened diaphragm and widened retrosternal space), increased translucency in the upper lungs with vascular attenuation and distorted arborization.

airspaces distal to the terminal bronchioles, accompanied by destruction of their walls and without obvious fibrosis.<sup>7</sup> The essential feature is that alveolar septal walls are lost, resulting in residual airspaces that are larger than in normal lung tissue. Emphysema is classified according to the anatomic site of septal loss as centrilobular (proximal acinar), panlobular (panacinar), paraseptal (distal acinar), and irregular.<sup>8</sup>

The normal alveolus (0.1 to 0.2 mm diameter) is smaller than the resolving power of the unaided eye, chest radiography, and HRCT. In addition, the x-ray attenuation due to any individual alveolar septum is quite small. Destruction of multiple alveolar septa is required to recognize early emphysema qualitatively at HRCT.

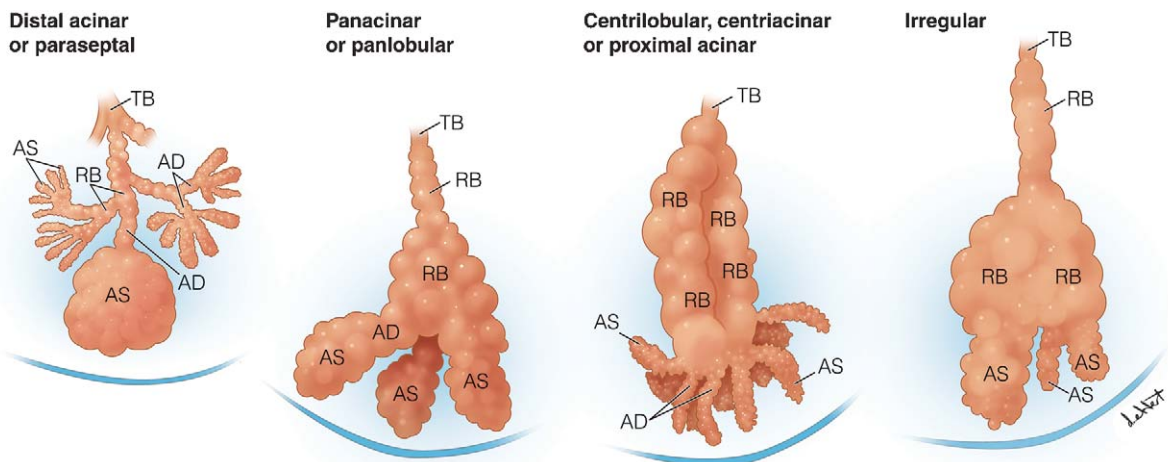
**CHEST RADIOGRAPHY**

Chest radiography provides the initial imaging tool for assessing COPD. Findings include hyperinflation of the lungs, flattening of the domes of the hemidiaphragms,

