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The role of computed tomography in a diagnostic approach to cystic lung diseases and their differential diagnosis

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Abstract

In everyday routine, lung cysts are commonly seen in Computed Tomography, as far as many different conditions and diseases are associated with air cysts. Thus, correct diagnosis of cystic lung diseases, which show a wide spectrum, is a challenge for radiologists. For diagnosis and differential diagnosis, first of all, cysts should be distinguished from such other air filled lesions, like cavities, bullae, pneumatocele, emphysema, honeycombing and cystic bronchiectasis. Second, cysts can be categorized as single/localized versus multiple/diffuse. Solitary/localized cysts include incidental cysts, congenital cystic diseases and cystic cancers. Multiple/diffuse cysts can be further categorized according to the presence or absence of associated radiologic findings. Multiple/diffuse cysts without associated findings include lymphangioleiomyomatosis and Birt-Hogg-Dubé syndrome. Multiple/diffuse cysts may be associated with ground-glass opacity or small nodules. Multiple/diffuse cysts with nodules include Langerhans cell histiocytosis, cystic metastasis and amyloidosis. Multiple/diffuse cysts with ground-glass opacity include pneumocystis pneumonia, desquamative interstitial pneumonia and lymphocytic interstitial pneumonia. The stepwise radiologic diagnostic approach can be helpful in reaching a correct diagnosis for various cystic lung diseases.

KEY WORDS: lung diseases; lymphangioleiomyomatosis; Birt-Hogg-Dubé syndrome; histiocytosis; langerhans cell; emphysema; cystic bronchiectasis; cystic cancer

Introduction

Many different cystic diseases or conditions can be encountered in chest, because of frequent use of CT scans in daily clinical practice. Lung cysts appear as round parenchymal lucencies or low-attenuating areas with a well-defined thin wall, surrounded by normal lung parenchyma [1]. For radiologic assessment of cystic lung diseases, it is important to differentiate true lung cysts from other air-filled lung lesions in the first step of the diagnostic process. Radiologic characteristics of lung cysts, including size, wall thickness, number, location, and distribution, and the associated radiologic findings provide the most helpful diagnostic clues for diagnosing specific cystic lung diseases. A definite diagnosis may require clinical correlation and, occasionally, biopsy. However, although a multidisciplinary approach is necessary to make the correct diagnosis, a radiologic-CT approach is particularly important in narrowing the differential diagnosis.

The purpose of this review is to provide a stepwise radiologic diagnostic approach for cystic lung diseases.

STEP 1. Air cyst identification

Cysts

A cyst appears as a round parenchymal lucency or low attenuating area with a well-defined interface with normal lung parenchyma. Cysts are usually thin-walled (<2mm) and occur without associated pulmonary emphysema on CT scans (Fig. 1A). Single or several cysts in a localized area of the lung should be distinguished from a cavity, pneumatocele, or bullae. Moreover, multiple cysts diffusely distributed in both lungs should be distinguished from emphysema, honeycombing and cystic bronchiectasis.

Cyst-like lesions

Cavity

Cavity is a gas-filled space that is observed as lucency or low-attenuated area within pulmonary consolidation, a mass, or a nodule (Fig. 1B) [1]. Cavity wall thickness may vary, but the wall is usually relatively thick [2,3]. Many different diseases present as cavitary lesions. This spectrum of diseases includes acute to chronic infections, chronic systemic diseases and primary or metastatic malignancies [3,4,5]. A cavity is differentiated from a cyst by the presence of a thicker wall and a more irregular shape.

Bulla

A bulla is an airspace measuring more than 1 cm that is sharply demarcated by a thin wall [1]. Radiologically, it appears as a rounded focal lucency or decreased attenuation more than 1 cm in size, and is bounded by a thin, usually almost undetectable wall that is not greater than 1 mm (Fig. 1C). Bullae are usually located in the subpleural lung rather than within the lung parenchyma. Multiple bullae are usually accompanied by adjacent paraseptal and centrilobular emphysema [1]. Bullae can be distinguished from cysts by their almost imperceptible thin-wall, subpleural location, and accompanying adjacent emphysema.

