



Review Article

Cystic Lung Diseases Causing Spontaneous Pneumothorax

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Received: May 5, 2022 | Revised: June 14, 2022 | Accepted: June 17, 2022 | Published: June 28, 2022

Abstract

Surgical specimens resulting from a spontaneous pneumothorax (SP) are commonly encountered in the general surgical pathology practice. Many of the SP cases are primary pneumothorax with no underlying lung diseases. Specimens with primary pneumothorax show nonspecific pneumothorax-related changes, which are important to recognize to exclude the true underlying lung diseases. A variety of disease entities may lead to diffuse cystic changes in the lungs, causing secondary pneumothorax. Some of the diseases are progressive and can cause irreversible damage to the lungs if not treated timely. Diagnosis of cystic lung diseases causing secondary pneumothorax is important for the treatment of the diseases and the prevention of future episodes of pneumothorax. Lymphangioliomyomatosis and Langerhans cell histiocytosis are two common conditions causing diffuse cystic changes in the lungs. They are discussed in greater detail in this review, given their overlapping features in patient characteristics, radiological findings, and pathologic findings.

Citation of this article: Zhang C. Cystic Lung Diseases Causing Spontaneous Pneumothorax. *J Clin Transl Pathol* 2022;2(2):48–52. doi: 10.14218/JCTP.2022.00011.

Introduction

Spontaneous pneumothorax (SP) is defined as the presence of air in the pleural cavity without obvious clinical history of trauma or iatrogenic causes. SP is not uncommon, and the incidence rate is about 20 cases per year per 100,000 population.^{1,2} Most cases of SPs can resolve following medical management, including observation, aspiration of air with tiny needles, and chest tube placements.³ Some patients with SP that failed medical management may undergo surgical interventions of pleurodesis with blebectomy.^{3,4} When underlying lung parenchymal diseases are suspected, a wedge lung biopsy may be performed at the time of pleurodesis. While many patients with SP cases have no underlying lung parenchymal diseases, i.e., primary pneumothorax, pleural abnormalities, and reactive

changes are almost always present in biopsies. A variety of disease entities may lead to diffuse cystic changes in the lungs, causing secondary pneumothorax. It is important to recognize pneumothorax-related nonspecific changes, as well as underlying cystic lung diseases that cause secondary pneumothorax.

Primary pneumothorax

About 61–85% of the SP cases belong to the category of primary pneumothorax (PP), which is defined as SP with no underlying lung diseases. PP usually occurs in young men with tall and thin body habits and is more common in cigarette smokers. These patients develop air accumulation in the pleura (bleb) and distal/peripheral lungs (bullae). The etiology is unknown, although some genetic and environmental risk factors have been implicated in several studies. The blebs and bullae may rupture and lead to pneumothorax, commonly due to strenuous exercise or weightlifting activities. While the majority of the patients with PP are successfully managed medically, surgical specimens from these patients are still encountered occasionally.⁵ PP is a diagnosis of exclusion. Specimens from these patients will show a spectrum of pneumothorax-related changes, which are important to recognize to exclude the true underlying lung diseases. The pneumothorax-related changes include pleural fibrosis with or without blebs, thick-walled blood vessels, and eosinophilic-rich chronic inflammation.^{6–8} The underlying lung parenchyma may show distal acinar emphysema and reactive pneumocyte hyperplasia.⁹

Secondary pneumothorax

Around 15–39% of the patients with SP have underlying lung diseases, which are demonstrated on radiologic imaging as diffuse cystic changes of the lung parenchyma.¹⁰ Many neoplastic and non-neoplastic conditions in the lungs may result in cystic changes, including emphysema, honeycomb changes due to usual interstitial pneumonia or chronic hypersensitivity pneumonia, long-standing pulmonary sarcoidosis, diffuse bronchiectasis, genetic disorders such as Birt-Hogg-Dubé syndrome, infectious diseases such as *Pneumocystis* pneumonia, and slow-growing malignancies such as low-grade sarcomas and MALT lymphoma. Aside from sarcomas and lymphomas, most of these conditions causing diffuse cystic changes in the lungs are diagnosed clinically and radiologically without the necessity of biopsies. Lymphangioliomyomatosis (LAM) and Langerhans cell histiocytosis (LCH) are two conditions causing diffuse cystic changes in the lungs, which commonly present as spontaneous pneumothorax and require surgical interven-

Keywords: Spontaneous Pneumothorax; Lymphangioliomyomatosis; Langerhans cell histiocytosis.