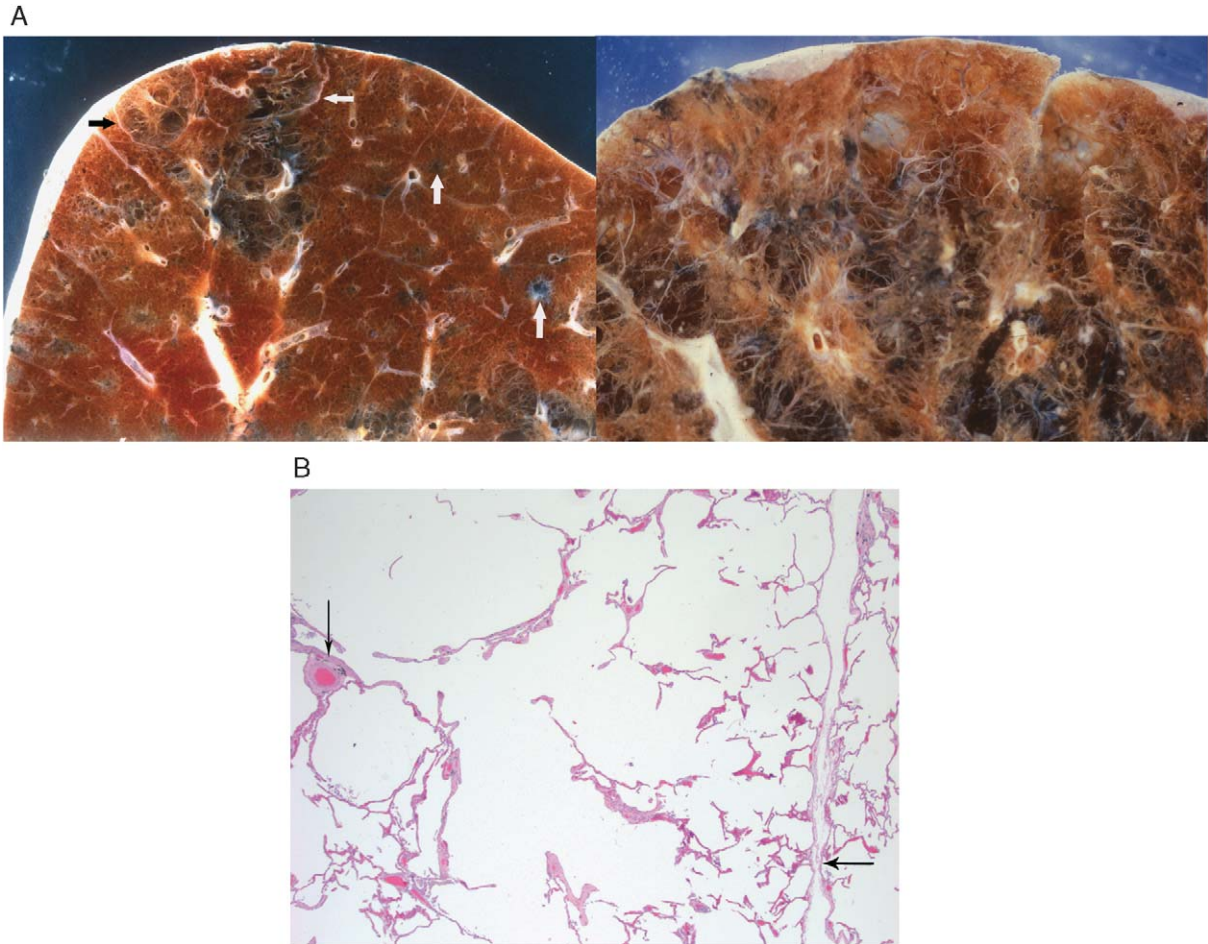
attenuation or absence of pulmonary vasculature, loss of the regular vascular branching pattern, widened retrosternal space (Fig. 2), large focal lucencies indicating bullae, and bronchial wall thickening. According to the combined American Thoracic Society/European Respiratory Society statement on COPD diagnosis and management, the chest radiograph helps in differential diagnosis. More specifically it helps exclude other diagnoses, such as pneumonia, cancer, congestive heart failure, pleural effusion, and pneumothorax.<sup>6</sup> Chest radiography is neither sensitive nor specific for diagnosing COPD, although it can help diagnose bullae.

**CT**

CT is better than chest radiography in qualitative assessment of emphysema,<sup>9</sup> demonstrating its extent, type, and spatial distribution. HRCT is even better than conventional CT in assessment of emphysema.<sup>10</sup> These days, with the common use of 64-detector-row CT scanners, routine chest CT scans acquired with 1.25-mm or 0.625-mm



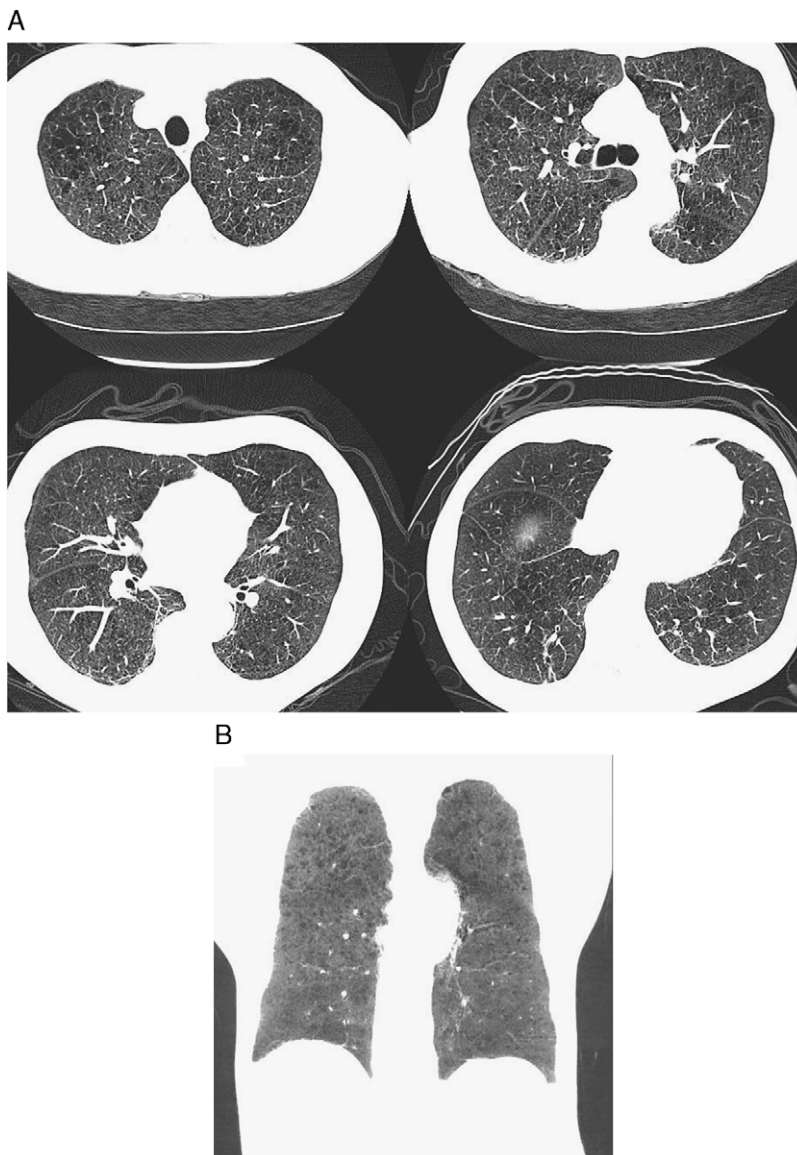
**FIGURE 3.** Types of emphysema: line diagram shows the parts of secondary pulmonary lobule that are affected in different types of emphysema. Respiratory bronchioles are primarily affected by centrilobular emphysema; peripheral alveolar ducts, sacs, and alveoli in paraseptal emphysema (PLE); all the components (ie, respiratory bronchioles, alveolar ducts, alveolar sacs, and alveoli) in panlobular emphysema (PLE), and any part in irregular or paracatricial emphysema.