Pneumatocele

A pneumatocele is a transient, thin-walled, gas-filled lesion, usually caused by pneumonia, trauma, or aspiration of hydrocarbon fluid [1]. The mechanism underlying their formation is believed to be a combination of parenchymal necrosis and check valve airway obstruction. Radiologically, a pneumatocele appears as an almost round, thin-walled airspace in the lung (Fig. 1D) [1]. Pneumatoceles can be accompanied by adjacent consolidation or ground glass opacity as a result of recent pneumonia; they may progressively increase in size over the following days or weeks, and then resolve after weeks or months [6].

Emphysema

Pulmonary emphysema can be classified into three major subtypes based on disease distribution within secondary pulmonary lobules: centrilobular or centriacinar emphysema, panlobular or panacinar emphysema, and paraseptal or distal acinar emphysema [1,7,8]. Centrilobular emphysema is the most common type of pulmonary emphysema, and is pathologically defined by the presence of destroyed centrilobular alveolar walls and enlarged respiratory bronchioles and associated alveoli [1]. Centrilobular emphysema typically appears in focal areas of decreased lung attenuation, usually without visible walls, and it has a predilection for the upper lungs [1,8,9]. Centrilobular emphysema is usually combined with a central dot which is a central bronchovascular bundle in the secondary pulmonary lobule (Fig. 3B). However, centrilobular emphysema may appear similar to thin-walled cysts. Paraseptal emphysema involves the more distal part of the secondary pulmonary lobule, and usually presents as a single row of elongated, thin-walled, air-filled structures that are distributed within the subpleural

lung. Panlobular emphysema involves the destruction of the entire secondary pulmonary lobule, and it involves lung parenchyma more diffusely, especially in the lower lungs [8]. Cysts are larger, fewer in number, lack a centrilobular location, lack a central core vessel, and have more visible walls compared with centrilobular emphysema.

Honeycombing

Honeycombing represents destroyed and fibrotic lung tissue containing numerous cystic airspaces with thick fibrous walls, indicative of the late stages of various lung diseases [1]. Radiologically, it appears as clustered cystic lesions with 1-3 mm-thick well-defined walls, which are typically 3-10 mm in diameter but may be occasionally larger (Fig. 3C) [1,9,10]. Honeycombing is characterized by multiple rows of air-filled spaces clustered in the subpleural region, predominantly in the lower lungs. Honeycombing usually accompanies other features of lung fibrosis, such as reticulation and traction bronchiectasis. It is the most distinguishing feature of usual interstitial pneumonia pattern, which is a hallmark radiologic pattern of idiopathic pulmonary fibrosis [10]. Cysts are larger in size, lack a subpleural distribution, do not show associated fibrosis, and are isolated lesions in comparison with honeycombing.

Cystic bronchiectasis

Bronchiectasis is an irreversible, localized, or diffuses bronchial dilatation, usually resulting from chronic infection, proximal airway obstruction, or congenital bronchial abnormalities [1]. Bronchiectasis may be classified as cylindric, varicose, or cystic, depending on the appearance of the affected bronchi [1]. Cystic bronchiectasis can also be mistaken for cysts when a dilated airway is viewed in cross-section (Fig. 3D). Bronchiectasis is usually distinguished from true cysts by careful examination of contiguous CT images. Findings such as tubular rather than spherical dimensions, branching patterns, associated bronchial wall thickening, centrilobular densities, and air-trapping are helpful for the diagnosis of bronchiectasis.

STEP 2. Are lung cysts solitary/localized or multiple/diffuse?

As a second step, after differentiating cysts from cyst mimickers, lung cysts can be categorized as solitary/localized cysts or multiple/diffuse cysts. Single or several cysts

in a localized area are classified as solitary/localized cysts, while multiple or numerous cysts distributed in both lungs are classified as multiple/diffuse cysts.

Solitary/localized cysts

Incidental cyst

A solitary cyst or several small lung cysts can be found incidentally on CT scans (Fig. 3A). Cysts are most likely to appear solitarily in the lower peripheral lungs and remain unchanged or slightly increase in size over time. Cysts are not associated with impairment in measures of spirometry, cigarette smoking, or emphysema. Therefore, incidental lung cysts could be a part of the normal aging process [11,12]. However, a single cyst may also be a remnant of a previous infection or trauma [13]. It is important to differentiate incidental lung cysts from other cystic lung diseases. Solitary or several small thin walled lung cysts incidentally found on CT in the old age group, may be a part of the normal aging process. Thus, old age, smaller number, and a lack of association with other radiologic findings are useful for the differentiation of incidental lung cysts from cystic lung diseases.

