Pathologic Review of Cystic and Cavitary Lung Diseases

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Joungho Han, M.D. Department of Pathology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 135-710, Korea Tel: +82-2-3410-2765 Fax: +82-2-3410-6393 E-mail: hanjho@skku.edu Pulmonary cystic and cavitary lesions caused by diverse etiologies are commonly encountered in chest imaging. The terms "cyst" and "cavity" are used to describe air-filled regions in the center of a nodule or consolidation of the lung. To date, only radiologic aspects of these lesions have been addressed. The morphologies of pulmonary cystic and cavitary lesions exhibit a broad spectrum, ranging from benign to malignant pulmonary diseases of acquired or congenital origin, including variable infectious diseases. In this review, we summarized the differential diagnosis of pathological entities to provide pathologists and radiologists with an overview of the diseases most commonly associated with pulmonary cystic and cavitary lesions in adults and children. The results showed slightly different patterns in the distribution of the diseases in the two groups. The most common causes of cavitary lesions include malignancy and infection in adults, and congenital malformation in children. Therefore, identification of pathologic entities correlating with the radiologic findings, clinical course, and location of the lesion is important in the evaluation of cystic and cavitary lung lesions in order to avoid unnecessary surgical procedures or delayed treatment.

Key Words: Lung; Cysts; Cavity; Congenital; Malignant neoplasms

Cystic and cavitary pulmonary lesions are commonly encountered during chest radiography, and their differential diagnoses include diverse benign and malignant diseases caused by many different processes of acquired or congenital origin.^{1,2} Morgagni firstly described the term "pulmonary cyst" in 1769, and Grawitz made the first attempt to classify this group of pathologies in 1880.3 Traditionally, the term "cyst" is used to describe an aircontaining space surrounded by a relatively thin wall (less than 4 mm), and the term "cavity" is used to describe an air-containing space within a pulmonary consolidation with a relatively thick wall (more than 4 mm) or within a surrounding infiltrate or mass identified upon radiological examination.¹ Pulmonary cystic and cavitary lesions may coexist. Sometimes, the appearance of cystic or cavitary lesions is influenced by the clinical course, symptom duration, and comparisons with previous imaging studies of cystic and cavitary pulmonary lesions caused by infections or progressive inflammatory disorders.^{1,2,4,5} Pulmonary infarcts due to emboli or trauma adopt acute or sub-acute courses, whereas chronic processes are more likely to be due to neoplastic diseases, long-standing inflammatory or fibrotic disorders, or congenital lesions.⁶ Active infectious processes and malignancies require a prompt diagnosis to minimize adverse outcomes and apply appropriate management. Other causes of cystic and cavitary pulmonary lesions with potentially devastating outcomes include pulmonary embolism and vasculitides, such as Wegener's granulomatosis.⁷ Furthermore, the presence of cystic and cavitary pulmonary lesions predisposes a patient to the occurrence of a spontaneous pneumothorax.^{1,8,9} Awareness of these broad categories may allow for a differential diagnosis to be made, although the diversity and biological behavior of cystic and cavitary pulmonary lesions causes considerable confusion to radiologists and clinicians. However, a few studies have focused on the radiologic aspects of cystic and cavitary pulmonary lesions,¹ and these studies reported that the lesions can be radiologically described as focal or diffuse.^{1,2} Here, we review the current understanding regarding pathologic entities that appear as cystic and cavitary pulmonary lesions in children and adults.

