Chapter 14
Mimics, Impersonators, and Semblances of Pulmonary Cysts

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Introduction

Pathologically, a cyst is defined as any round circumscribed space surrounded by a wall, either epithelial or fibrous, of varying thickness [1]. The Fleischner Society Guidelines define a pulmonary cyst radiographically as a round parenchymal lucency or low-attenuating area with a well-defined interface with normal lung [2]. Cysts can have variable wall thickness, though they are most often thin-walled with a mural diameter of less than 2 mm. Most commonly cysts contain air, but they also may be fluid-filled or contain solid material on occasion. Typically, cysts occur without associated emphysematous change.

There is considerable overlap between the radiological appearance of cysts and numerous other radiographical and pathological entities [3]. For example, a bulla is defined as a focal lucency measuring more than 1 cm in diameter, which is bordered by a thin wall no greater than 1 mm in thickness [4]. Bullae, in comparison to cysts, occur in the presence of emphysematous change. Moreover, a cavity is defined as a lucency or low-attenuation area, which tends to occur within an area of pulmonary consolidation, nodule, or mass [2]. Cavities may or may not contain air-fluid levels. Usually wall thickness of a cavity is greater than 4 mm though notably in the case of cavitating consolidation, the consolidation will often resolve leaving only a thin

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wall. Furthermore, a pneumatocele is a round thin-walled airspace in the lung, which occurs in response to various causative factors such as trauma, aspiration, or acute pneumonia by a process of parenchymal necrosis and check-valve airway obstruction [5].

Given the overlap with other radiological entities there is often diagnostic uncertainty in terms of the radiological diagnosis of cystic lung disease. In this chapter, we consider in more detail a range of common conditions whose radiographical features mimic those of the true diffuse cystic lung diseases (DCLDs).
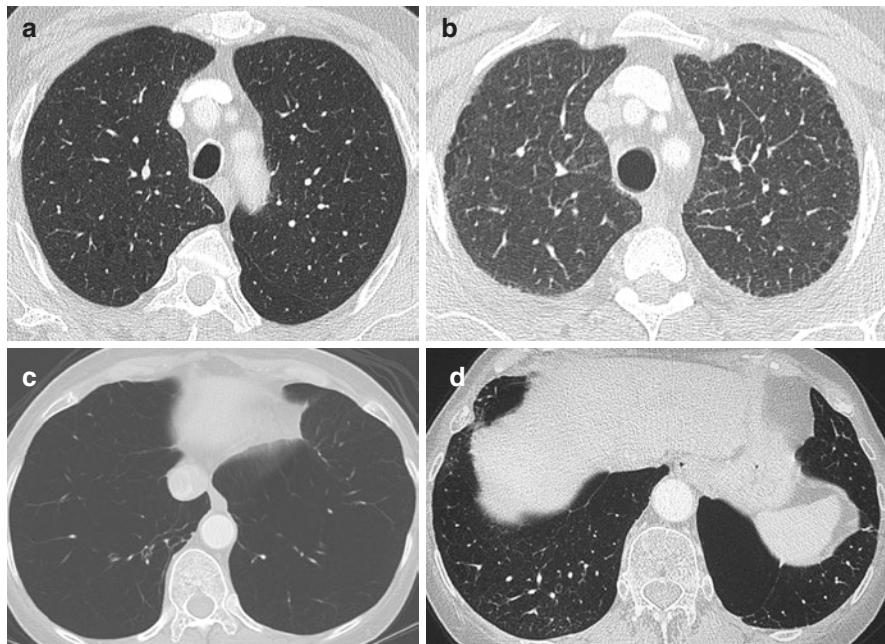
Emphysema

Emphysema can be pathologically defined as a condition of the lung characterized by abnormal, permanent enlargement of airspaces distal to the terminal bronchiole, accompanied by the destruction of their walls, and without obvious fibrosis [6].