Abbreviations: SP, spontaneous pneumothorax; LAM, lymphangioliomyomatosis; LCH, Langerhans cell histiocytosis.

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Table 1. Comparison between LAM and LCH

	LAM	LCH
M:F	M << F	M = F
IHC markers	HMB45, SMA, PR, cathepsin K	S-100, CD1a, langerin
Treatment	mTOR inhibitors; lung transplantation	Smoking cessation; steroids
Prognosis	Progressive	Good

IHC, immunohistochemistry; LAM, lymphangiomyomatosis; LCH, Langerhans cell histiocytosis; mTOR, mammalian target of rapamycin.

tions/biopsies. LAM and LCH can be difficult to differentiate clinically, radiologically, and even histologically, especially at the late, fibrotic stages of the diseases. The differentiation of the two diseases is important given their vastly different management and prognosis (Table 1).

LAM

LAM is defined as a locally destructive mesenchymal neoplasm per WHO classification. It is a rare disorder characterized by the proliferation of smooth muscle-like cells (LAM cells) throughout the interstitium of the lung, seeming to spread via the lymphatic tracts.¹¹ Proliferating LAM cells form cellular clusters and cysts, destroying healthy lung parenchyma. Some cases of LAM are in the setting of tuber sclerosis complex (TSC-LAM), but the majority of cases are sporadic (S-LAM). In both situations, the neoplastic proliferation of LAM cells is caused by the growth-activating mutations in the *TSC1* and *TSC2* genes.^{12,13} In TSC-LAM, mutations are present in all cells including the germ line (first hit) and neoplastic cells (second hit). Patients with TSC-LAM may have other TSC-associated tumors such as cardiac hamartoma, renal angiomyolipoma, and brain subependymal giant cell astrocytoma.¹⁴ Mutations only occur in neoplastic cells (first and second hits) in S-LAM.

Clinically, LAM, especially the sporadic forms, occurs almost exclusively in women, most commonly women of reproductive ages. Most patients with early-stage diseases are asymptomatic. The most common presenting symptom is progressive shortness of breath on exertions. About one-third of patients with LAM present with spontaneous pneumothorax. The pulmonary function continues to decline with the progression of the disease. Chest CT imaging shows multiple air-filled, thin-walled cysts of variable size throughout the entirety of the lung parenchyma. Reticulation due to fibrosis can be prominent at the end stage of the disease.

Microscopically, LAMs cells are spindle to epithelioid, forming cellular clusters, often associated with thin-walled cysts (Fig. 1). There is no significant cytologic atypia, mitotic activity, or necrosis. LAMS cells are usually positive for smooth muscle actin, desmin, estrogen receptor, and HMB45. The expression of the progesterone receptor is frequently higher than that of the estrogen receptor.¹⁵ Cathepsin K is a papain-like cysteine protease that is commonly used in the diagnosis of perivascular epithelioid cells (PECs) tumors. A recent study shows that cathepsin K is a more sensitive marker than HMB45 in diagnosing pulmonary LAM.¹⁶ LAM cells resemble PECs on morphology and immunoprofile; however, the cell and organ origin of LAM is unclear. Benign metastasizing leiomyoma (BML), a rare disorder in women with a history of uterine leiomyoma, resembles LAM because they both show smooth muscle-like morphology, and express SMA and ER/PR, and can undergo cystic change. However, BMLs generally do not express HMB45 and cathepsin K, and they do not harbor mutations in the *TSC1* and *TSC2* genes.