**FIGURE 4.** Centrilobular emphysema (CLE): A, The gross pathology specimen on the left shows multiple severely emphysematous secondary pulmonary lobules (horizontal arrows) having well-defined white peripheral fibrous septa. Small foci of mild CLE (vertical arrows) are characteristically located about halfway between the center and periphery of secondary lobules. Emphysema appears dark in this photograph and relatively normal lung medium brown. The specimen on the right shows advanced centrilobular emphysema, with destruction involving the entire secondary pulmonary lobule and little sparing of the periphery. B, Histopathologic (hematoxylin and eosin-stained) image shows preferential centrilobular loss of alveolar septa near the centrilobular arteriole (vertical arrow), with relative preservation of alveoli at the periphery of the secondary lobule (horizontal arrow). Image width is approximately 5.5 mm.



**FIGURE 5.** Centrilobular emphysema (CLE) and edema: A, Chest radiographs, postero-anterior and lateral views, show hyperinflation of the lungs (flattened diaphragm), increased translucency in the upper lungs with vascular attenuation and loss of arborization. B, Emphysematous spaces outlined by edema fluid filling the surrounding airspaces give an appearance of reticulation in this patient with lung edema superimposed on confluent, upper-lung predominant CLE.



**FIGURE 6.** Centrilobular emphysema: A, Transverse computed tomography images shows centrilobular hypoattenuation with upper lung predominance. Note the resemblance of the macroscopic pathologic image in Figure 4A. B, Coronal minimum intensity projection image brings out the distribution and extent of emphysema.

collimation are in effect contiguous HRCT scans, whether ordered as such or not. Contiguous thin sections are very helpful in detecting early centrilobular emphysema (CLE), when the lucencies are still small. Thus, the identification of structural alterations in COPD has become easier and subclinical emphysema is easily detected. Furthermore, the quality of postprocessed images has improved on modern multidetector CT scanners; one postprocessing technique of particular interest is the minimum intensity projection, which helps bring out the morphology of emphysema. Beyond demonstrating the structural alterations of emphysema, CT has also been validated in its quantification.<sup>11,12</sup>

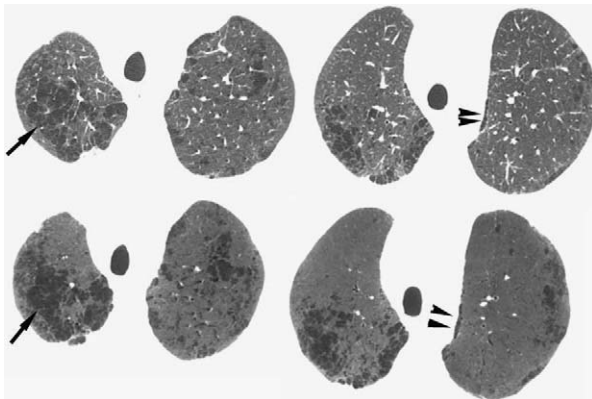
### CLE

CLE is defined by preferential loss of septa at the center of primary lobules; that is, around respiratory bronchioles.

Destruction of respiratory bronchioles progresses distally and also involves adjacent units. Early in the course of the disease there is relative sparing of the distal alveolar ducts, alveolar sacs, and alveoli (Fig. 3), resulting in observable sparing at the periphery of the lobule (Fig. 4). The process affects the upper lungs more than lower and posterior segments more than the anterior. Cigarette smoking is the most common cause of CLE.