Emphysema is a term used interchangeably with chronic obstructive pulmonary disease (COPD) and is associated with a high burden of morbidity and mortality. COPD is currently the third leading cause of mortality worldwide [7, 8].

While emphysema tends to be strongly associated with smoking, there are other conditions that can cause this structural disorder in the lungs. Alpha-one antitrypsin deficiency (AATD) is a genetic disease characterized by low circulating levels of the alpha-1 antitrypsin protein (AAT) and is inherited in an autosomal co-dominant fashion. AAT is an important and potent protease inhibitor synthesized and secreted by the liver. It functions mainly in the lungs to protect elastic structures against proteases such as neutrophil elastase. Mutations in the SERPINA1 gene on chromosome 14q32, the gene that encodes for AAT, alter the configuration of the protein in multiple ways to inhibit its release from hepatocytes, thereby leading to reduced circulating levels systemically. Homozygosity for the PI*Z allele is associated with low AAT serum levels and high risk of clinical disease. The imbalance of protease and antiprotease caused by reduced AAT levels results in destruction of alveolar walls and interstitial tissues leading to early and rapidly progressive emphysema, particularly when compounded by cigarette smoking [9]. Radiologically it is associated with extensive basal-predominant panlobular emphysema [10, 11] and the distribution itself may trigger diagnosis of the disease as this is an unusual pattern in any other context [12]. Treatment options center around lifestyle modifications and treatment of ensuing COPD, cirrhosis, or panniculitis; however, intravenous AAT replacement therapy is employed in more severe cases in countries where it is available and is the only treatment known to target the underlying cause of the disease [13–15].

The radiological evaluation of emphysema involves CT as the core imaging modality. While plain chest radiography can be utilized in the early stages of workup, it does not allow advanced assessment of the extent of emphysematous changes. Several distinct morphological subtypes of emphysema exist and can be characterized on CT (Fig. 14.1). There is a degree of correlation between certain clinical features of COPD and imaging abnormalities, which can help stratify clinical risk

Fig. 14.1 Emphysema. Panel A illustrates centrilobular emphysema with multiple areas of low attenuation representing central destruction of the secondary pulmonary lobule. Paraseptal emphysema is visible in panel B toward the posterior pleural surface. These areas of hypoattenuation represent selective destruction of the distal acinus. Panel C shows severe panlobular emphysema with diffuse destruction of lung parenchyma across the entirety of the secondary pulmonary lobule. Panel D demonstrates a large bulla in the left lung base

for patients [16, 17]. For example, centrilobular emphysema and panlobular emphysema are associated with greater dyspnea and reduced walk distance compared to paraseptal emphysema where there can be less of a symptom burden [16].

Centrilobular emphysema, the most common emphysematous subtype, predominantly affects the upper lobes and is defined by small areas of low attenuation. Pathologically, these low attenuation areas are representative of areas of destruction in the center of the secondary pulmonary lobule and are surrounded by normal lung. These areas tend to be poorly defined due to their thin walls and are traversed by centrilobular arteries or arterioles, which mark their center. The areas can range in size from 1 to 3 mm and correlate with pathologically defined centrilobular emphysema [18]. Centrilobular emphysema tends to occur in older patients and is exquisitely associated with smoking status [19]. As the disease progresses, there is increased destruction of the lobular unit and confluence of the observed areas of low attenuation on CT. At this stage, the surrounding walls become almost imperceptible or disappear altogether, and the centrilobular distribution becomes less apparent.

Paraseptal emphysema is the pattern observed when the distal acinus is selectively destroyed [20]. Lesions form near the pleural surface and in the interlobar

fissures, and can often coalesce to form large hyperlucent areas bordered by inter-lobular septae, which are intact but thickened by associated fibrosis due to the high level of airway inflammation [21]. Paraseptal emphysema tends to occur in the middle and upper zone subpleural areas as well as along the mediastinal fissures. Minimal subpleural paraseptal emphysema can be encountered in nonsmokers [22]. Paraseptal emphysema can occur in rows where it can sometimes be confused with the honeycomb change characteristic of fibrotic interstitial lung diseases [23].

