REVIEW ARTICLE

Cystic Diseases of the Lung: High-Resolution Computed Tomography Findings

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Introduction

High-resolution computed tomography (HRCT) is the radiographic imaging technique that best detects the changes in lung structure that occur during interstitial diseases.[1] It has been proved better than conventional chest x-rays and thick-section computed tomography in detecting and assessing the pattern and extension of the various interstitial lung diseases that present cysts.[2] Correlation with clinical and functional conditions is better with HRCT than standard radiography.[2,3] HRCT measurement of the extension of the assessed cystic disease is consistent with gas exchange alterations and severity of airway obstruction.[4]

However, HRCT gives a macroscopic view. The radiographic signs are nonspecific so conclusions on the etiology of the findings are normally based on associated and indirect signs. Although some diseases can have common findings, making differentiation difficult, others have specific characteristics that frequently indicate diagnosis. Although HRCT is central to the assessment of interstitial lung disease, clinical, functional, and analytical aspects must be taken into account in the final diagnosis.[2]

HRCT allows the study of the lung parenchyma with sufficient spatial resolution to assess the structures that make up the secondary lobules (less than 1 mm).[5]

A lung parenchyma scan with 1 mm or 1.5 mm thick sections[2,5-7] is performed and reconstructed by using a high-spatial-frequency algorithm with acquisition data of 120kV and between 160 and 220 mA,[5-8] sections being obtained during both inspiration and expiration.[7,8]

Lung cysts are defined as abnormal lung parenchymal spaces filled with air or liquid, with walls of varying thickness, and covered with epithelium.[5] From the radiographic point of view, cysts can be defined as air-filled spaces of variable size with distinct borders and thin walls (less than 3 mm).[6]

The objective of this article was to review HRCT findings of a wide variety of diffuse cystic pulmonary diseases related to airway obstruction: honeycomb lung, histiocytosis X, lymphangioleiomyomatosis, tuberous sclerosis, and interstitial lymphoid pneumonia, as well as other diseases that imitate diffuse cystic processes such as emphysema and cystic bronchiectasis.

This article does not cover infectious diseases or neoplastic processes that can produce lung cysts or localized congenital cystic diseases (cystic adenomatoid malformation). We do mention, however, pathological processes commonly encountered in daily practice that can imitate cystic diseases of the lung.

Cystic Diseases of the Lung

Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis is a type of diffuse interstitial lung disease characterized by the presence of usual interstitial pneumonia in the histological examination of the lung parenchyma. It is the most common of the diffuse interstitial lung diseases, prevalence ranging between 13 and 20 cases per 100 000 inhabitants.[3]

From the pathologist's point of view, honeycomb lung is defined as destruction and fibrosis of the lung parenchyma with the formation of cystic spaces, a situation that represents a complete loss of the acinar and bronchial architecture and indicates the final phase of pulmonary fibrosis.[3,6,9] The cystic spaces represent dilated respiratory bronchioles.[10,11] Honeycomb lung cysts are of similar size, between 3 and 10 mm in diameter, with well-defined walls and mainly patchy, subpleural distribution.[12,13] Forced exhalation reduces the size of the cysts, indicating their connection to the airways.[6]

Pathological and radiographic findings of honeycomb lung are constants[10,14] regardless of the etiology that determined the fibrosis. Nevertheless,