CLE can seldom be distinguished from other forms of emphysema by chest radiography, but it can occasionally be brought out by filling of surrounding airspaces by edema, hemorrhage, or pneumonia; the small centrilobular emphysematous spaces appear as small lucencies within the consolidation. Sometimes these features give the impression of reticulation (Fig. 5).

HRCT is the best technique for diagnosing CLE, with sensitivity, specificity, and accuracy of 88%, 90%, and



**FIGURE 7.** Centrilobular emphysema: Transverse computed tomography images in the first row and minimum intensity projection images in the second row show confluent centrilobular hypoattenuation with posterior lung predominance (arrows), corresponding to the macroscopic pathologic image in Figure 4B. Also note paraseptal emphysema in the left upper lobe (arrow heads).

89%, respectively.<sup>13</sup> A window width of 1500 HU and window level range of -700 to -550 HU are optimal.<sup>13</sup> Centrilobular low-attenuation spaces with imperceptible walls, in a nonuniform distribution, are the principal feature of CLE.<sup>14</sup> Upper lungs, especially the posterior lobes are more affected in cigarette smokers (Fig. 6). Postprocessing of images can bring out the distribution of emphysema (Figs. 6B, 7). Vascular architecture in the low-attenuation regions is usually preserved.

**PANLOBULAR EMPHYSEMA**

Panlobular emphysema (PLE) is defined by uniform loss of alveolar septa throughout the primary and secondary lobules, including the respiratory bronchioles, alveolar ducts, and alveolar sacs (Figs. 3, 8). Owing to uniformity, PLE changes are subtle and difficult to recognize in any given region pathologically and radiographically. PLE typically involves the lower lungs predominantly, with relative sparing of the upper lungs, especially in nonsmokers. Alpha-1-antitrypsin (AAT) deficiency is the most common cause of PLE, but it also occurs from intravenous injection of crushed

methylphenidate (Ritalin) tablets,<sup>15</sup> Swyer-James syndrome, old age, and rarely from cigarette smoking (without AAT deficiency).

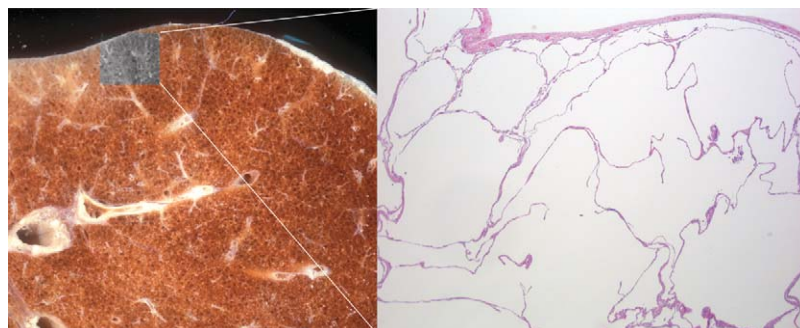
The prototype disease in this category is AAT deficiency. AAT binds and inactivates neutrophil elastase, which is a product of inflammation. This inactivation limits the tissue destruction that would otherwise accompany the inflammatory response. In nonsmokers, there is limited if any neutrophil accumulation in the lungs. In smokers, however, there is persistent inflammation with accumulation of neutrophils. In persons with normal AAT levels, neutrophil elastase is neutralized. Low levels or absence of AAT leads to unrestricted activity of the neutrophil elastase. Symptoms appear early compared with CLE, possibly from the larger surface area being affected. In patients who abuse Ritalin, the pathogenesis of emphysema is not clearly elucidated. Increased inflammation and elastase activity have been proposed.<sup>15</sup>

On chest radiographs, the findings are lower-lung translucency, hyperinflation, and flattening of the diaphragm. There are no distinguishing features of PLE other than the characteristic lower-lung predominance (Fig. 9). Swyer-James syndrome and advanced smoking-related CLE are some times difficult to distinguish from AAT deficiency-related PLE.

In PLE, CT shows panlobular decrease in attenuation and loss of vessel caliber (Fig. 10). It occasionally can be difficult to distinguish PLE from obliterative bronchiolitis. In addition, patients with AAT deficiency may have associated bronchiectasis or bronchial wall thickening.<sup>16</sup> Even with CT, it can be difficult to distinguish PLE from CLE. The study by Copley et al<sup>13</sup> showed low sensitivity (48%) for detection of PLE; it was often confused with CLE. The specificity and accuracy were high, at 97% and 89%, respectively. HRCT is better than conventional CT at detection of PLE.<sup>17</sup> Ritalin lung at CT shows PLE, with features and distribution otherwise indistinguishable from AAT deficiency (Fig. 11).<sup>18</sup> However, histopathologic features are characteristic, with talc or other excipient material showing birefringence under polarized light (Fig. 12).