Panlobular emphysema refers to diffuse destruction of lung parenchyma across the entire secondary pulmonary lobule rather than the central destruction pathognomonic of centrilobular emphysema [24]. It tends to affect the lower lobes and is highly associated with AATD [25]. It can also occur in cigarette smokers, usually in combination with centrilobular emphysema, and also in those who abuse certain intravenous drugs [26].

Bullae are defined as avascular low-attenuation areas greater than 1 cm in diameter with a thin but perceptible wall [4] and are found in all subtypes of emphysema. They are most closely associated with paraseptal emphysema and are often found in the upper lobes of the lung [27]. Bullae may be associated with adjacent atelectasis whereby the bulla becomes so large it impairs the expansion of the adjacent normal lung [28].

The distinct morphological subtypes of the spectrum of emphysema on CT scanning can help to distinguish disease phenotypes as well as allow assessment of disease severity for patients [16, 17]. CT appearances of emphysema can mimic DCLDs as all subtypes are marked by hyper-lucency with some element of a surrounding wall. Careful observation of spirometric airflow limitation, documentation of patient exposure history, and assessment of symptomatic burden can lead to the correct diagnosis and identify potential treatment strategies for the patients affected by this disease.
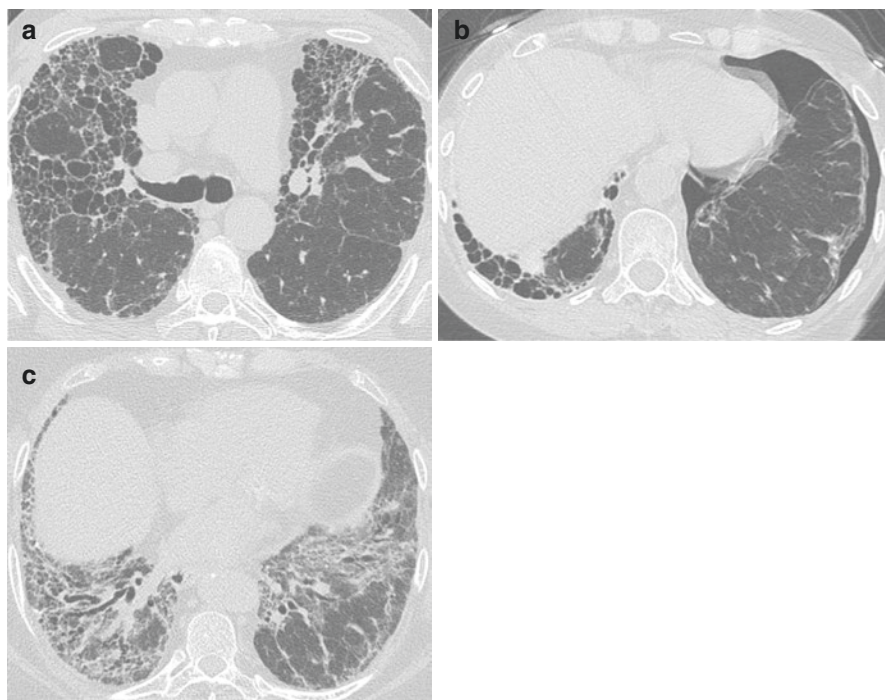
Interstitial Lung Disease

The term "interstitial lung disease" (ILD) is a broad classification encompassing a range of lung diseases that cause diffuse alterations to the lung parenchyma over time. The term represents a diverse group of conditions of varying severity, etiology, and prognosis but which are unified by the pathophysiological end-points of acute lung injury leading to chronic interstitial inflammation, damage to parenchymal tissues, fibroblastic change, and eventual distortion of normal lung architecture [29]. Previously investigation of diffuse ILDs often required lung biopsy [30], but advanced CT techniques allow current diagnostic criteria to rely more on imaging interpretation, abrogating the need to histologically demonstrate the underlying pathology in a substantial proportion of patients [31, 32]. Fibrotic ILDs can present with numerous radiological patterns, and a number of these may involve cystic appearing structures such as honeycombing and clustered traction bronchiectasis.