The proteins tuberin and hamartin encoded by TSC genes

are inactivators of mTOR, therefore inactivating mutations in TSC genes leads to increased mTOR activity. Some patients with LAMs benefit from treatments with mTOR inhibitors such as sirolimus, which suppresses disease progression, stabilizes lung function, and improves the quality of life.^{17,18} End-stage diseases are treated with lung transplantation, although Recurrence of LAM in the grafts has been reported.^{19–21}

LCH

LCH is defined as a proliferative, usually clonal, disorder of Langerhans cells, with associated interstitial changes in the lung tissue per WHO classification. It is characterized by peribronchiolar accumulation of Langerhans cells, which are specialized epithelium-associated dendritic cells regulating mucosal immunity of the airways. Cigarette smoking induces the production and activation of cytokines such as GM-CSF and TGF- β , which activate the proliferation of Langerhans cells.^{22,23} Persistent activation of Langerhans cells further recruit other immune cells, forming peribronchiolar cellular nodules. These cellular nodules undergo cystic changes and fibrosis over time, destroying the lung parenchyma.

LCH occurs in young adult smokers. About 2/3 of patients with LCH have respiratory symptoms such as shortness of breath and cough. About 16% of patients with LCH present with spontaneous pneumothorax.²⁴ The disease is limited to the lungs in most cases of LCH, but a small proportion of patients present with symptoms secondary to diseases outside of the thorax. Characteristic radiologic imaging findings include nodular infiltrates and cystic changes that are predominantly in the upper and middle lobes of the lung.²⁵

Microscopically, the diagnosis of LCH relies on identifying the peribronchiolar cellular lesions, which consist of LCs, histiocytes, lymphocytes, and eosinophils (Fig. 2). LCH is also known as eosinophilic granuloma because of the frequent presence of abundant eosinophils. However, the absence of eosinophils does not exclude this diagnosis. LCs are histiocyte-like cells with abundant pale, eosinophilic cytoplasm, characteristic indented/folded nuclei, frequent nuclear grooves, and intranuclear inclusions. The other smoking-related changes such as emphysematous change and accumulation of pigmented alveolar macrophages within the lumens of terminal bronchioles and adjacent alveolar spaces (respiratory bronchiolitis) are often present. In long-standing disease of LCH, the biopsy may show cysts and stellate scars without obvious cellular lesions (so-called burnt-out LCH). In such a situation, immunohistochemical stains may be helpful to highlight the LCs in small aggregate and single-cell forms. LCs stain positively for S100, CD1a, and Langerin.²⁶ Electron microscopy study demonstrates cytoplasmic tennis racket-shaped Birbeck granules in LCs.²⁷ Mutations of *BRAF* or *MAP2K1* genes in lesional LCs are seen in up to 50% of cases.^{28,29} The most identified mutation is *BRAF* V600E, which is also prevalent in many other