Intrapulmonary bronchogenic cyst

The bronchogenic cyst is a developmental anomaly that results from abnormal budding or a branching defect between the 26th and 40th gestation days [14,15,16]. Although a bronchogenic cyst usually presents as a middle mediastinal mass along the tracheobronchial tree, it can also present as a lung mass in about one-third of the cases, with a predilection in the lower lobes [13,16]. Intrapulmonary bronchogenic cysts are usually filled with fluid, and air-filled intrapulmonary bronchogenic cysts are rare [13]. Radiologically, an intrapulmonary bronchogenic cyst appears as a well-defined, homogeneous, spherical lesion with a smooth or lobulated margin on CT. Cysts contain usually fluid and rarely air with or without air-fluid level (Fig. 3C) [13,16,17]. Air-filled intrapulmonary bronchogenic cysts are sometimes difficult to differentiate from lung abscess or infected bullae. Clinical manifestations and previous chest radiographs and CT scans may be helpful for differentiation.

Congenital cystic lung diseases

Congenital Pulmonary Airway Malformation Congenital pulmonary airway malformation (CPAM) is a heterogeneous group of cystic and non-cystic lung lesions that result from abnormal bronchial structure proliferations [14]. CPAM, formerly known as congenital cystic adenomatoid malformation, usually presents during childhood and rarely in adulthood. CPAM is classified into subtypes based on cyst size and location, as well as other associated congenital abnormalities [2]. Most CPAMs derive their blood supply from the pulmonary artery and drain via the pulmonary veins [14]. Radiologically, large cysts, small cysts, and microcystic or solid lesions are observed according to the CPAM subtypes. Radiologic findings correlate well with the underlying histopathological characteristics [17]. CT shows lesions with a solitary well-defined thin-walled cyst or multiple cysts of varying sizes with variable densities, depending on the fluid contents of the cysts (Fig. 3B) [14].

Solitary cystic cancer

Cystic primary lung cancer is often missed or misinterpreted, which is most likely due to their unique imaging appearance, showing overlap with benign entities such as infection.

Cystic lung cancers are predominantly adenocarcinomas in about 80% of cases, with squamous cell carcinomas as the second most common subtype.

A rare number of other tumour types like adenosquamous, neuroendocrine and lymphoma have been reported [18].

Multiple underlying histopathologic substrates (eg. focal tumour proliferation, fibrosis, lepidic tumour growth along alveolar walls, emphysema) relate to the imaging features of cystic lung cancer and are responsible for either the solid component, septations, ground glass, and cystic air spaces. The most widely quoted mechanism of air space formation is ″check-valve″ ventilation. The air can enter in inspiration but cannot return during expiration due to partial obstruction of the terminal airway proximal to the cystic air space due to tumour cells and fibrosis.This leads to development, persistency and enlargement of the cystic air space [5].

STEP 3. Are multiple/diffuse cysts associated with other radiologic findings

Multiple/diffuse cysts can be further categorized according to the presence or absence of other associated radiologic findings. Radiologists should carefully review CT images for cysts as well as identify any other associated findings such as nodules, ground-glass opacity, or extrapulmonary lesions in areas visible in chest CT.

Multiple/diffuse cysts only (without associated other radiological findings) Lymphangioleiomyomatosis

Lymphangioleiomyomatosis (LAM) is a rare disease that predominantly affects the lung parenchyma of women of childbearing age [19,20,21]. LAM can occur sporadically, but is more common in patients with tuberous sclerosis complex (TSC-LAM) [21,22,23]. Cysts in the lung parenchyma may be the result of terminal bronchiole obstruction by LAM cells with associated air-trapping, which is thought to cause progressive dilatation of the distal airspaces leading to cyst formation and/or from degradation of the lung parenchyma due to an imbalance between proteases and protease inhibitors [21]. Cysts are typically round or ovoid and are usually 2-10 mm in diameter, but can occasionally be as large as 30 mm [20,21,22]. The lung parenchyma between cysts is typically normal (Fig. 4A).

