Differential diagnosis of cystic lung diseases

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Summary

A lung cyst is defined as a round parenchymal lucency or area of low attenuation with a thin wall. Although lymphangioleiomyomatosis (LAM) and Langerhans cell histiocytosis (LCH) are the most frequently encountered causes, the differential diagnosis for diseases characterised by diffuse lung cysts is broad ranging from isolated chest disorders to rare multisystem diseases. This article will illustrate and describe the spectrum of diseases associated with air cysts at high-resolution CT (HRCT), highlighting disorders in which the HRCT findings can be diagnostic.

KEY WORDS: lung cysts, HRCT, cystic lung disease, differential diagnosis.

Introduction

Pulmonary diseases characterised by diffuse cystic air spaces are uncommon disorders. The CT findings of these conditions (distribution, shape and ancillary sign) are sometimes quite characteristic and give clues for the specific diagnosis without further investigation. This article will illustrate and describe the spectrum of diffuse cystic lung diseases on HRCT, including rare entities and with particular attention to characteristic patterns of the cystic abnormalities. The pathological basis as well as the mechanisms leading to cyst formation in the various cystic lung diseases is also briefly described.

Multiple diffuse cysts: LAM, LCH

LAM

Lymphangioleiomyomatosis (LAM) is a rare disease in which an abnormal proliferation of smooth muscle cells in the pulmonary interstitium results in thickening of the walls of lymphatics and blood vessels and in a partially or completely occlusion of the lumina of bronchioles (1).

This condition is a multisystemic disease that can also involve the abdomen (usually with renal angiomyolipomas) and it may occur isolated or in association with tuberous sclerosis (2). LAM disease occurs almost exclusively in women of childbearing age, from 20 to 35 years old; however, it also can present after menopause, particularly in women undergoing estrogen hormonal treatment (3).

> **The most useful sign in differentiating LAM from LCH is the distribution of cysts: in LAM the distribution of cysts is diffuse in the lung with involvement of the costophrenic recesses, whereas in LCH the costophrenic sulcis are typically spared.**
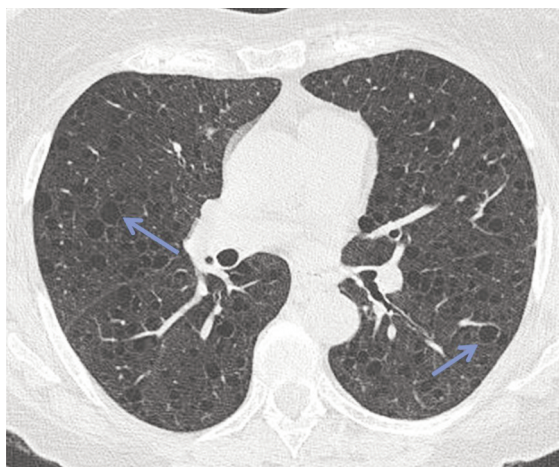
Clinically, it presents most commonly with dyspnea or recurrent pneumothoraces, due to the rupture of subpleural cysts; the involvement of venous and lymphatic vessels by the LAM cells may lead respectively to pulmonary hemorrhage with haemoptysis, and chylothorax.

At high-resolution computed tomography (HRCT) imaging, LAM is characterized by diffusely distributed multiple pulmonary cysts that are likely the result of focal bronchiolar dilatation caused by a valve-like effect secondary to progressive airway obstruction. Cysts are not related to fibrosis and therefore they are surrounded by relatively normal lung parenchyma.

Cysts are numerous and distributed throughout all lung zones, without any upper or lower lobes predominance. They have regular round shape and a thin wall, and are almost of equal in size (generally a few millimeters) (Figure 1).

On HRCT, other associated abnormalities in LAM may include pneumothoraces, chylous pleural effusion and lymphonode enlargement.

Obviously, the sole HRCT features of LAM are diagnostic in the correct clinical context, especially when typical pulmonary cysts are associated with renal angiomyolipoma. In such case scenarios, no lung biopsy is required to confirm the diagnosis (4).

The differential diagnosis for LAM, based on CT imaging, especially includes Langerhans cell histiocytosis (LCH) and emphysema.

Figure 1 - LAM. High-resolution CT (HRCT) in a patient with LAM. The cysts are diffuse in distribution, thin-walled and regularly round (arrows).

Figure 2 - LCH. High-resolution CT (HRCT) image shows bizarre cysts and cavitated nodules (arrow) in the upper lobes.