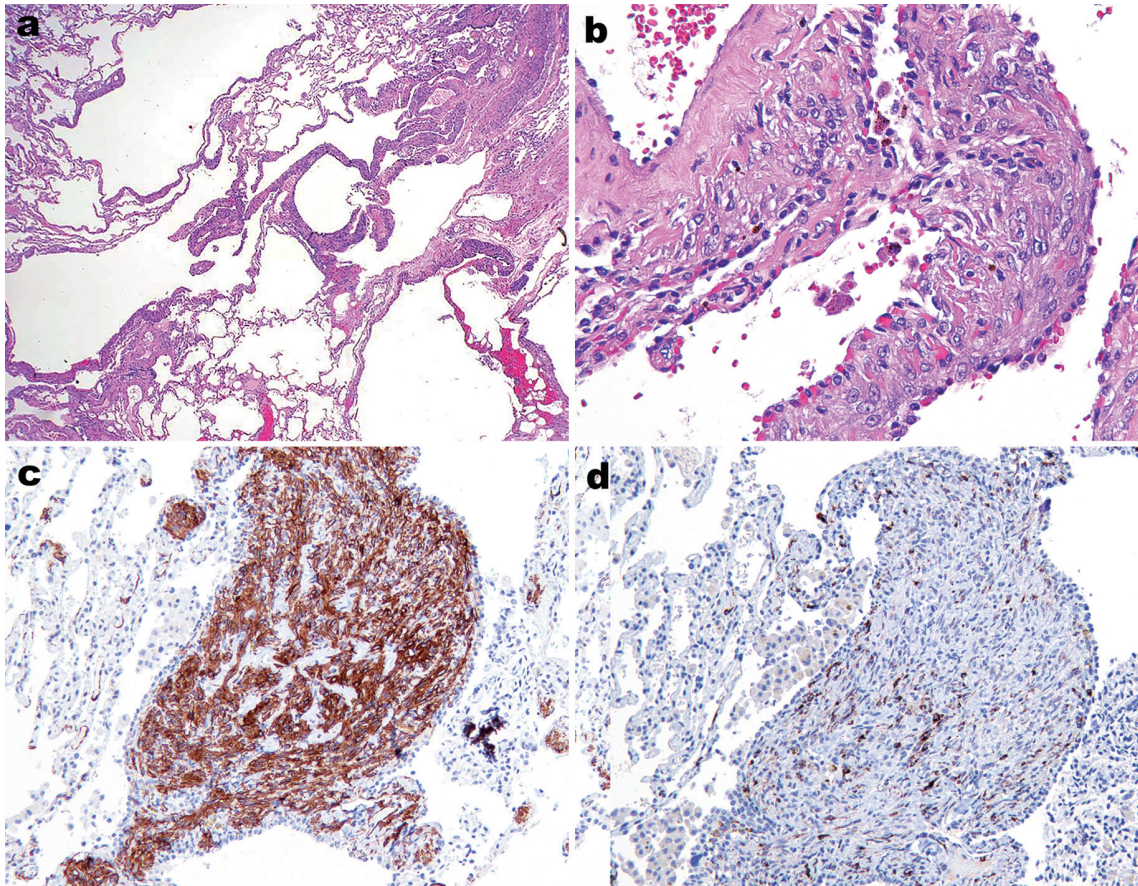


Fig. 1. Lymphangioliomyomatosis (LAM). (a) Low magnification view showing multiple cysts with thin and focally thickened cyst walls (40×); (b) High magnification view of the thickened cyst wall containing spindled epithelioid smooth muscle-like LAM cells. There is no significant cytologic atypia or mitotic activity (200×); (c) Immunohistochemical stain for smooth muscle actin (SMA) is diffusely positive in LAM cells (100×); (d) LAM cells are focally positive for HMB45 immunohistochemical stain (100×).

tumors including melanoma. LCH with cystic changes needs to be differentiated from other diseases with cystic change, such as LAM and metastatic sarcomas.

The key management strategy of pulmonary LCH is smoking cessation and avoidance of second-hand smoke exposure, which stabilize disease progression, sometimes induce regression and even complete resolution of the disease.³⁰ Short-term corticosteroids in a combination of chemotherapy agents are effective in the improvement of lung function in some patients with progressive disease despite smoking cessation.³¹ Patients with identified causative mutations may be treated with targeted therapies such as BRAF inhibitors. The prognosis of LCH is overall good but variable. The majority of the patients with LCH experience a very little decline in lung function after smoking cessation, but still, some patients develop progressive lung disease with end-stage fibrosis requiring lung transplantation.³²

Conclusions

When interpretate surgical specimens resulting from SP, it is important to recognize pneumothorax-related nonspecific changes, as well as underlying cystic lung diseases that cause secondary pneumothorax. LAM and LCH both occur in young adults presenting with SP, and they can be difficult to differentiate clinically, radiologically, and even histologi-

cally, especially at the late, fibrotic stages of the diseases. The key to the differentiation on biopsy is to identify the cellular lesions, which are diagnostic for the diseases with the help of a few immunohistochemical markers (Table 1). The differentiation of the two diseases is important given the vastly different management and prognosis.

Acknowledgments

None.

Funding

None.

Conflict of interest

None.

Author contributions

Dr. Zhang is the sole author of this article.