Birt-hogg-dubé syndrome

Birt-Hogg-Dubé syndrome (BHD) is an uncommon, autosomal-dominant, multiorgan systemic condition characterized clinically by fibrofolliculomas, pulmonary cysts, and renal neoplasms [24,25,26,27]. On CT, more than 80% of adult patients with BHD have multiple lung cysts, and lung parenchyma except for multiple lung cysts generally appears normal [4,24,28]. The presence of lung cysts is significantly associated with spontaneous pneumothorax [2]. Radiologically, multiple thin-walled lung cysts are predominantly seen in lower, peripheral lung zones and along the mediastinum (Fig.4B) [25,26]. These cysts are surrounded by normal lung parenchyma. The shape and size of cysts are variable; they can be round, oval, lentiform, lobulated, or irregularly shaped, and generally have perceptible thin walls. Large cysts, particularly those in the lower lungs, have a lobulated, multiseptated appearance [26]. Predominant distribution of cysts in the lower medial lung zone is a characteristic finding.

STEP 4. Multiple/diffuse cysts associated with other radiological finding

The next step is to identify radiological findings accompanying the cysts. Multiple/diffuse cysts can be devided into two categories according to associated radiological findings as follows: multiple/diffuse cysts with nodules and multiple/diffuse cysts with ground-glass opacity.

Multiple/diffuse cysts with nodules

Pulmonary langerhans cell histiocytosis

Pulmonary Langerhans cell histiocytosis (PLCH) is a rare interstitial lung disease that typically affects young adults and is associated with cigarette smoking [21,23,27]. PLCH is characterized by peribronchiolar infiltration by Langerhans and inflammatory cells and formation of granulomas, leading to stellate interstitial nodules [23,29]. These stellate nodules can later cavitate, resulting in bronchial dilatation and formation of thin – and thick-walled cysts and cavities. Radiologically, nodules are the predominant features in the early stages, while cysts tend to develop later. In the early stages, small (1-10 mm) irregularly shaped nodules appear in a bilateral symmetric pattern with upper-middle lung dominance and a spared lung base and costophrenic angle. As the disease progresses, cystic degeneration appears as round or oval to bizarre with thin-wall and associated nodules (Fig. 5A) [21,23,29]. Cysts usually measure < 10 mm in diameter but may be as large as 20 mm. Bizarre-shaped cysts associated with nodules predominantly in the upper lung are a key imaging discriminator for PLCH in a young smoker.

Cystic metastasis

Cystic lung metastasis is most frequently seen in patients with angiosarcoma or squamous cell carcinoma mainly in the head and neck [30,32]. Radiologically, multiple solid nodules and multiple thinwalled cysts, often admixed with hemorrhagic change, are common features of metastatic angiosarcoma [31]. Cystic metastasis from angiosarcomas shows variability in the walls, air-fluid levels, and vessels or bronchi penetrating the cysts (Fig. 5B) [30,32]. As with other lung metastases, cystic metastasis tends to show different sizes and a basilar predominance [33]. Pneumothorax is a potential complication of cystic metastasis. A patient’s previous malignancy history is critical for diagnosis. If new lung cysts are detected in patients with a known malignancy,

cystic metastasis should be considered, and adequate tissue confirmation is required for diagnosis.

Amyloidosis

Amyloidosis is a rare disease characterized by extracellular deposition of abnormal insoluble proteins [34,35]. Pulmonary amyloidosis can present with cystic lung disease, and amyloid-associated cystic lung disease is rare. Amyloid-associated cystic lung disease can occur with Sjögren's syndrome and mucosa-associated lymphoid tissue lymphoma [35]. Radiologically, lung cysts are commonly numerous (more than 10), are often peribronchovascular or subpleural and are frequently associated with nodular lesions that are often calcified [35]. Cysts tend to be multiple, round or lobulated, small to moderate in size, and thin-walled [31,35]. Other associated findings include interlobular septal thickening, honeycombing, ground-glass opacity, circumferential thickening of the tracheal wall, and lymphadenopathy [34] (Fig. 5C).