**PARASEPTAL EMPHYSEMA**

This form of emphysema is less well described than CLE, and its etiology is less well understood. Other names for this condition are distal acinar emphysema, superficial



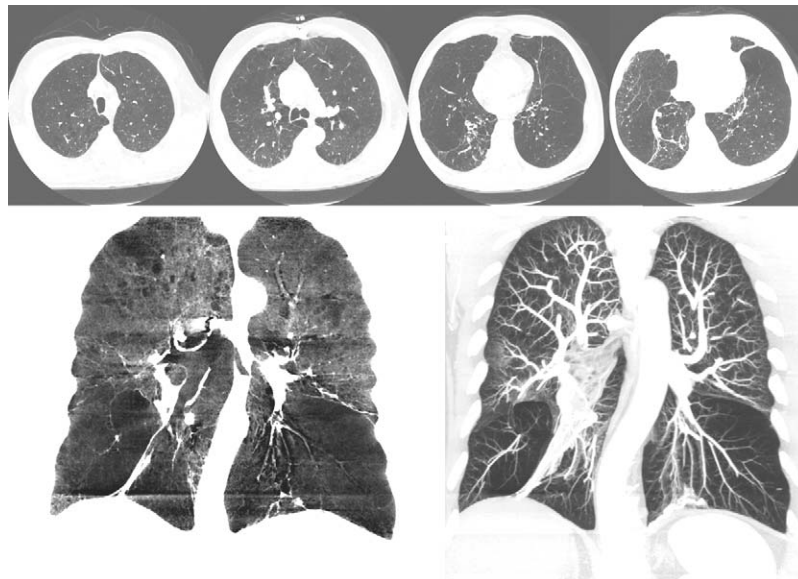
**FIGURE 8.** Panlobular emphysema from  $\alpha$ -1-antitrypsin deficiency: this gross specimen shows uniform loss of alveolar septa throughout the secondary pulmonary lobule, with no spared areas. The histopathologic image on the right shows uniformly dilated airspaces with no evidence of peripheral sparing.



**FIGURE 9.** Panlobular emphysema (PLE) from  $\alpha$ -1-antitrypsin deficiency: chest radiographs in postero-anterior and lateral projections show hyperinflation and increased translucency in the lower lungs with vascular attenuation, indicating PLE.

or mantle emphysema, and linear emphysema. Paraseptal emphysema (PSE) affects the most distal parts of the acinus, the alveolar sacs and ducts, and spares the respiratory bronchioles, hence the name distal acinar emphysema (Figs. 3, 13). It occurs most commonly in the upper lungs, especially the posterior upper lobes and anterior upper lobes, in a subpleural location, and it can also involve the posterior lower lobes.<sup>19</sup> PSE has been implicated as a cause of spontaneous pneumothorax, typically in tall, thin men in the third or fourth decade.<sup>20,21</sup> PSE may also occur in association with CLE.

PSE is difficult to diagnose at chest radiography. At CT, however, it has a characteristic appearance. It is usually in the periphery of the upper lungs, and the dilated distal airspaces are rectangular and they share walls (Fig. 14). PSE may progress to bullous emphysema. Another condition that can resemble PSE is honeycombing. However, honeycomb cysts are round, as opposed to rectangular. In addition, the walls of honeycomb cysts are usually thicker than those of PSE and the cysts are usually smaller. Furthermore, PSE occurs mostly in the upper lungs and is always subpleural, whereas honeycombing occurs



**FIGURE 10.** Panlobular emphysema (PLE) from  $\alpha$ -1-antitrypsin deficiency: computed tomography images (first row) show confluent lower-lung predominant panlobular hypoattenuation, indicating PLE. The confluence, panlobular distribution, lower-lung predominance, and vascular attenuation are better shown by the coronal minimum intensity projection and maximum intensity projection images (second row).