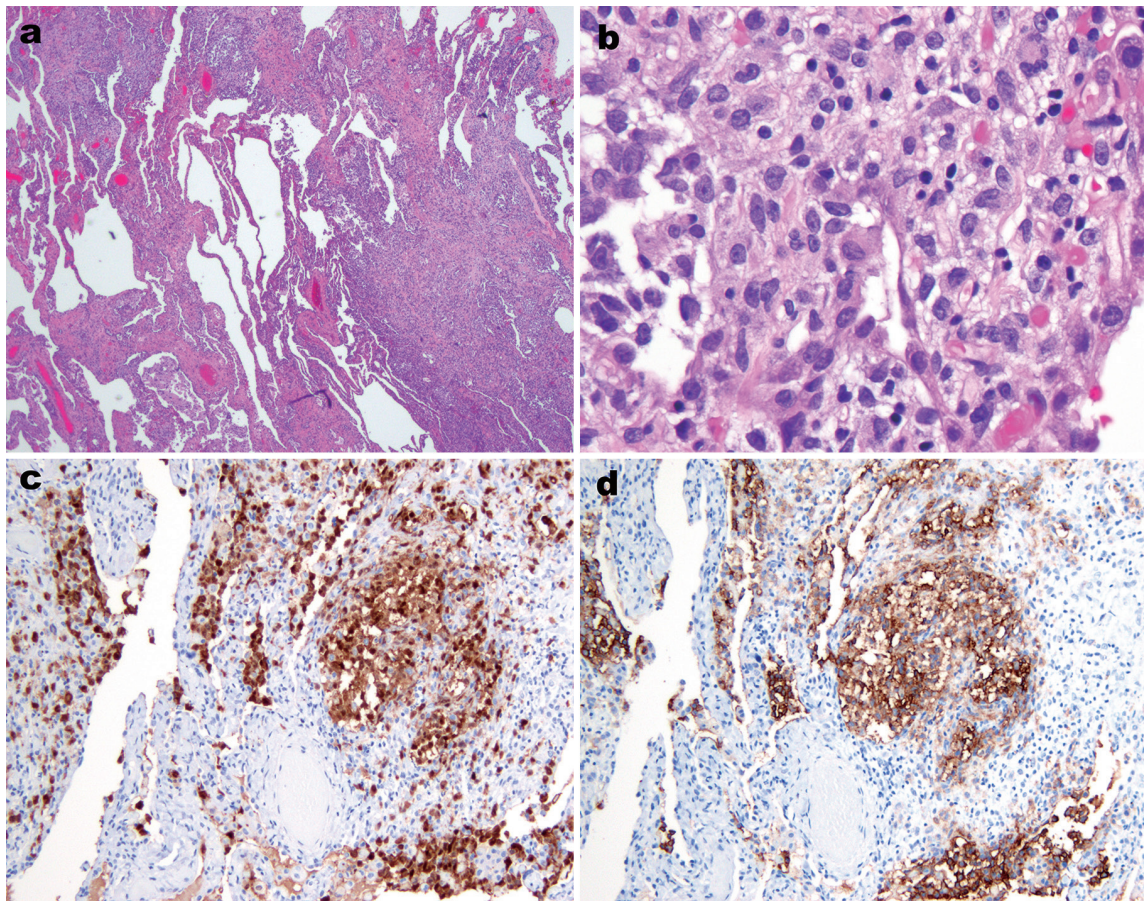


Fig. 2. Langerhans cell histiocytosis (LCH). (a) Low magnification view showing multiple enlarged air spaces separated by nodular, cellular areas (40×); (b) High magnification view of the cellular areas containing histiocyte-like Langerhans cells with abundant pale, eosinophilic cytoplasm, indented/folded nuclei, nuclear grooves, and intranuclear inclusions (400×); (c) The Langerhans cells are diffusely positive for S100 immunohistochemical stain (nuclear and cytoplasmic staining) (100×); (d) Immunohistochemical stain for CD1a highlights the majority of the Langerhans cells (cytoplasmic staining) (100×).

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