Multiple/diffuse cysts with ground-glass opacity
Lymphoid interstitial pneumonia

Lymphoid interstitial pneumonia (LIP) is an uncommon benign polyclonal lymphoproliferative disease [21]. Idiopathic LIP is categorized as a rare idiopathic interstitial pneumonia. Most cases of LIP are associated with various underlying disorders, including HIV infection, connective tissue diseases such as Sjögren's syndrome, Hashimoto's thyroiditis, and systemic lupus erythematosus [21]. Radiologically, a combination of ground-glass opacity, poorly defined centrilobular nodules, small subpleural nodules, interlobular septal thickening, thickening of the bronchovascular bundles, and scattered cysts in lower lungs are seen (Fig. 6A) [20]. Lung cysts are present in up to 68% of patients; they are usually fewer in number but are distributed diffusely in both lungs, although they are often subpleural and peribronchovascular. Cysts in LIP are generally < 3 cm in diameter, are variable in shape, and may be the sole manifestation of this disease. In most cases, follow-up CT reveals the resolution of groundglass opacity, and cysts are the only residual finding in more chronic cases. Lymphadenopathy can be present, but pleural effusion or airspace consolidation is extremely rare [31]. The diagnosis of LIP should be considered in patients with lung cysts and immunological abnormalities.

Desquamative interstitial pneumonia

Desquamative interstitial pneumonia (DIP) is characterized by the accumulation of numerous pigmented macrophages within most of the distal airspace of the lung [31]. According to the international multidisciplinary classification of idiopathic interstitial pneumonias, DIP is classified as a smoking-related interstitial lung disease. Up to 90% of DIP patients have a smoking history, but other conditions besides smoking, such as occupational exposure to certain inhaled toxins, drugs, viral illnesses, and autoimmune diseases, can also cause DIP [31]. Radiologically, DIP presents with patchy ground-glass opacity with a predilection for the basal and peripheral lungs. Reticular density may also be present. Small (usually < 2 cm), well-defined, thin-walled cysts are seen within ground-glass opacity, which is an important finding in DIP (Fig. 6B) [13,36]. Honeycombing is also possible, but uncommon. Cysts in DIP have imperceptible walls, and they are mostly discrete but occasionally can be clustered and are surrounded by ground-glass opacity. Cysts in DIP are believed to represent dilated bronchioles and alveolar ducts, and in the later stages of DIP, cysts may also represent early centrilobular emphysema or honeycombing [23,34]. The presence of small cysts admixed within groundglass opacity is a unique feature of DIP. This feature is reported in approximately one-third of DIP patients.

Pneumocystis jirovecii pneumonia

Pneumocystis jirovecii pneumonia (PCP) is a fungal infection that has a strong association with immunocompromised conditions such as human immunodeficiency virus (HIV) infection [9,33,35]. Radiologically, ground-glass opacity indicating acute pneumonia is the dominant feature of this condition. The pattern of these opacities is often bilateral, multifocal, and mainly symmetrical, and distributed in the central portions of the lungs. Opacities can predominate in the upper lung zones in patients receiving prophylactic therapy for this infection. Thin-walled cysts are now recognized as a relatively common manifestation of this infection and are reported in as many as one-third of all patients. Cysts are usually variable in size, shape, and wall thickness, and are usually multiple and bilateral, subpleurally or intraparenchymally located, and are predominantly in the upper lung zone (Fig. 6C) [9]. PCP is associated with an increased incidence of spontaneous pneumothorax, which is believed to occur in association with ruptured subpleural cysts.

Conclusion

Many different conditions and diseases can be associated with lung cysts. Computed Tomography is the most informative, noninvasive diagnostic method for not only finding them, but also for their detailed characterization and differentiation. Knowing the main and associated radiological signs of different cystic conditions is very helpful for the correct diagnosis, although final diagnosis may require clinical and laboratory correlation and sometimes biopsy, for morphological diagnosis. The stepwise radiologic approach offers easier solution for accurate diagnosis of different cystic lung diseases. Correct CT diagnosis is also crucial for clinicians, for better management and treatment.