The most useful sign in differentiating LAM from LCH is the distribution of cysts: in LAM the distribution of cysts is diffuse in the lung with involvement of the costophrenic recesses, whereas in LCH the costophrenic sulcis are typically spared. The cysts in LAM are typically thin walled and regularly round in shape, whereas in LCH cysts have usually a bizarre shape.

Lung nodules are usually absent in LAM (or, when present, they are single or scattered), whereas they are a classical feature in early LCH.

Sometimes the most challenging differential diagnosis is between LAM and emphysema. However, identification of residual core lobular structures in the center of "cysts", typical of emphysema, may be helpful in differentiating these conditions.

LCH

Langerhans cell histiocytosis (LCH) is an idiopathic disorder caused by a clonal proliferation of Langerhans cells that infilter the lung parenchyma and other organs. As reported by Lee at al. (5), in 60% of cases there is an isolated pulmonary disease, 20% of cases also have bone involvement and another 20% have multivisceral disease.

Langerhans cells are normally localized in epithelia, lymphonodes, thymic epithelium and bronchial epithelium, representing an immature form of dendritic cells with antigen presenting functions and characteristic cytoplasmic organelles known as Birbeck granules. Histologically, LCH is characterized by the proliferation of Langerhans cells and formation of granulomas within bronchioles, associated to an involvement

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of the interstitium and pulmonary vasculature.

LCH occurs almost exclusively in young patients, between the ages of 20 and 40 years, and in particular in which are current smokers (6).

Patients may be asymptomatic or present with dyspnea and cough; less frequently they report chest pain, fever and pneumothorax during the course of the disease.

A remission of disease can be achieved in the majority of patients especially in those that stop to smoke.

The HRCT appearances of LCH are often characteristic and reflect the temporal phase of the disease.

In the early stages, centrolobular nodules (which correspond with Langerhans cell granulomas) are the predominant features: nodules are multiple and they are usually <5 mm in size.

The presence of cysts usually develop only during the later stages of the disease.

Cysts in LCH probably arise because of focal dilatation of bronchi caused by destruction of small airway bronchial walls due to Langerhans cell lesions and reflect Langerhans cell granuloma induced fibrosis rather than bronchial dilatation.

This process may start from non-cavitary nodules that progressively become thick-walled cavitary nodules and then thin-walled cysts, with a predominant presence of both thin- and thick-walled irregular cystic spaces.

The cysts are usually most profuse in the upper lobes, with relative sparing of the costophrenic recesses and the medial tips of the middle lobe and lingula; with increasing severity, the cysts may assume bizarre shapes mimicking bronchiectasis and are different sizes (from 1 to 3 cm) (Figure 2).

The combination of nodules, cavitating nodules and cysts, localized in the upper lobes, in a young smoker is highly suggestive for CT diagnosis of LCH; however, to identify the pathognomonic Birbeck granules at electron microscopy, for having a pathological confirmation of the diagnosis, bronchoalveolar lavage (BAL) may be

usefull, with an high specificity and more safety than transbronchial lung biopsy (TBB) (7).

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Scattered cysts with ancillary CT signs: LIP, HP,DIP

LIP

Lymphocytic interstitial pneumonia (LIP) is an uncommon, benign, lymphoproliferative disorder characterized by a diffuse and interstitial proliferation of small lymphocytes and plasmacells (8).

LIP is very rarely idiopathic condition, but is often associated with collagen vascular disorders (particularly Sjogren's syndrome), or AIDS. Less commonly, LIP is associated with autoimmune thyroid disease, Castleman's disease, *myasthenia gravis*, pernicious anemia and chronic active hepatitis (9, 10).

Histologically, LIP is characterized by nodular infiltrates of lymphoid cells with peribronchiolar distribution that develop to the cystic air space formation due to the partial airway obstruction (11).

LIP is more frequently seen in 50 years old and older women. Symptoms are usually dyspnea or cough.

> **LIP can be distinguished from LAM and LCH for the presence of ground glass and reticulation, and absence of profuse cysts.**

The disease usually responds to treatment with corticosteroid, but it may be complicated by progressive pulmonary fibrosis or malignant lymphoproliferative disorders (12-14).

The predominant abnormalities on HRCT evaluation are as follows: patchy ground-glass opacity, lung cysts scattered, interlobular septal thickening, fine reticular opacities and lymphonodes enlargement (Figure 3).