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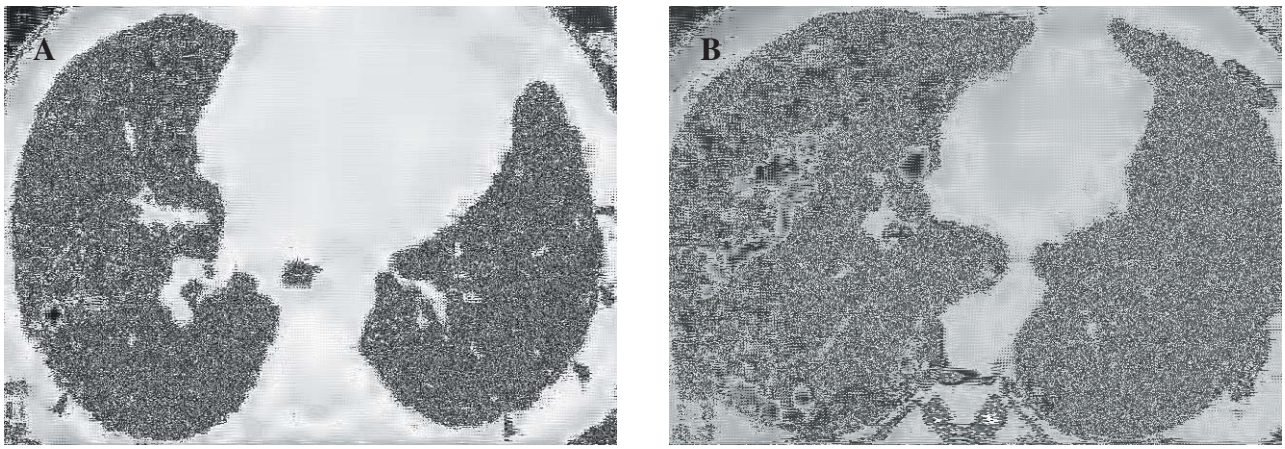

Figure 1. Examples of pulmonary fibrosis and emphysema. A: Idiopathic pulmonary fibrosis. High resolution axial section in the lower lobes shows subpleural septal thickening (black arrowheads), traction bronchiectasis (white arrows), and honeycomb cysts, stacked in rows, with well-defined walls, mainly in subpleural zones. B: Patient with paraseptal and centrilobular emphysema. High resolution computed tomography shows the subpleural bullae distributed in a single row in the peripheral pleura as well as in the interlobar fissures and mediastinal pleura (white arrowheads).

there are factors revealed in HRCT such as localization, distribution of the cysts, and other alternative findings that help establish a more specific diagnosis.[15]

Honeycombing can present as the final phase of many processes that affect the lung parenchyma[16] given that it reflects the fibrosis that develops in the end stage.[6] Idiopathic pulmonary fibrosis is the most common cause of honeycombing—accounting for 50% of cases,[17] although end-stage honeycombing can also present in other diffuse cystic lung diseases.[16]

Staples et al[18] studied 23 patients with idiopathic pulmonary fibrosis using conventional chest x-ray and HRCT and found that x-ray detected honeycombing in 7 patients (30%) while HRCT was able to diagnose 21 (91%).[18] The rate of detection of honeycomb lung in idiopathic pulmonary fibrosis using HRCT is approximately 90%.[3,19-24]

HRCT findings characteristic of idiopathic pulmonary fibrosis and that are considered diagnostic[3] are the presence of irregular septal enlargements in subpleural regions and lower lung zones and honeycombing. Cysts are typically peripheral and stacked in rows (Figure 1).[5,10]

Honeycombing cystic spaces in HRCT normally measure 1 cm diameter, although size can vary from a few millimeters to a few centimeters, and walls are clearly definable and between 1 mm and 3 mm thick.[12,13] The cysts are filled with air and present less attenuation than adjacent normal lung tissue. The cysts share walls and are normally distributed in adjacent rows, this characteristic differentiating them from pleural emphysema, in which the airspaces characteristically present in a single row (Figure 1).[1,25,26] The cyst distribution is peripheral and subpleural and partly preserves the parahilar lung parenchyma even at advanced stages.[1,26]

Honeycombing usually appears in association with other signs of pulmonary fibrosis such as intralobar septal thickening, traction bronchiectasis and bronchiolectasis, and subpleural septal thickening; interlobar septal thickening, however, is uncommon.[1]

In many cases, the presence of honeycombing together with irregular, peripheral, septal thickening in HRCT leads to the diagnosis of idiopathic pulmonary fibrosis.[13,22-24]

A definitive diagnosis of idiopathic pulmonary fibrosis can be determined with the presence of a histological pattern of usual interstitial pneumonia provided that other causes of the interstitial pulmonary disease have been ruled out, respiratory function tests indicate restriction and/or altered gas exchange, and conventional radiography and HRCT findings are consistent with the diagnosis.[9] When lung biopsy is not available, other diagnostic criteria have been established with a sensitivity of over 90%.[3]