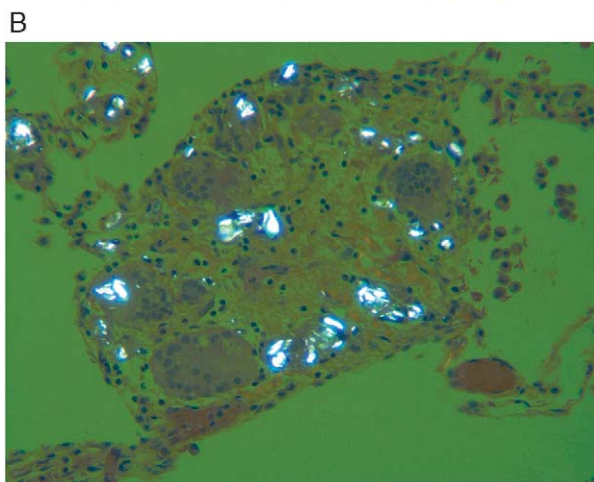
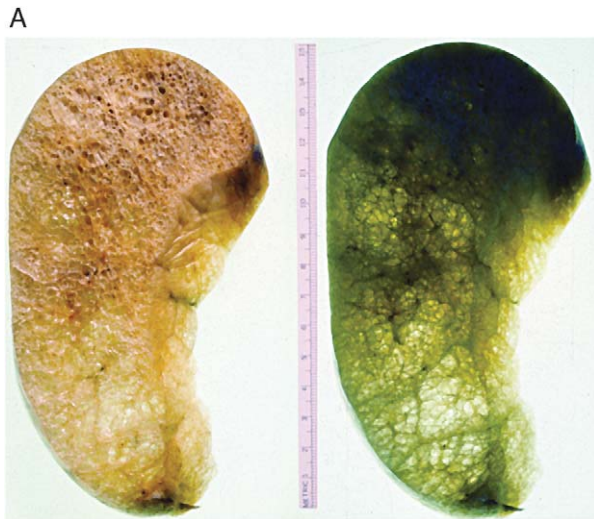
**FIGURE 11.** Ritalin lung with panlobular emphysema: chest radiographs, postero-anterior projection, and computed tomography (coronal reformatted image) show basal-predominant panlobular hypoattenuation similar to that found in  $\alpha$ -1-antitrypsin deficiency.

mostly in the bases in the setting of pulmonary fibrosis and can extend deep into the lung beyond the immediately subpleural region.

**PARACATRICIAL OR IRREGULAR EMPHYSEMA**

Paracatricial emphysema (PCE) occurs around a scar, and its causes include tuberculosis, silicosis, sarcoidosis, paracoccidioidomycosis, and bronchioloalveolar carcinoma. PCE is secondary to airspace distortion by scarring rather than primary destruction of alveolar septa. Any part of the acinus may be affected (Fig. 3).

At imaging, this form of emphysema generally surrounds the scar. It has been well described in advanced stages of sarcoidosis and progressive massive fibrosis from silicosis and coal workers pneumoconiosis (Fig. 15). Confluence of lung nodules increases the incidence of PCE in silicosis,<sup>22</sup> and a similar mechanism probably operates in advanced sarcoidosis. PCE may contribute to airflow obstruction in the setting of progressive massive fibrosis.

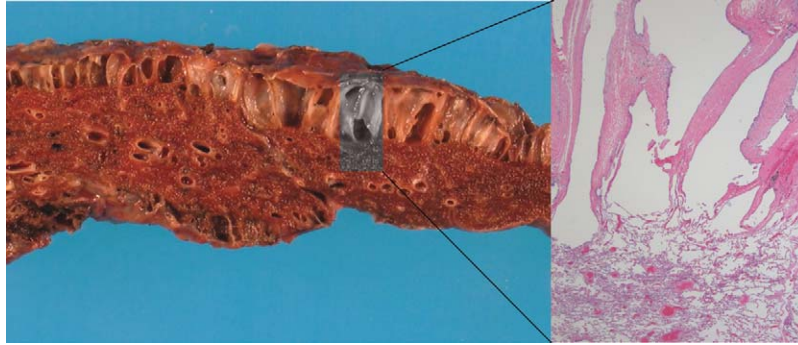


**CHRONIC BRONCHITIS**

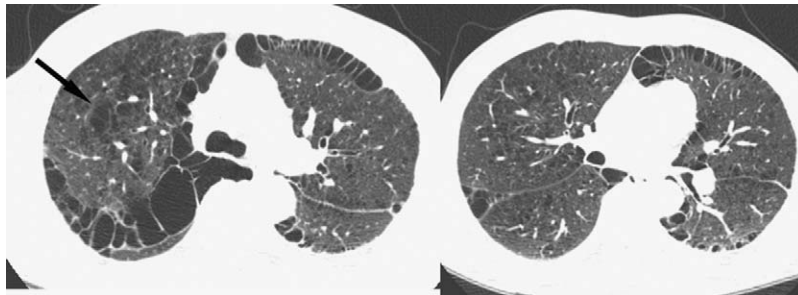
Chronic bronchitis, usually caused by cigarette smoking, is defined as the presence of chronic productive cough for at least 3 months in each of 2 successive years in a patient in whom other causes of productive chronic cough have been excluded.<sup>7</sup> This clinical definition does not require abnormal pulmonary function tests or radiographic findings. Bronchial gland hypertrophy, goblet cell metaplasia, and excess mucus production are some of the pathologic findings of chronic bronchitis. In the airways, there may be squamous metaplasia of the epithelium, loss of cilia and ciliary dysfunction, and increased smooth muscle and connective tissue.