Cysts are seen in about two-thirds of patients (15). They usually are thin walled, small (though larger up to 3 cm in size have been reported), and display a scattered distribution.

Surgical lung biopsy is required to confirm the clinical-radiological diagnosis of LIP, and in some cases to exclude low-grade lymphoma.

LIP can be distinguished from LAM and LCH for the presence of ground glass and reticulation, and absence of profuse cysts.

The cysts in LIP are more scattered than those observed in LCH. In addition, upper lobes nodules are not a feature of LIP.

HP

Hypersensitivity pneumonitis (HP) is an immunologically mediated granulomatous inflammatory disease involving the lung parenchyma and terminal airways secondary to repeated exposure and inhalation of a variety of agents, ranging from organic particles to chemotherapy agents, in a sensitized host.
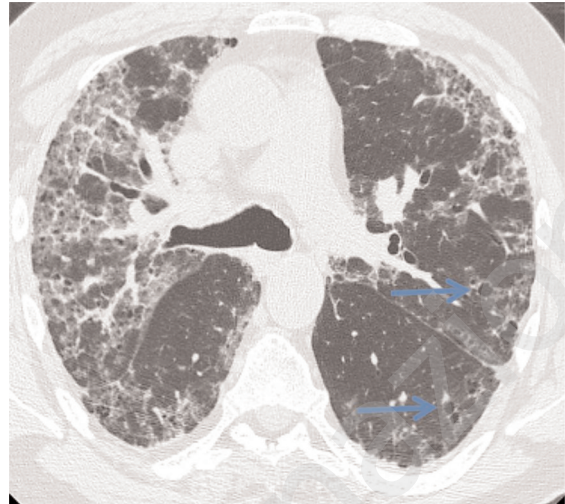

Figure 3 - LIP. High-resolution CT (HRCT) scan obtained at level of tracheal carina shows thin-walled cystic air spaces (arrows), areas of ground-glass attenuation and randomly distributed centrilobular nodules.

It is most commonly caused by thermophilic actinomycetes present in moldy hay and contaminated humidifiers or air conditioners, or proteins contained in birds' serum, droppings and feathers.

> **The diagnosis of subacute and chronic HP is often not suspected clinically before HRCT or lung biopsy. In the subacute phase of LP, HRCT is generally characterized by ground-glass opacity and poorly defined centrilobular nodules (secondary to cellular bronchiolitis).**

The most common histologic features of HP are cellular bronchiolitis and peribronchiolar interstitial alveolitis due to bronchocentric lymphocytic infiltration and poorly defined non-necrotizing granulomas (16).

Clinically, HP can assume acute, subacute or chronic forms, which correspond to varying CT patterns.

Heavy exposure to the inciting antigen may lead to the acute form of HP, characterized by dyspnea and fever developing within 4 to 8 hours after exposure and resolving within a few days, and identification of serum precipitins.

In subacute HP the presentation is more insidious, due to repeated exposures to relatively low doses of antigen leading to slowly progressive dyspnea over several weeks or months.

Chronic HP is caused by continued, low-level antigen exposure over months or years that may result in pulmonary fibrosis.

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In the subacute phase of HP, HRCT is generally characterized by ground-glass opacity and poorly de-

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fined centrilobular nodules (secondary to cellular bronchiolitis) (17). Coexisting areas of decreased attenuation due to constrictive bronchiolitis may lead to the so called "head-cheese pattern".

The centrilobular nodules are typically poorly defined, measure less than 5 mm in diameter and have a prevalent middle and lower lung zones distribution; in some patients, centrilobular nodules may be the only finding or the predominant abnormality seen in HP (18).

The mosaic perfusion areas in HP often have a lobular distribution and increase in size on CT expiratory scans.

Approximately 10% of patients with subacute HP have lung cysts, probably secondary to partial small-airway obstruction by the bronchiolitis. Cysts are randomly distributed, thin-walled, ranging from 3 to 25 mm in maximal diameter and 1 to 15 in number (19).

For a radiological diagnosis of HP, the presence of cysts can be really helpful when they are found in association with the more classical signs of the disease, such as centrilobular nodules and mosaic attenuation pattern.

In chronic HP, fibrotic abnormalities can be found on HRCT. The fibrotic abnormalities may configure either a nonspecific interstitial pneumonia (NSIP) or a usual interstitial pneumonia (UIP) pattern (20, 21).