Histiocytosis X, Langerhans' Cell

Langerhans' cell histiocytosis (LCH) is a granulomatous disease which mainly affects middle-aged and young adults. The basic lesion consists of a granuloma of Langerhans cells, monocytes, lymphocytes, and eosinophils.[3,5,6]

There are 3 forms of the disease: *a)* Letterer-Siwe disease, or disseminated acute LCH with severe organ disfunction, which mainly affects infants less than 2 years old; *b)* Hand-Schüller-Christian disease, or disseminated, chronic LCH without severe organ dysfunction, which mainly affects children between 2 and 6 years old; and *c)* eosinophilic granuloma or limited, nonprogressive LCH, which is the most common form and mainly affects men in whom it is the most common lung disease between the ages of 20 and 40 years.[3,5,6]

Letterer-Siwe disease presents a disseminated and multiorgan pattern (spleen, liver, lymphatic glands,

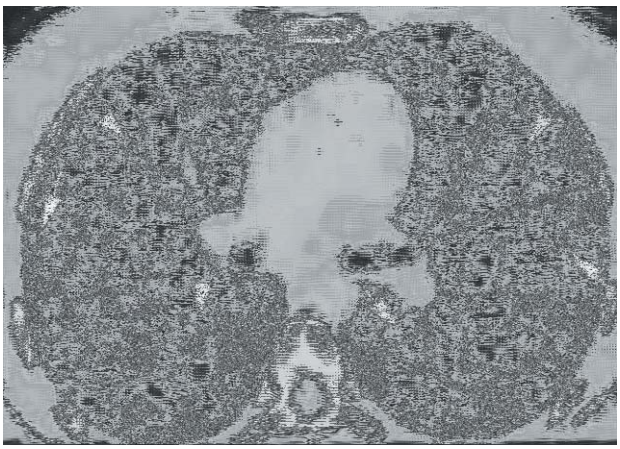

Figure 2. Langerhans' cell histiocytosis X. Small-size nodules (arrows), some of which are cavitated (arrow heads), of peribronchovascular distribution in central and upper lung fields, as well as cysts of less than 1 cm in size with thin, well-defined walls in the lower right lobe.

lungs, and bones), and is nearly always fulminant and frequently fatal.[5] Hand-Schüller-Christian disease presents the typical triad of bone lesions, exophthalmus, and diabetes insipidus. Pulmonary LCH, or eosinophilic granuloma, mainly affects young adults, as mentioned above, and is closely related to smoking (more than 90% of patients with histiocytosis X are active smokers).[2] It is uncommon among black people.

Pulmonary histiocytosis X is characterized in the initial phases by a granulomatous reaction in the bronchiole, with proliferation and infiltration of the bronchiolar wall and adjacent vessels by Langerhans histiocytes and eosinophils. Bronchiolar destruction causes progressive fibrosis of the alveolar wall and the formation of cysts, distorting the lung architecture.[2]

Histologic diagnosis is based on the presence of large, characteristic histiocytes (Langerhans' cells) that contain rod- or racket-shaped organelles (Birbeck granules).[3,27]

The typical pattern that pulmonary eosinophil granuloma presents in HRCT is the presence of cysts in 70% to 90% of cases, and nodules.[28,29]

Mainly middle and upper zones are affected.[30,31] Radiographic findings early in the disease are usually nodules that range between 1 mm and 10 mm in size[5] and have centrilobular distribution representing the peribronchiolar involvement. Nodules tend to present soft margins and cavitation is not uncommon (Figure 2). As the disease progresses, nodules tend to decrease in number and even completely disappear[32]; a cystic pattern predominating in the later stages. The cysts are of variable size, usually between 2 mm and 20 mm,[6] are round, oval, or irregular in shape, and thick walled. As they develop, the walls become progressively thinner. In this phase the cysts tend to join, forming grotesque shapes.[33]

The parenchyma between the cysts tends to present a normal appearance except when cysts coexist with nodules. Pneumothorax is a fairly common finding, with an incidence of around 15%.[5] The disease tends to produce pulmonary fibrosis in the end stages. Focal air trapping can be seen in HRCT during expiration. Another finding that is unusual in diffuse interstitial diseases but that appears in LCH is the preservation of lung volumes.[5]