Honeycombing is defined as subpleural, clustered, multi-layered, or multi-tiered cystic air spaces with well-defined walls [33]. It is often difficult to distinguish from

paraseptal emphysema. While honeycombing involves stacked cystic structures, paraseptal emphysema presents as a linear arrangement of cysts without stacking. The cystic spaces in honeycomb lung are associated with irregularly thickened walls and range in diameter from 3 to 10 mm. Pathologically these cystic areas represent dilated and thickened terminal bronchioles and most commonly occur in patients with end-stage ILD [34]. Demonstration of honeycombing in association with peripheral subpleural basal-predominant reticular opacities and traction bronchiectasis leads to a radiological diagnosis of definite usual interstitial pneumonia (UIP) and negates the need for surgical lung biopsy as a confirmatory diagnostic test [35]. Probable UIP is marked by the abovementioned features but without demonstration of honeycombing. In these cases, the clinical context is combined with imaging results, and surgical biopsy may be employed if the risk: benefit ratio is favorable for the individual [35].

UIP is the typical radiological pattern observed in idiopathic pulmonary fibrosis (IPF) (Fig. 14.2a) but can also be observed in other disease processes, including

Fig. 14.2 Interstitial lung disease. Panel A demonstrates the CT findings in a patient with usual interstitial pneumonia pattern associated with idiopathic pulmonary fibrosis. The constellation of findings includes honeycombing, traction bronchiectasis, and subpleural reticular opacities thus demonstrating definite UIP. Panel B illustrates honeycombing in a patient with rheumatoid arthritis associated interstitial lung disease. Also noted is an incidental left-sided spontaneous pneumothorax. Panel C shows significant architectural distortion associated with fibrotic nonspecific interstitial pneumonitis

rheumatoid arthritis-interstitial lung disease (RA-ILD) (Fig. 14.2b), drug-related ILD, sarcoidosis, and some occupational lung diseases [36]. Furthermore, honeycombing can occur in some cases of nonspecific interstitial pneumonia (Fig. 14.2c) though it is usually a very late sign in longstanding NSIP and tends to not be the predominant feature on imaging [37, 38]. Clusters of cystic lesions seen with ILDs such as NSIP and hypersensitivity pneumonitis can often represent traction bronchiectasis rather than true honeycombing. If bronchiectasis is the cause of these clusters, the cysts tend to be larger than the cysts of honeycombing and are more regular in size [38].

Although cystic areas can be seen in a variety of fibrotic ILDs, careful demographic and clinical history-taking combined with the presence of other (noncystic) interstitial abnormalities on chest radiology often makes it rather straightforward to distinguish these ILDs from true DCLDs.
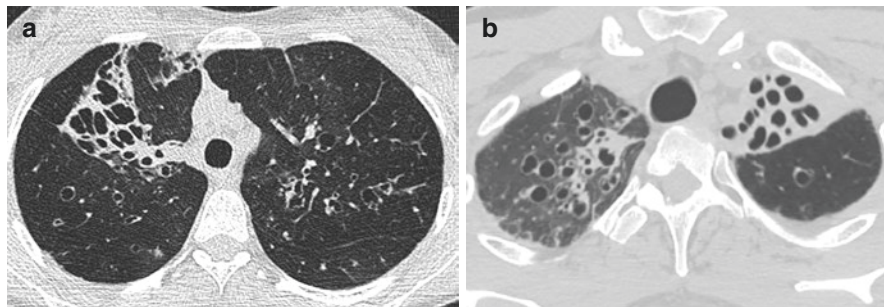
Bronchiectasis