Chest radiographs are normal in a substantial number of patients with chronic bronchitis. Terms such as “increased lung markings” or “dirty lung” have been applied to describe the bronchial wall thickening (Fig. 16). HRCT shows

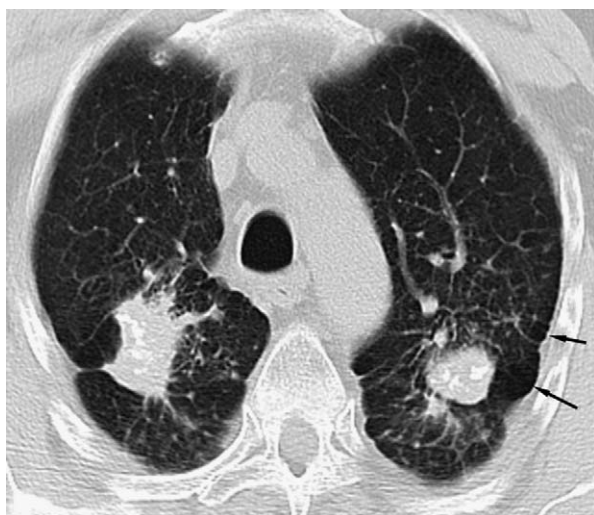
**FIGURE 12.** Ritalin lung with panlobular emphysema (PLE): A, Incident light image of a transverse section through the base of a lung shows uniform enlargement of airspaces with particularly severe emphysema toward the bottom of the image. The backlit image on the right highlights the severe loss of light-attenuating lung tissue. The lower lung PLE is also better shown. B, Histopathologic image viewed under polarized microscope shows many brightly birefringent (white) crystals of magnesium silicate (talc) surrounded by multinucleate foreign body giant cells.



**FIGURE 13.** Paraseptal emphysema: the gross specimen of the lung on the left shows an abrupt transition from essentially normal lung tissue (bottom) to dilated airspaces adjacent to the pleura (top). The histopathologic image on the right shows subpleural airspace enlargement in which the residual alveolar septa are thickened and fibrotic; residual alveolar lung tissue (bottom) is essentially normal. Vertical dimension is approximately 5.5 mm.



**FIGURE 14.** Paraseptal emphysema: computed tomography shows rectangular cysts sharing walls in subpleural upper lobes and the superior segment of the left lower lobe. Centrilobular emphysema is also evident in the upper lobes (arrows).

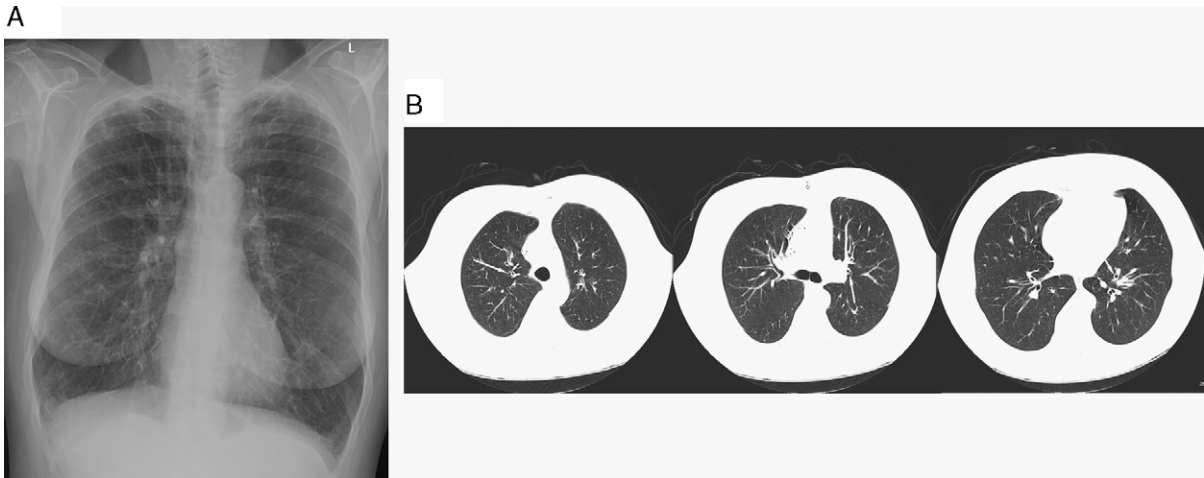


**FIGURE 15.** Paracatricial emphysema (PCE) from progressive massive fibrosis caused by silicosis: computed tomography images in lung window show conglomerate masses in the posterior upper lobes with surrounding low attenuation (arrows) indicating PCE. Hyperinflation of the anterior upper lungs is from traction by the conglomerate masses.