DIP

DIP is an uncommon disorder characterized histologically by macrophage accumulation filling the alveolar ducts and bronchiole, mild inflammation of the alveolar walls and minimal fibrosis.

> The most common findings on HRCT in DIP is the presence of bilateral ground-glass opacities, that usually display a lower lobe distribution. Ground-glass opacities can be either diffuse or patchy.

DIP occurs most commonly in patients between 30 and 50 years of age, approximately 90% of which is current cigarette smokers; rarely, DIP can be associated with a variety of conditions in non-smokers, including drug reactions, asbestosis and human immunodeficiency virus (HIV) infection. It is more common in men than in women.

The clinical symptoms usually consist of progressive dyspnea and dry cough; the prognosis is good, improving with smoking cessation and corticosteroids therapy. The most common findings on HRCT in DIP is the presence of bilateral ground-glass opacities, that usually display a lower lobe distribution (22). Ground-glass opacities can be either diffuse or patchy.

In almost all of patients a fine reticular pattern due to intralobular linear thickening is seen, involving mainly the subpleural lung regions and lung bases.

Traction bronchiectasis and honeycombing are uncommon.

Small cysts have been reported in one third of patients with DIP (22). The cysts are usually round, thin-walled, and less than 2 cm in diameter (4).

Table 1 provides a ready-reference to the main cysts features in the most common pulmonary cystic disease.

Rare causes of multiple lung cysts

Although centrilobular emphysema, LAM, LCH, LIP, HP, DIP are the most frequently encountered causes of thin-walled cysts at HRCT, differential diagnosis of diffuse cystic lung disease is more extensive than previously described (23) (Table 2).

Amyloidosis with cysts

Pulmonary amyloidosis occurs as part of a systemic disease or a localized process restricted to the lung (primary pulmonary amyloidosis) with tracheobronchial, nodular parenchymal, diffuse parenchymal interstitial or diffuse alveolar septal distribution (24). Diffuse alveolar septal amyloidosis can rarely be associated with cysts formation (25). The mechanism of parenchymal cyst formation has been postulated to be the result either of airway narrowing by inflammation

> In Amyloidosis with cysts, CT showed multiple cystic lesions of various size up to 1.5 cm. The cysts were located mainly over the hilar and central zone, and high density areas were seen around the cysts.

Table 1 - Summary of HRCT features of cysts in pulmonary cystic disease.

	Cysts Distribution	Cysts Shape	Cysts Wall	Cysts Size
LAM	Diffuse	Regularly round	Thin	Homogeneous, generally small (few millimeters)
LCH	Upper and middle lobes; spares of the costophrenic recesses and the medial tips of the middle lobe and lingula	Bizarre	Thin and thick	Varying in size (ranging from 10 mm to 30 mm)
LIP	Scattered	Round	Thin	From 1 mm to 30 mm
HP	Scattered	Round	Thin	From 3 mm to 25 mm
DIP	Upper or lower lobes	Round	Thin	Generally very small (< 2 mm)

Table 2 - Summary of HRCT features of rare diffuse cystic lung diseases.

Diagnosis	Clinical Features and associations	Distinct HRCT Features
Amyloidosis, LCDD	Renal failure, Sjögren disease, multiple myeloma, macroglobulinemia	Cysts and large nodules
Birt-Hogg-Dubé syndrome	Skin lesions, renal neoplasms, colonic polyposis	Basilar subpleural lentiform cysts
Neurofibromatosis	Cutaneous and subcutaneous neurofibromas, meningoceles, kyphoscoliosis, ribbon deformity of the ribs	Cysts and ground-glass centrilobular opacification with upper lobe predominance
Tracheobronchial papillomatosis	Papillomas in the upper respiratory tract	Bilateral solid nodules and multiple cysts in the posterior regions
Cystic fibrohistiocytic tumor	Fibrous histiocytomas of the skin, pneumothorax	Multiple bilateral pulmonary cysts, nodules or masses
Mesenchimal cystic hamartoma	Pneumothorax	Pulmonary masses with multi-lobulated cysts of varying size
Pulmonary blastoma	Shortness of breath and chest pain	Well-defined mixed solid and cystic large mass
Cystic metastases	History of malignancy	Peripheral or random distribution

and amyloid deposition (check valve mechanism) and increased fragility and rupture of alveolar walls due to amyloid deposition, or ischaemia resulting from amyloid deposition around capillaries. In the reported cases, CT showed multiple cystic lesions of various size up to 1.5 cm. The cysts were located mainly over the hilar and central zone, and high density areas were seen around the cysts corresponding at histological

examination to amyloid deposits (26) (Figure 4).
Some reported cases have shown both pulmonary lymphocytic infiltration and amyloid deposition, often in association with Sjögren's syndrome, raising the possibility that in this patients the cysts formation is related to the lymphocytic infiltration rather than the amyloid deposition, since cystic change is recognised to occur in lymphocytic interstitial pneumonia (LIP) (27, 28).