A firm diagnosis is made on HRCT findings, transbronchial biopsy, and bronchoalveolar lavage ($CD1^+$ cells representing more than 5% of macrophage lineage cells). Open lung biopsy must be resorted to in case of doubt.[3]

Lymphangioleiomyomatosis

Lymphangioleiomyomatosis (LAM) is a rare disease of unknown etiology characterized by proliferation of smooth muscle of benign aspect, predominantly peribronchovascular, that leads to the obstruction of lymphocytes, blood vessels and bronchioles.[3,5,34-38]

The etiology of lymphangioleiomyomatosis is unknown, but pathological, clinical, and radiographic signs are similar to those of tuberous sclerosis, leading some authors to consider LAM as a forme fruste of tuberous sclerosis[3,39,40] Findings frequently associated with tuberous sclerosis such as renal angiomyolipoma have been described for LAM.[3,39-41]

The earliest histologic anomaly in LAM is the proliferation of muscle cells near small blood vessels and pleura,[3,42,43] probably contributing to cyst formation by the obstruction of the small airway.[44] Other studies have indicated that elastic fiber deterioration could be involved in cyst formation.[45] Hyperplasia of type 2 alveolar pneumocytes has also been described.[46,47]

LAM only affects women, usually of reproductive age, and the average age of presentation ranges from 30 to 35 years.[48] The disease can also present after menopause, however,[49] and has been described in a 72-year-old woman.[50]

In addition to the symptoms typical of diffuse interstitial pulmonary diseases, symptoms characteristic of LAM are recurring pneumothorax (69%), chylothorax (23%), hemoptysis (20%), and, less often, ascites, pleuropericardial effusion, chyloptysis, and chyluria.[3,48]

Hormone treatments have improved the historically poor prognosis of LAM.[3,48,51] There are indications that treatment with oophorectomy and/or progesterone could improve prognosis in some patients.[48] Estrogen and progesterone receptors in affected tissue have been identified by immunohistochemical[52,53] and biochemical[54,55] techniques, although their presence is not clearly associated with a better response to hormone treatment.[48]

Characteristic HRCT findings are the presence of numerous, thin-walled cysts surrounded by normal lung parenchyma (Figures 3A and 3B).[48,56-58] The cysts are uniformly distributed throughout the lung, without central, peripheral, or basal predominance.[46] The cysts typically measure less than 2 cm diameter, although

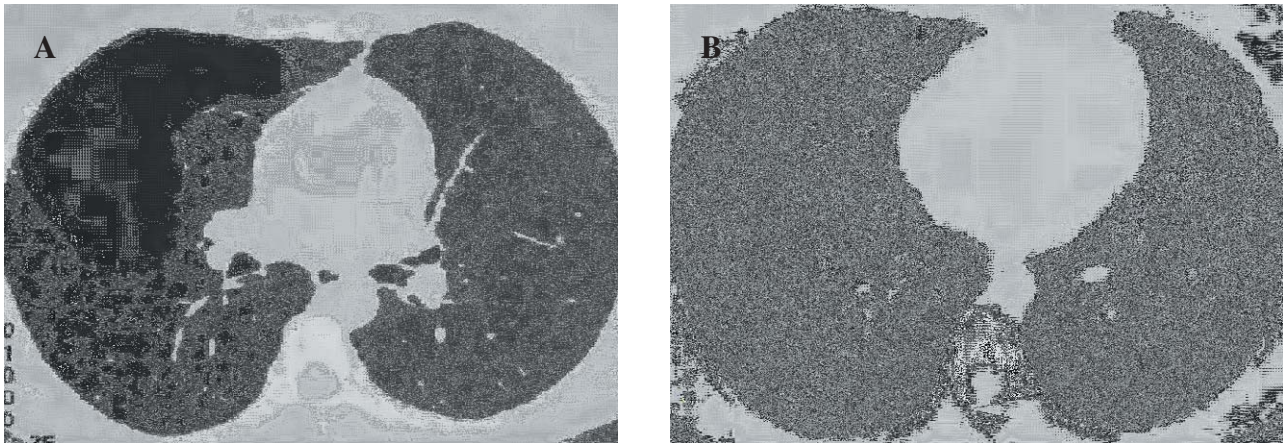

Figure 3. From a 35-year-old woman with lymphangioleiomyomatosis. Multiple, thin-walled, well-defined cysts of varying sizes are apparent, distributed diffusely in the upper lobes (A) and the middle and lower lung fields (B).