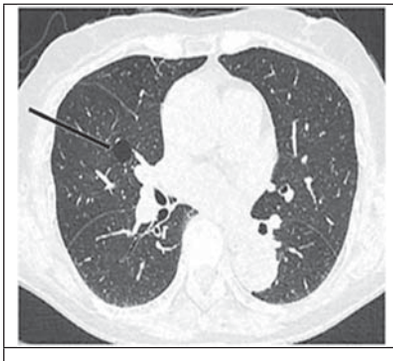


Fig. 1. A

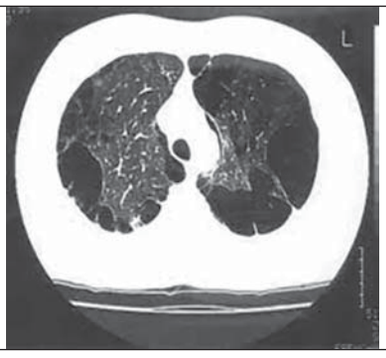


Fig. 1. C

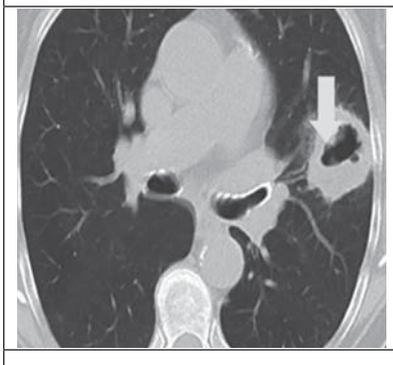


Fig. 1. B

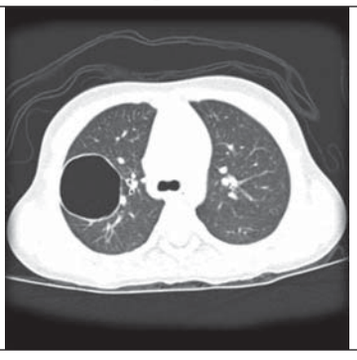


Fig. 1. D

Fig. 1. A. *Cyst: round air-filled lesion with well-defined thin wall surrounded by normal lung (arrow).* ***B.*** *Cavity: air-filled lesion with thick wall within mass.* ***C.*** *Bulla: air-filled lesion, more than 1 cm in diameter, bounded by very thin imperceptible wall and associated with adjacent centrilobular emphysema.* ***D.*** *Pneumatocele: thin-walled, air-filled lesion caused by pneumonia.*

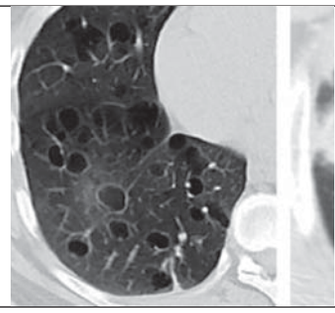
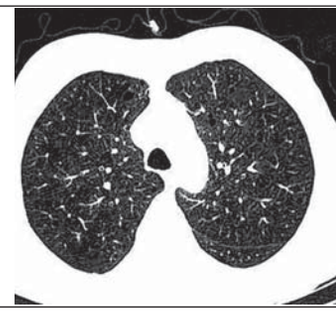


Fig. 2. A



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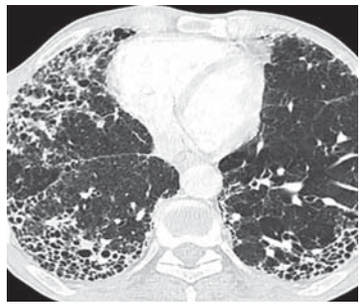

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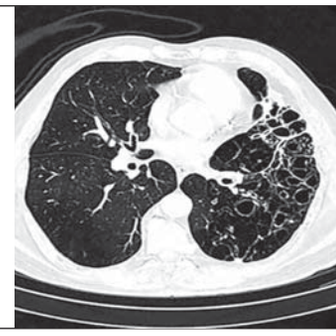