Light-chain deposition disease (LCDD)

Light-chain deposition disease (LCDD) occurs in middle-aged patients (75% of cases in association with multiple myeloma or macroglobulinemia) and commonly involves the kidneys. Although lung involvement is rare, LCDD can result in respiratory failure and require lung transplantation (29). The light chains are secreted by a plasma clone and deposit in the alveolar walls, small airways and vessels. HRCT manifestations most commonly include nodules, lymphadenopathy and cysts (23). Cysts formation presumably has similar pathogenesis of pulmonary amyloidosis and is believed to correspond to dilation of the small airways (24).

HRCT manifestations of LCDD may include nodules, lymphadenopathy, and cysts.
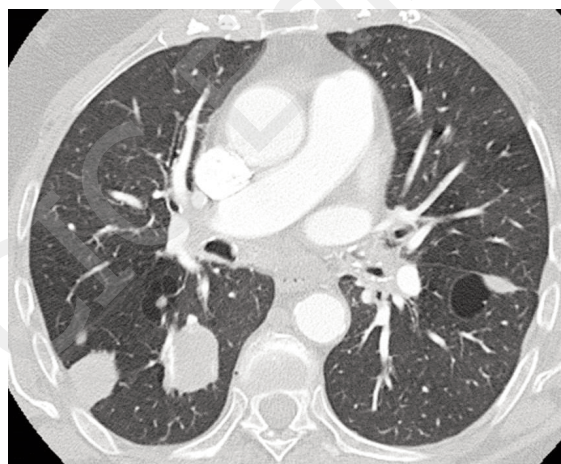

Figure 4 - AMYLOIDOSIS. A section CT passing under the tracheal carina shows multiple bilateral cysts of various sizes typically mainly located over the hilar and central zone. High density areas in the fissures and in the superior segment of the lower right lobe correspond to amyloid deposit at histological examination.

Birt-Hogg-Dubé syndrome

This syndrome is a rare autosomal dominant charac-

> **In BHD the cysts are scattered, lentiform or oval, sometimes several cm. large, thin-walled with lower-medial predominance in subpleural zone.**

terized by the presence of cutaneous hamartomas (predominantly fibrofolliculomas) distributed over the face, neck and upper trunk, renal tumors (ranging from benign oncocytomas to renal cell carcinomas) and diffuse cystic lung disease. Patients may have isolated lung cysts without involvement of skin and/or kidney and frequently develop pneumothoraces. The majority of patients has identifiable mutations in the folliculin gene (FLCN, also known as BHD) that interestingly is also associated with dysregulation of mTOR signalling pathway in pulmonary LAM (30-33). HRCT findings in Birt-Hogg-Dubé syndrome show thin-walled cysts (80%). Radiologically, the cysts are scattered, thin-walled with lower-medial predominance in subpleural zones (23). Typically, these cysts are often lentiform or oval and some of them may be large (i.e. measuring several centimeters) (34).

Neurofibromatosis

Neurofibromatosis has variable manifestations in the thorax and lungs including intrathoracic neurogenic tumors, meningoceles, kyphoscoliosis, ribbon deformity of the ribs, cutaneous and subcutaneous neurofibromas of the chest wall and interstitial lung disease (ILD) as distinct clinical entity, not associated to smoking (35-38). Histological documented lymphoplasmocytic inflammation of the alveolar septa in neurofibromatosis could lead to cyst formation by check valve mechanism

> **Typical findings on HRCT include cysts and ground-glass centrilobular opacifications with upper lobe predominance. Indeed the main differential radiological diagnosis is with LCH, LIP and HP.**

but the exact aetiology is still uncertain. Typical findings on HRCT include cysts and ground-glass centrilobular opacifications with upper lobe predominance. Indeed the main differential radiological diagnosis is with LCH (39), LIP and HP (19, 40).