CYSTIC PULMONARY LESIONS

In children, the most common cause of cystic pulmonary le-

sions is congenital, such as bronchopulmonary foregut malformation.¹⁰⁻¹² This condition includes bronchogenic cysts, pulmonary sequestration, congenital pulmonary airway malformation (CPAM), congenital lobar emphysema or congenital lobar over-inflation, bronchial atresia, and congenital pulmonary cysts. Cystic and cavitary lesions produced by bronchogenic cysts are lined with pseudostratified respiratory epithelium containing mucous glands, cartilage, and smooth muscle, and are filled with clear or proteinaceous material (Fig. 1A, B).¹³ Pulmonary sequestration of the intralobar (80%) and extralobar (20%) types exhibits dilated bronchioles containing a mucous plug, which is the same pattern as bronchiolitis obliterans organizing pneumonia (Fig. 1C, D). In addition, fibrosis is evident in peribronchiolar parenchyma and in systemic arteries with adjacent bronchi. CPAM is composed of a solid and cystic mass of pulmonary tissue, and is subclassified into types 0 to 4. The lesions are lined by flattened type 1 and 2 pneumocytes or pseudostratified columnar epithelium, with or without underlying skeletal muscle or cartilage (Fig. 1E, F).^{10,14} In particular, CPAM types 0 and 4 appear as large cystic pulmonary lesions.¹¹ Emphysema is characterized by permanently enlarged airspaces distal to terminal bronchioles with destruction of alveolar walls, which radiologically appears as a focal, low attenuated area usually without visible walls. In the case of panacinar emphysema (i.e., panlobular emphysema, associated with alpha-1-antitrypsin deficiency), decreased attenuation causes a more diffuse lesion. Histology

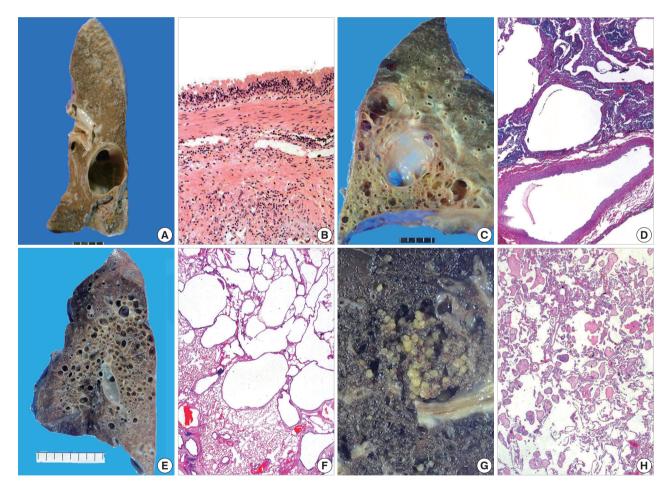


Fig. 1. Gross images and light microscopic findings of cystic pulmonary lesions. (A, B) Bronchogenic cyst. (A) Cyst located in the right lower lung zone filled with luminal inflammatory exudates. (B) The cyst is lined by respiratory epithelium and fibrotic thick wall with surrounding smooth muscle in the cyst wall. (C, D) Intralobar sequestration. (C) Portion of sequestered from bronchial tree and vascular supply shows obstructive pneumonia and cyst formation. (D) Chronic inflammation with lymphoid hyperplasia and foamy macrophages is seen. Note a thick elastic artery from a systemic vessel. (E, F) Type 2 congenital pulmonary airway malformation. (E) Multiple small cysts are diffusely distributed throughout the lung. (F) Dilated bronchioles are lined with flattened cuboidal epithelium, which blend with adjacent normal parenchyma. (G, H) Placental transmogrification. (G) Cut surface shows thin cysts filled with grayish yellow villous structures mimicking placental chorionic villi. (H) Villous structures have an edematous core lined with single-layered epithelial cells.

Table 1. Cystic pulmonary lesions relating to age

Mainly benign cystic lesions	Malignant cystic lesions
Neonates and children	
Sequestration/bronchopulmonary foregut malformations	Cystic mesenchymal neoplasm, e.g., pleuropulmonary blastoma
Bronchogenic cyst	
Pneumatoceles	
Interstitial emphysema	
Other cystic lesions	
Cystic bronchiectasis	
Post-traumatic or postinfectious cysts	
Adults	
Cysts in chondroid hamartoma	Mucinous adeno carcinoma
Nodular lymphoid hyperplasia	Cystic metastasis of sarcoma
Placental transmogrification	
Metastasizing leiomyoma	
Multiple cystic fibrohistiocytic tumor or metastasizing dermatofibroma	

Modified from Ryu JH, Swensen SJ.¹ Cystic and cavitary lung diseases: focal and diffuse. Mayo Clin Proc 2003; 78: 744-52.