Fig. 2. D

Fig. 2. A. *Multiple or numerous air-filled lesions distributed in both lungs.* ***A.*** *Multiple cysts of variable sizes and shapes with thin wall.* ***B.*** *Centrilobular emphysema: centrilobular lucencies without distinct walls, central dot within lucency represents branch of pulmonary artery.* ***C.*** *Honeycombing: multiple rows of air-filled spaces with thick wall clustered in subpleural region.* ***D.*** *Cystic bronchiectasis: tubular rather than spherical dimensions with branching pattern and associated bronchial wall thickening.*

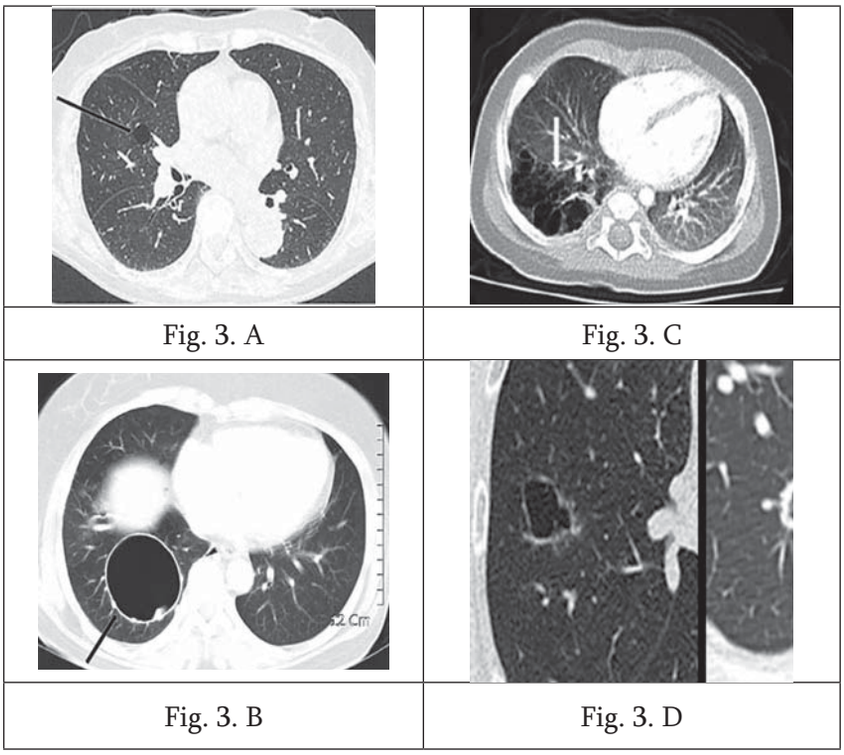

Fig. 3. A	Fig. 3. C
Fig. 3. B	Fig. 3. D

Fig. 3. A. *Incidental cyst in 66-year-old woman. CT shows round 14-mm-sized thin-walled cyst (arrow) in right middle lobe.* ***B.*** *congenital cystic adenomatoid malformation (CPAM) in a 10-month-old infant. several small cysts (arrow) in the right lower lobe.* ***C.*** *Bronchogenic cyst in 55-year-old woman. CT shows well-defined air-filled cyst (arrow) in right lower lobe, suggesting bronchogenic cyst.* ***D.*** *Surgically proved solitary cystic lung cancer.*

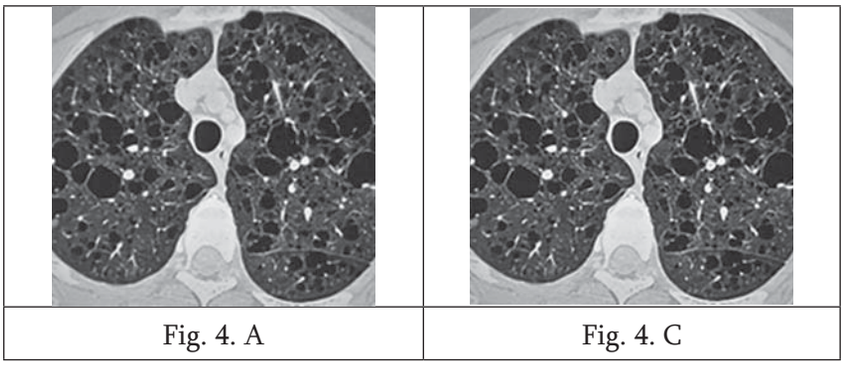

Fig. 4. A	Fig. 4. C

Fig. 4. A. *Lymphangioleiomyomatosis (LAM) CT shows numerous cysts in both lungs. Cysts are round or ovoid and relatively uniform in size and shape. Cysts are diffusely distributed without zone predominance in both lungs.* ***B.*** *Birt-Hogg-Dubé syndrome (BHD) Multiple lower zone predominant thin-walled cysts of varying size, many of which are about the pleura, particularly the paramediastinal pleura.*