larger cysts have been described. Wall thickness varies from almost imperceptible to nearly 4 mm but is relatively thin in most cases.[46,57] The presence of nodular opacities, histologically consistent with hyperplasia of type 2 pneumocytes, has been described in some patients.[8,47] Thickened interlobular septal lines and vascular destruction do not normally occur.[58] Pneumothorax occurs in 30% to 40% of cases[46,47] and can be bilateral and recurrent. Chylothorax is another common finding.[59]

Uniform distribution of the cysts in both lungs helps distinguish LAM from other causes of diffuse cystic pulmonary disease, particularly Langerhans' cell disease,[60] which affects the upper 2 thirds of the lung while leaving the bases relatively clear. Langerhans' cell histiocytosis is also associated with pulmonary nodules, which are rarely found in LAM.[29,47,60]

The diffuse distribution of the LAM cysts and the presence of normal parenchyma between them makes them easily distinguishable from honeycomb cysts.[1,2]

Final diagnosis of LAM is normally made on histological confirmation of tissue obtained either by fine-needle aspiration[61] or open biopsy.[3] Tissue obtained by transbronchial or pulmonary biopsy undoubtedly provides much more information[48,62] but is unnecessary in most cases.[61]

Tuberous Sclerosis

Tuberous sclerosis is an autosomal dominant disease that affects both sexes equally. Pulmonary involvement, however, is almost entirely confined to women, only one case having been described in a man.[57] The incidence of pulmonary involvement is approximately 26%[63] but the disease is clinically silent and does not normally manifest until a patient is in the third or fourth decade of life.[62]

Tuberous sclerosis is classically characterized by the triad of mental retardation, epilepsy, and juvenile sebaceous adenoma, but can include a wide variety of anomalies such as renal and hepatic angiomyolipomas, cardiac rhabdomyomas, retinal phakomas, osteosclerotic lesions, and subungual fibromas.[59]

The earliest symptom of lung involvement is dyspnea. Pneumothorax can also be a form of presentation and has been described in nearly 50% of tuberous sclerosis patients.[10,32]

The pathological, clinical, and radiographic signs of tuberous sclerosis in the lung are similar to those of LAM, which is sometimes considered to be a forme fruste of tuberous sclerosis.[39,40] HRCT findings are similar in the 2 diseases,[57] the only difference being that chylothorax is unusual in tuberous sclerosis.[64] This observation has been upheld by the recent finding of somatic mutations of the tuberous sclerosis complex gene 2 in the lung tissue of women with LAM.[29] The cystic changes in the lung are indistinguishable. The cysts also have fine walls and are distributed evenly throughout the lung (Figures 4A and 4B).

The prevalence of renal angiomyolipomas in tuberous sclerosis is approximately 50%,[65] similar to the prevalence described in LAM.[13,20,40,66] Evidence of renal angiomyolipomas in abdominal computed tomography can help differentiate LAM from Langerhans' cell disease and other cystic diseases of the lung.

A firm diagnosis of tuberous sclerosis complex is made based on clinical criteria.[67]

Lymphocytic Interstitial Pneumonia

Lymphocytic interstitial pneumonia is defined as a diffuse lymphoid hyperplasia characterized by infiltration of the pulmonary interstitium by mononuclear cells, mostly lymphocytes.[3,5,68] The disease typically affects patients with human immunodeficiency virus, Sjögren syndrome, or Castleman disease,[2,69,70] as well as collagen and autoimmune diseases (Hashimoto thyroiditis,