showing bronchial atresia and deficiency of cartilage in the involved lobe suggests developmental emphysema rather than an acquired one.¹⁴ Lymphoid interstitial pneumonia (LIP) is a rare disease with a pathology of diffuse pulmonary lymphohistiocytic proliferation and characterized by predominant interstitial involvement sparing blood vessels and airways as well as relative preservation of the pulmonary architecture.¹⁵ LIP is the most common form of classically described interstitial pneumonia in children and is most often associated with underlying autoimmune disease and immunodeficiency status.¹⁶ Thin-walled perivascular cysts may be found in the advanced stage of LIP.¹⁷ Peripheral cyst of pulmonary maldevelopment in Down syndrome consists of rare intrathoracic cystic lesions in neonates and children.¹⁰ Neoplasms, such as pleuropulmonary blastoma or posttraumatic or post-infectious cysts,¹ are also rare causes of cystic lesions in children, and aneurysmal dilation of pulmonary small arteries is one of the congenital causes of cavitary pulmonary lesions in neonates and children.^{1,18}

The causes of cystic and cavitary pulmonary lesions differ in adults in whom a simple cystic pathology is most common.³ In some cases, CPAM may be a rare congenital malformation diagnosed during adulthood in patients that usually present with recurrent respiratory infections and thin-walled multi-septated cystic lesions.¹⁴ However, these congenital malformations are not prevalent in adults. Other causes of focal or multifocal cystic lung lesions are: bullae (or blebs), pneumatocele, penetrating or closed chest trauma, LIP, lung lesions associated with Down syndrome, Ehlers-Danlos syndrome, follicular bronchiolitis, or metastatic diseases including metastasizing leiomyoma, in rare cases.^{1,2,13,14} Placental transmogrification is a rarely encountered cystic lesion in adults, and is a rare histologic subtype of bul-

lous emphysema that has no connection with the cystic lesion and bronchial tree (Fig. 1G, H). Diverse histological patterns, such as myxoid villous structures mimicking placental chorionic villi with large, thin-walled emphysematous bullae, may be interpreted as a cystic lesion upon radiological examination.¹⁹ Examples of these cystic lesions are listed in Table 1.

CAVITARY PULMONARY LESIONS

Cavity-forming pulmonary lesions are uncommon in the absence of a concomitant underlying disease because cavities are pathologically formed by necrotic tissue expelled by an underlying lesion.² Different mechanisms have been proposed to explain necrotizing pneumonia, lung abscess formation, and pulmonary septic embolic processes.²⁰ In septic emboli transferred from other infectious foci, septic occlusion of small, peripheral, pulmonary arterial branches results in cavitary pulmonary lesions.²¹ Aneurysmal dilation of pulmonary small muscular arteries in arteriovenous malformation (Fig. 2A, B) may elicit different pathogenetic causes of cavitary lesions in neonates.^{1,18}

In adults, the two main causes of cavitary pulmonary lesions include malignancy and infection. The thickness of the thickest portion of cavity wall, the characteristics of its inner lining (irregular or smooth), and its nature and location are important for determining the benignity of cavitary pulmonary lesions by radiology.^{1-3,22} For example, cavity-forming carcinomas can have a smooth or irregular inner contour, and cavities associated with an abscess are shaggy. Cystic or cavitary lesions with a maximal wall thickness of 1 mm based on radiologic findings are generally regarded as benign, those with a maximal wall thickness of > 1 to <4 mm are usually regarded as benign, and lesions with