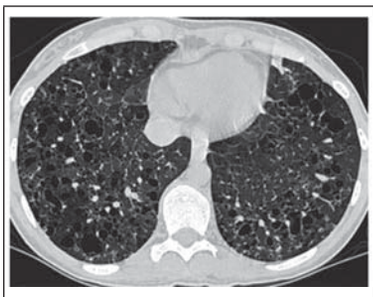

Fig. 5. A

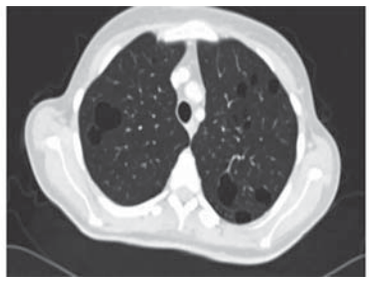

Fig. 5. B

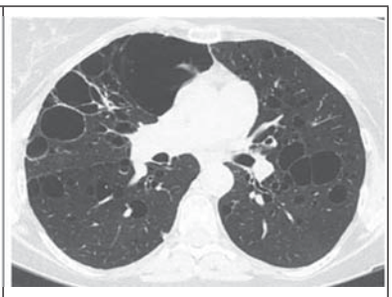

Fig. 5. C

Fig. 5. A. *Histiocytosis X CT shows multiple, irregular and round, thick and thin-walled cysts with small irregular nodules in both lungs, suggestive of PLCH, which was subsequently confirmed histologically.* ***B.*** *Cystic metastases from angiosarcoma. Multuple oval shaped, thin walled cysts are identified in both lungs,* ***C.*** *Amyloidosis High resolution CT scan of a 56-year-old woman, nonsmoker, with AL amyloidosis and lung involvement. Bilateral pulmonary cysts of widely varying sizes and asymmetric distribution are noted.*

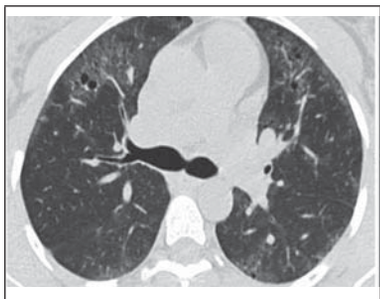

Fig. 6. A

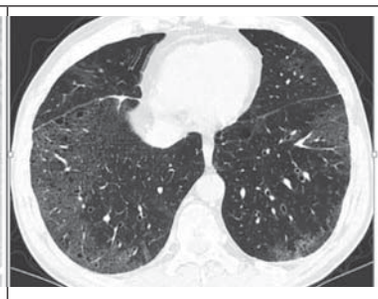

Fig. 6. B

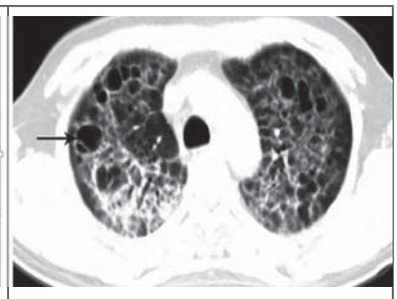

Fig. 6. C

Fig. 6. A. *Axial computed tomography image from a patient with lymphoid interstitial pneumonia showing thin-walled lung cysts in areas of ground glass opacities.* ***B.*** *Desquamative interstitial pneumonia in a 52-year-old smoker. CT shows GGO with tiny cysts in both lungs, mainly lower peripheral lungs, almost symmetrically distributed.* ***C.*** *Chest CT of a PCP in an AIDS patient. Patchy shadows and multiple cysts are shown in the upper lobes of lungs.*

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