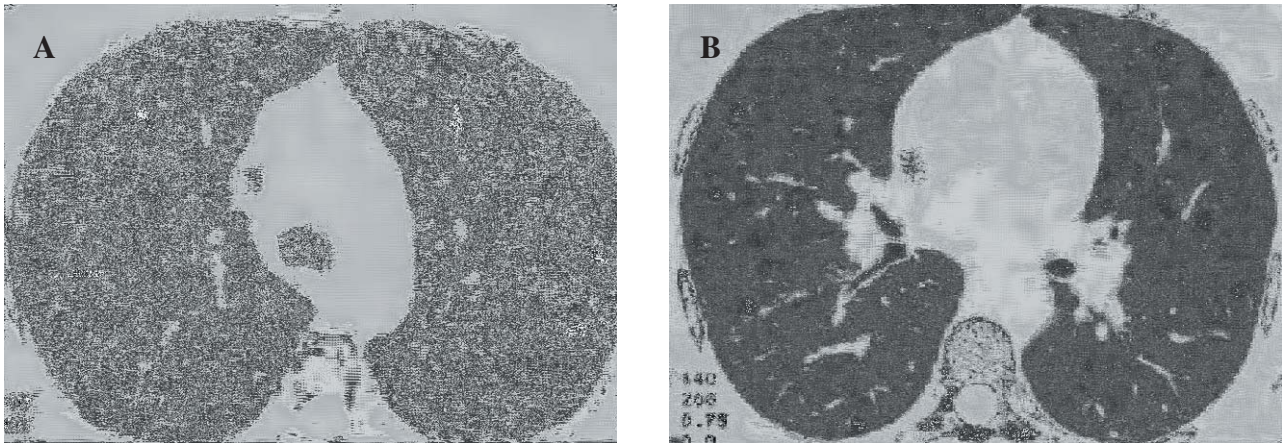

Figure 4. Patient of 40 years of age with tuberous sclerosis, showing thin-walled cysts of varying sizes, the biggest being 1 cm, in the upper (A) and lower (B) lobes, similar to lymphangioleiomyomatosis cysts (arrows).

myasthenia gravis, pernicious anemia, or biliary cirrhosis).[3]

The most common HRCT findings are areas of ground-glass attenuation and the presence of cysts and nodules,[71] the nodules representing the lymphoid aggregates that characterize the disease (Figure 5).[5]

The cysts are not as uniformly sized as in the other diffuse cystic diseases described, and their distribution is predominantly subpleural although in some cases they can present diffuse distribution throughout the lung.[2] Other findings typical of lymphocytic interstitial pneumonia are ill-defined centrilobular nodules (from 3 mm to 30 mm in diameter) and ground-glass parenchymal opacities. These 3 findings are key features for distinguishing this disease.[72,73] A reticular pattern is observed in about 50% of cases.

A definitive diagnosis is made by open biopsy.[3,68]

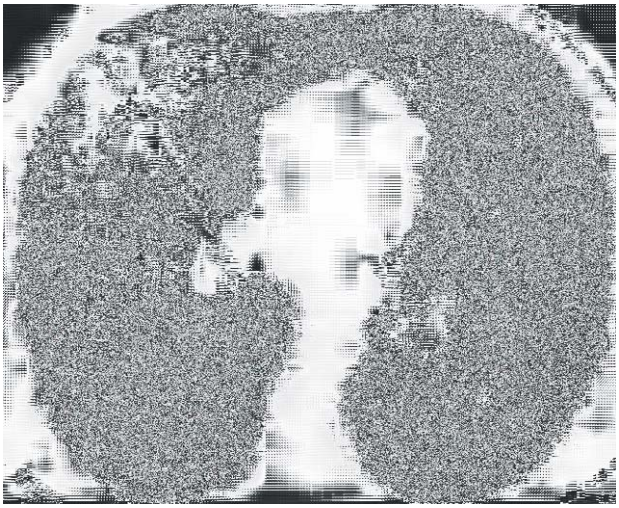

Figure 5. From a 28-year-old patient with human immunodeficiency virus and lymphocytic interstitial pneumonia. High resolution computed tomography shows a pattern of diffuse ground-glass attenuation in the middle lung field as well as predominantly subpleural cysts (arrows).

Diseases That Simulate Cystic Processes

There are other diseases that can simulate diffuse cystic diseases of the lung. The 2 most common are cystic bronchiectasis and emphysema.

Cystic Bronchiectasis

Cystic bronchiectasis, particularly when diffuse, can imitate cystic diseases of the lung in the HRCT. There are certain differences, however, that help differential diagnosis.