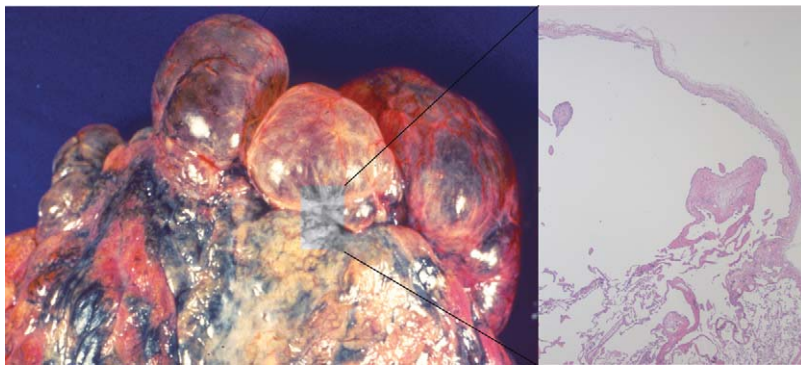
bronchial wall thickening better than chest radiographs, but this finding is not specific for chronic bronchitis. Occasionally, the dominant CT feature in patients diagnosed to have chronic bronchitis is CLE, which often coexists with chronic bronchitis.<sup>23</sup> Other findings include centrilobular opacities reflecting bronchiolar inflammation or thickening.

**BULLA VERSUS BLEB**

Strictly defined, a bulla is any emphysematous space that is more than 1 cm in diameter (Fig. 17) whereas a bleb is a collection of air trapped between the layers of the visceral pleura.<sup>24</sup> A bleb is thus a variant of interstitial emphysema, which is distinct from the types of emphysema discussed above. It is reported by surgeons in cases of spontaneous pneumothorax and may result from rupture of peripheral alveoli.<sup>25</sup> Bullae occur in emphysematous regions of the lung, whereas blebs occur typically in the lung apices. Complicating the clean dichotomy above is the fact that young thin spontaneous pneumothorax patients frequently have bulla-like subpleural separations of lung tissue from the pleura, but in the absence of emphysema elsewhere. As both true blebs and these lesions are associated with spontaneous pneumothorax and because CT does not have sufficient resolution to determine whether the origin of the abnormal



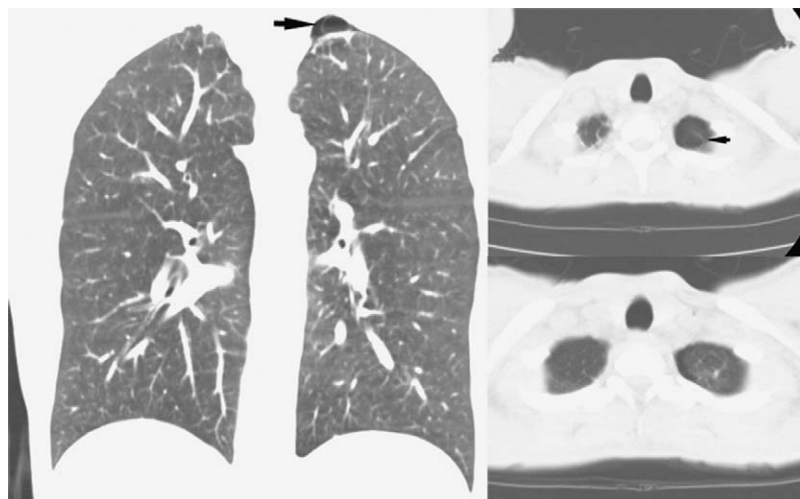
**FIGURE 16.** Chronic bronchitis: postero-anterior radiograph (A) and computed tomography (B) show bilateral bronchial wall thickening, the so-called, "dirty lung."



**FIGURE 17.** This gross specimen of the lung shows several apical bullae resembling rounded protrusions from the lung surface. The histopathologic image on the right from the edge of a bulla shows the abrupt transition from relatively preserved alveoli (bottom right) to severely emphysematous tissue in the bulla. Note that the base of the bulla is not sealed off from adjacent lung by fibrosis. Pleura is at the top. Vertical dimension is approximately 5.5 mm.



**FIGURE 18.** Bullous emphysema: postero-anterior radiograph and coronal computed tomography multiplanar reformation and maximum intensity projection images show a large bulla in the right upper lobe with atelectasis of the adjacent lung (arrows).



**FIGURE 19.** Apical bleb: computed tomography through the lung apex and multiplanar reformation show a left apical bleb floating in small pneumothorax (arrows). Also note unruptured blebs in the right lung apex.

airspace is intrapleural or subpleural, the common practice is to call both lesions blebs.

CT is the best modality available to detect a bulla (Fig. 18) or a bleb (Fig. 19), but they can be visible on chest radiographs when large enough. Distinguishing the two is based mostly on location, given that blebs are usually located at the apices, whereas bullae can be located anywhere.

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