Cystic lung tumors

> **Mesenchymal cystic pulmonary hamartomas and pulmonary blastomas are described as pulmonary masses with cysts. Usually the combination of these nodules or masses suggests the cancerous aetiology of these cysts.**

Some primary lung tumors and lung metastases may display cystic abnormalities on CT. Some mesenchymal neoplasms with different degree of malignancy such as advanced tracheobronchial papillomatosis, cystic fibrohistiocytic tumor, mesenchymal cystic pulmonary hamartomas and pulmonary blastoma may be

associated with a cystic pattern (41).
In advanced tracheobronchial papillomatosis and cystic fibrohistiocystic tumor cystic lesions are often multiple and bilateral (42, 43). Mesenchymal cystic pulmonary hamartomas and pulmonary blastomas are described as pulmonary masses with cysts. Usually, the combination of these nodules or masses suggests the cancerous aetiology of these cysts.

Advanced tracheobronchial papillomatosis

In less than 1% of cases tracheobronchial papillomatosis spreads into the lung parenchyma from larynx, trachea and mainstem bronchi, and appears on HRCT as characterized by bilateral solid nodules and multiple cysts (less numerous than in LAM or LCH) with thin or thick walls. These cysts are typically localized in the posterior regions (4, 42, 44).

Cystic fibrohistiocytic tumor

This tumor is extremely rare and represents in most cases a metastatic localization from a benign or low-grade cellular fibrous histiocytomas of the skin, though occasionally may be primary. On HRCT, it usually occurs as multiple bilateral pulmonary cysts that represent a sort of cystic changes of multiple pulmonary nodules or masses. Pneumothorax is a frequent associated feature (45, 46).

Mesenchimal cystic hamartoma of the lung

Mesenchymal cystic pulmonary hamartoma is a rare subtype of pulmonary hamartoma that can occur in adults and children. On CT it usually manifests as pulmonary masses with multilobulated cysts of varying size. The lesions may be multiple and bilateral and cause frequently pneumothorax. The differential diagnosis should include atypical cystic chest masses such as cystic adenomatoid

> **Cystic adenomatoid malformation, lung cystic fibrohistiocytic tumor and pulmonary blastoma should be suspected in presence of atypical cystic chest masses.**

malformation, lung cystic fibrohistiocytic tumor and pulmonary blastoma (47, 48).

Pulmonary blastoma

Pulmonary blastomas are a rare group of primary lung tumors (0.25-0.5% of lung malignancy) that are composed of immature malignant epithelial and/or mesenchymal tissues resembling early embryological lung tissues in histological specimen. On CT, pulmonary blastoma is usually described as well-defined mixed solid and cystic large mass measuring 1.5 cm to 13 cm with variable contrast enhancement and necrotic cen-

tre, which may completely opacify the hemithorax and cause mediastinal shift. Pleural effusion is a less frequent associated feature, though atypical cases of pulmonary blastoma manifesting as recurrent pleural effusions in the absence of a detectable lung mass were reported (49-51). Childhood pulmonary blastomas are considered different entities from adult pulmonary blastomas and may occur in combination with pre-existing benign cysts (either cystic adenomatoid malformations or bronchogenic cysts of the lung). In children the tumor mass may completely opacify the hemithorax and cause mediastinal shift (52, 53).

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Cystic pulmonary metastases

Cystic pulmonary metastases occur most frequently in tumors of epithelial origin (oropharyngeal squamous cell cancer, pancreatic adenocarcinoma, transitional cell carcinoma of the bladder) and less frequently in tumors of mesenchymal origin and lymphoma (54). Mesenchymal neoplasms in which pulmonary cysts have been reported include benign mestastasing leiomyoma (55), leiomyosarcoma (54), synovial cell sarcoma (54), epithelioid cell sarcoma (56) and endometrial stromal sarcoma (ESS) (57). Immunostains are useful in distinguishing metastatic ESS from lymphangioleiomyomatosis: HMB45 antibody and CD34 are commonly positive in lymphangioleiomyomatosis and negative in ESS (57). On chest CT as with other metastatic lesions, cystic metastases tend to have different sizes, various shapes and a basilar predominance (42, 43).

> **Immunostains are useful in distinguishing metastatic ESS from lymphangioleiomyomatosis: HMB45 natibody and CD34 are commonly positive in lymphangioleiomyomatosis and negative in ESS.**

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