Bronchiectasis is defined as irreversible abnormal dilatation of the bronchial tree, particularly the proximal and medium-sized bronchi [39]. Bronchiectasis most commonly occurs as a consequence of other conditions and involves destruction and weakening of the bronchial walls through multiple processes such as inflammation, edema, and fibrosis [40]. These factors combine to attract multiple pathogens to the areas of damaged lung, and over time bronchiectatic lungs can often become a nidus for colonization with resistant bacteria [41]. The end result is marked architectural distortion of lung tissue [42]. Causes of the disease are most likely infective, most notably primary lung infection, aspiration pneumonia, and immunodeficiency, but can also be caused by connective tissue disorders, genetic diseases such as cystic fibrosis, and toxin exposure [43]. Clinically bronchiectasis is suspected in patients who present with increased cough, sputum production, and hemoptysis.

Bronchiectasis is often characterized as cylindrical, cystic, or varicose, and differentiation of these three subtypes is made on CT imaging [44]. Airway dilatation is the most common finding on HRCT and can be seen either as parallel lines, so-called tram lines, or end-on where it is seen as ring-shaped shadows. If the airway diameter is more than one and a half times the accompanying vessel's diameter, this indicates the presence of cylindrical bronchiectasis. This finding is also termed the "signet-ring" sign where the dilated airway is air filled and contiguous with the small opacity of the pulmonary artery [45] (Fig. 14.3a). In addition to dilatation of the airway, lack of tapering of the bronchus and bronchial wall thickening are seen and the combination of all three features is more specific for bronchiectasis than for other conditions that can also be associated with mild bronchial dilatation such as asthma.

Varicose bronchiectasis is diagnosed wherever alternating areas of bronchial dilatation and constriction occur in nearby proximity [46]. Constricted areas can give rise to post-obstructive pneumonitis and thereby cause additional damage to

Fig. 14.3 Bronchiectasis. Panel A depicts bronchiectasis, dilated bronchioles can be seen throughout and there are examples of signet-ring formation where the dilated bronchiole is wider in diameter than the accompanying vessel. Panel B is from a patient with cystic fibrosis and demonstrates the severe apical cystic bronchiectasis associated with these cases

lung parenchyma [47]. Cystic bronchiectasis occurs in more severe cases where unchecked inflammation can result in neovascularization and angiogenesis [48]. This causes cyst-like structures to form off the damaged bronchial wall, and these tend to cluster, often into areas which resemble clusters of grapes [47]. This bronchiectasis subtype mimics DCLDs most closely [2] (Fig. 14.3b).

The distribution on HRCT of bronchiectasis can be indicative of the underlying cause [49]. Cystic fibrosis is commonly associated with upper lobe predominant findings on CT, which tend to be particularly severe in terms of the level of parenchymal distortion [50] (see Fig. 14.3b). Primary ciliary dyskinesia, which causes bronchiectasis due to impaired mucus clearance, has a predilection for middle and lower zones, while idiopathic bronchiectasis tends to occur in the lower zones [51]. There is some evidence that the extent of bronchiectasis on HRCT correlates with disease severity with evidence of mucus plugging and bronchial wall thickening correlating with decline in FEV_1 over time in a repeated measure study [52]; however, this assertion has not been borne out in subsequent studies [53]. The pattern of disease does not seem to correlate well with clinical severity measures except that cystic bronchiectasis can be associated with hemoptysis [44].