The most useful characteristic is an evident connection between the air space with the bronchial tree. Bronchiectasis is simply a saccular dilation of the bronchus,[10] and therefore the air space that the saccular bronchiectasis forms is directly connected to the airway. This continuity can be difficult to distinguish when visualized in the transverse plane, especially in HRCT as there are spaces between sections, but the connection between the dilated bronchus and the airway is easily seen in views running parallel to the bronchus.[10]

The presence of the signet ring sign, where the dilated bronchus represents the ring and the accompanying bronchial artery represents the stone of the ring, also helps distinguish cystic bronchiectasis (Figure 6). This sign is only visible in transversal views of the bronchus.[5] Tram track lines corresponding to thickened bronchial walls and tubular opacities that represent mucus-filled bronchi are typical radiographic signs which also help diagnosis.[10]

Diseases which can be associated with bronchiectasis include congenital tracheobronchomegaly or Mounier-Kuhn syndrome, Williams-Campbell syndrome, and cystic fibrosis.

Tracheobronchomegaly is a relatively diffuse disease which is characterized by a distinct dilatation of the trachea and the main bronchi.[10,74-77] The dilatation and the abnormal functioning of the airways allow the

accumulation of secretions and the appearance of recurrent or chronic respiratory infections together with the presence of bronchiectasis, fibrosis, or emphysema.[77] Tracheobronchomegaly can be diagnosed with conventional chest x-ray by measuring the transversal and sagittal diameters of the trachea and the bronchi.[10] Often associated with tracheobronchial diverticulosis, tracheobronchomegaly can be studied with conventional computed tomography as well as HRCT,[75-77] although HRCT is particularly useful in demonstrating associated bronchiectasis.[74,76]

Williams-Campbell syndrome presents defective distal cartilage of the third order bronchi which, when visible by HRCT, practically confirms diagnosis.[78] Characteristic findings consist of cystic bronchiectasis limited to the fourth, fifth, and sixth bronchial generations.[78,79] HRCT sections on expiration reveal collapse of bronchi as well as distal air trapping attributable to defective cartilage. This last combination practically confirms diagnosis of the syndrome.[79]

Cystic fibrosis is characterized by the presence of diffuse bronchiectasis[80,81] mainly in the upper lobes.[80] Bronchiectasis is identified in only 34% of these patients.[82]

Emphysema

Emphysema is characterized by an abnormal enlargement of the distal air spaces at the bronchiole terminals, together with destructive changes in the alveolar walls.[6]

The most common types of emphysematous changes which can imitate cystic pulmonary diseases are centrilobular and paraseptal emphysema.[17]

In centrilobular emphysema, the airspaces which surround the respiratory bronchioles are destroyed.[6] Characteristics that allow centrilobular emphysema to be differentiated from other cystic pulmonary diseases include the presence of localized areas of poor attenuation without defined walls and the distribution of the vessels relative to the cystic spaces. In emphysema the vessels can cross cystic spaces while in other cystic pulmonary diseases the vessels surround the cysts or are independent of them.[60]

In paraseptal emphysema, selective involvement of distal acinar cells occurs around the secondary lobule, near the interlobular septa and subpleural regions.[6] Changes can usually be distinguished from those of most cystic pulmonary diseases except, in some cases, honeycomb lung.[17] Characteristics that help differentiate paraseptal emphysema from real cysts are the apical distribution of paraseptal emphysema compared with the predominantly basal honeycombing of lung fibrosis and the number of rows of cysts seen at the periphery of the lung (Figure 1).[5] Paraseptal emphysema normally has only a single subpleural row, whereas honeycomb lung normally has 2 or more rows of small cystic spaces with thickened walls, all around the perimeter of the lung.[5,10]

Figure 6. Cystic bronchiectasis. Sequential image with high-resolution reconstruction of the lower left lobe which shows distinct cystic dilatation of the bronchi, most of them filled with air, with several "signet ring" signs (arrows), of peribronchovascular distribution.

Conclusion

HRCT has proved to be extremely useful in the study of diffuse cystic diseases of the lung. The technique provides an excellent picture of cysts and additional information about their characteristics (distribution, size, location, and wall thickness), all of which can help establish a more specific diagnosis. Easy availability, speed, diagnostic precision, and the relatively low doses of radiation involved compared with conventional computed tomography have made HRCT the technique of choice for the study of these diseases.

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