Neoplastic Processes

Cavitary and cystic change is an unusual but documented occurrence in lung neoplasms, and in certain cases cavitary lung tumors can be difficult to differentiate from DCLDs. Detailed description of the neoplastic causes of DCLDs is provided in Chap. 11 of this textbook. In those with primary lung malignancy, cavitary change has been detected in up to 22% of CT images [54, 55]. Squamous cell carcinoma accounts for the vast majority of the cases of cavitary primary lung malignancy, up to 80% in some reports [56] (Fig. 14.4). Adenocarcinoma represents the remainder of cases. In general, cavities associated with malignancy are solitary; however, very
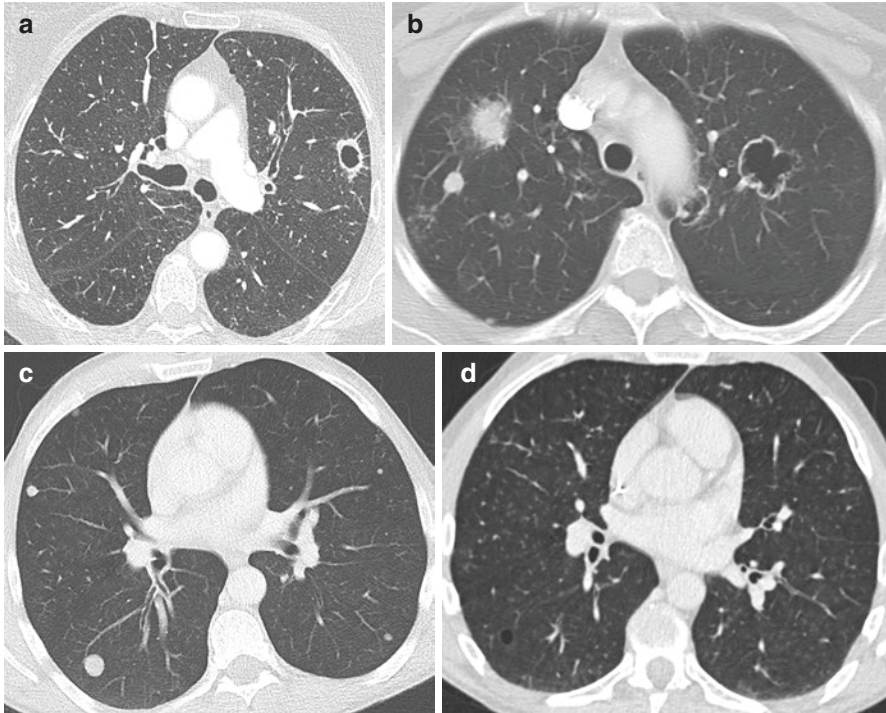
Fig. 14.4 Neoplastic processes. Panel A illustrates a cavitary mass in a patient with primary squamous cell carcinoma of the lung. Panel B illustrates a similar cyst-like structure in a patient with metastatic endometrial sarcoma. Panel C demonstrates a metastatic urothelial cancer with a moderate-sized metastasis in the posterior right lower lobe. This metastasis has become cystic after treatment of the urothelial cancer, panel D

rarely bronchoalveolar cell carcinoma can present with multiple cavitary lesions [57]. The proposed mechanism for cavity and cyst genesis in lung cancer is that unchecked rapid growth of the tumor exceeds the tumor's own blood supply and central necrosis occurs [55]. Recently it has been shown that a very high proportion of those primary tumors that cavitate exhibit overexpression of epidermal growth factor receptor (EGFR), which may contribute to their rapid growth and central necrosis and add some merit to this proposed mechanism [58]. Patients with a cavitating primary lung malignancy have a worse prognosis than those who do not have cavitary lesions, particularly for those patients with squamous cell carcinoma [59].

In addition to cavitating primary lung malignancies, cystic change can be frequently associated with metastatic malignancies, especially sarcomas arising from a variety of different sites [59]. Cystic metastases associated with sarcoma carry a particularly poor prognosis due to the lesions' tendency toward pneumothorax formation [60]. Direct extension of the metastasis to the pleural space is the most common mechanism by which this occurs. The cystic metastasis associated with rare

endometrial stromal sarcomas (see Fig. 14.4) can very closely resemble DCLDs on chest imaging, and should be a key differential diagnosis when evaluating DCLD patients [61].

Infectious and Inflammatory Causes

Multiple infectious and inflammatory processes can contribute to cyst formation (see Chap. 10 for a more in-depth discussion of the infectious etiologies of DCLDs). Many of these processes involve cavitation, which can further evolve into cystic change. The radiologic appearances of these various processes can overlap significantly with DCLDs to confer considerable diagnostic uncertainty. Cavitation can occur with a variety of organisms and form via a process of suppurative necrosis, especially in the case of bacterial pneumonia. Radiographically these cavities are surrounded by areas of consolidation and can often transform further to form lung abscesses, clearly circumscribed collections of pus occurring due to liquefactive necrosis of lung tissues [62]. Classically pulmonary abscesses are easily visualized on chest radiograph due to the presence of a thick-walled cavity containing an air-fluid level (Fig. 14.5). With treatment, the air-fluid level will resolve, consolidation
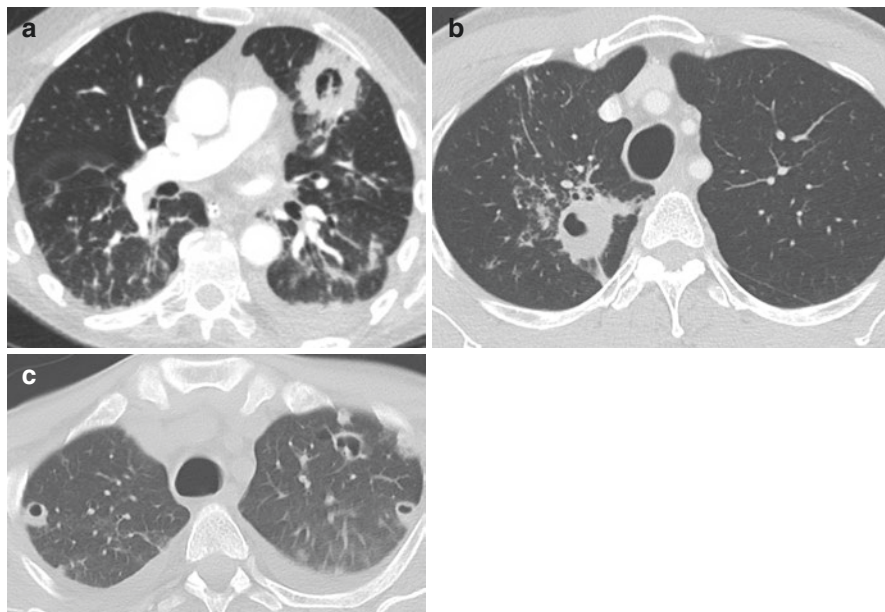
Fig. 14.5 Infectious processes. Panel A shows cavitary transformation in a case of necrotizing pneumonia due to the *Rhizopus* fungus. Panel B demonstrates a thick-walled cavity in the right upper lobe in a patient with pulmonary *Mycobacterium tuberculosis* infection. Panel C shows multiple septic emboli that have cavitated

will reduce and eventually disappear, and the wall of the cavity will become thinner. However, the cavity can persist for months after treatment of the active infection and can on occasion be mistaken for cystic lung disease [62].

Mycobacterium tuberculosis (TB), the leading cause of infectious disease mortality worldwide, is a common cause of cavitary lung disease, though TB can often take any radiographic form on imaging investigations [63]. Multiple components of the *M. tuberculosis* cell wall combine to make the bacterium highly antigenic and so a cascade of cytokines is initiated that results in formation of a protective granuloma [64]. Continual development of these TB granulomas leads to central caseating necrosis, which are the pathological hallmark of TB infection in all tissues but most notably in the lungs [65]. Cavities associated with pulmonary tuberculosis tend to be large and located in the apical regions. They are most often associated with a thick wall and surrounding consolidation and may contain an air-fluid level, which represents active infection [63] (see Fig. 14.5). Occasionally cavities can be small and numerous and over time, with treatment, may resolve their thick wall and surrounding consolidation leaving them to more closely mimic DCLDs [66]. With treatment, much of the radiographical evidence of infection will resolve, but it is common for patients to continue to display changes of pulmonary tuberculosis on imaging many years after their infection has been treated.

Septic pulmonary emboli occur when blood clots containing infectious materials embolize from their source to the lungs via the pulmonary arterial vasculature. They can occur as sequalae of a spectrum of infectious conditions; risk factors include intravenous drug use, indwelling vascular catheters, thrombophlebitis, and suppurative diseases of the head and neck [67]. The embolus itself leads to focal infarction in the pulmonary vasculature similar to nonseptic emboli [68]. However, because they contain material from an infected primary source, release of infective materials leads to the formation of a focal abscess. These tend to cavitate centrally and can be numerous giving the appearance of multiple pulmonary cysts [68] (see Fig. 14.5).

A pneumatocele is a space in the lung, which is surrounded by a thin wall and filled with gas and as such there is often very high overlap between the radiologic appearance of pneumatoceles and pulmonary cysts [2]. Most commonly, pneumatoceles occur as sequelae of infection such as *Pneumocystis jiroveci* and *Staphylococcal aureus*, but they can also occur in the setting of blunt trauma to the thorax, ingestion of hydrocarbon, and following prolonged positive pressure ventilation most commonly in neonates [69, 70]. Pneumatoceles tend to be transient and radiographically appear as smooth, rounded, thin-walled air spaces [2] (Fig. 14.6). Generally, patients with pneumatoceles are asymptomatic; however, very rarely these can rupture, resulting in pneumothorax [71]. Pneumatoceles usually resolve within 6 weeks, but rarely they can become secondarily infected and persist [72]. On a very rare occasion, pneumatoceles can cause significant tension, in which case drainage may be needed to improve hemodynamic instability [73].

Fig. 14.6 Pneumatocele. The rounded lucency in the lung parenchyma represents a pneumatocele. It has a thin wall and is surrounded by normal lung
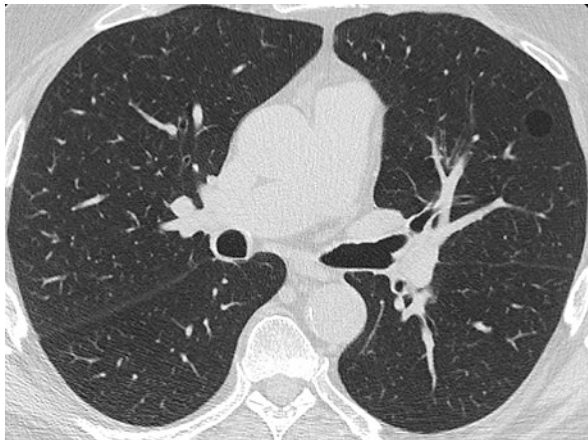
Conclusion

Cysts are increasingly visualized on CT imaging of the lungs and can pose a diagnostic challenge. Diagnosis involves careful attention to the existence of such cyst mimics and the knowledge that these mimics are more common than true diffuse cystic lung diseases. If these conditions have been ruled out following careful clinical and radiological correlation, patients can be investigated for processes, which cause true cystic lung disease.

Key Learning Points
- Pulmonary cysts and cyst mimics are increasingly identified due to the routine use of chest CT scanning in clinical practice.
- The most common situations where radiologic findings can mimic DCLDs include emphysema, bronchiectasis, and neoplastic and infectious etiologies.
- Certain genetic diseases such as alpha-one antitrypsin deficiency, cystic fibrosis, and primary ciliary dyskinesia can cause radiological patterns that mimic DCLDs. While alpha-one antitrypsin deficiency causes panlobular emphysema, both cystic fibrosis and primary ciliary dyskinesia can cause bronchiectasis.
- Honeycomb change and traction bronchiectasis associated with fibrotic ILDs can also mimic the cysts of DCLDs. However, the other associated radiological interstitial findings typically make it easy to distinguish between the cystic change of ILDs from the typical DCLDs.
- Pneumatoceles can be seen following certain infections, trauma, or aspiration events and tend to follow a benign course with spontaneous resolution in a few weeks.

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