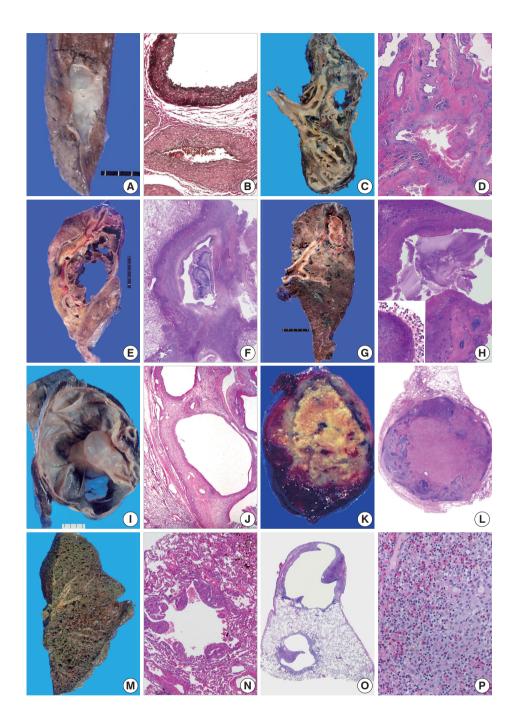


Fig. 2. Gross images and light microscopic findings of mainly cavitary pulmonary lesions. (A, B) Arteriovenous malformation. (A) A parenchymal thin-walled cyst with smooth inner surface is observed in the lower lobe. (B) Abnormal aneurysmal dilatation of pulmonary small muscular artery. Note the thick venous walls. (C, D) Pulmonary tuberculosis. (C) Lung parenchyma is destroyed by multi-septated cavities. (D) Multifocal necrotizing granulomas with chronic inflammation. (E, F) Invasive aspergillosis. (E) A large necrotic cavity is located in the right middle lobe. (F) Fungus ball is identified within the cavity. (G, H) Pulmonary actinomycosis. (G) A thick-walled cavity is observed in the upper lobe. (H) The cavity contains large colonies of microorganisms. The inset indicates filamentous organisms with neutrophils. (I, J) Metastasizing leiomyoma. (I) Multilocular cystic mass with thin fibrotic wall, containing white tan serous fluid. (J) Bundles of cigar-shaped spindle cells are identified in the multilocular cyst wall. (K, L) Wegener's granulomatosis. (K) A solid nodule with multiple punctate or geographic necrosis. (L) Multifocal cavitation is seen within the consolidated mass. (M, N) Lymphangioleiomyomatosis. (M) Multicystic and cavitary lesions are diffusely distributed throughout the parenchyma. (N) Proliferation of myoid cells invades the pulmonary parenchyma as well as the walls of the airways, blood vessels, and lymph vessels. (O, P) Langerhans cell histiocytosis. (O) Multiple nodular infiltrates form prominent cystic and cavitary changes. (P) Mixed infiltrates of Langerhans cells as well as many eosinophils are shown.

maximal wall thicknesses of 5 to 15 mm are equally divided between benignity and malignancy. For lesions with a maximal wall thickness >15 mm, 95% of them are likely to be malignant, although it should be noted that there is an overlap in wall thickness between malignant and benign lesions, such as in aspergilloma.^{23,24} In addition to these factors, epidemiologic differences also exist. Tuberculosis is the predominant infectious cause of cystic and cavitary pulmonary lesions in Korea, which predominantly occurs in patients less than 50 years of age. Large cavities in the upper lobe are significantly associated with mycobacterial infection,²⁵ but the location is of limited help in the differential diagnosis of most cavitary lesions (Fig. 2C, D). Invasive aspergillosis is a common infection cause of cavitary pulmonary lesions (Fig. 2E, F),^{1,2,24} and gram-positive and gramnegative bacterial pneumonia, such as Streptococcus pneumoniae or Haemophilus influenza, can cause the cavitations, although community-acquired pneumonia is not typically accompanied with cavity formation in the lung.^{1,2,25,26} A lung abscess is a common bacterial cause of cavitary pulmonary lesions. Pulmonary actinomycosis (Fig. 2G, H) is a rare disease and is commonly misdiagnosed as other chronic suppurative cavitary lung diseases.⁴ Together with infectious etiologies, the incidence of pulmonary malignancy has increased as another important cause of cavitary lesions that pathologists and radiologists commonly encounter; 161,920 incident cases were reported in Korea in 2009,27 and 221,130 incident cases in the United States in 2011.28 Cavitation has been noted in 7-20% of primary lung cancers that have thick cavity walls.^{2,29} Cavitation may be ascribed to treatmentrelated necrosis, internal cyst formation, or internal desquamation of tumor cells and subsequent liquefaction. The process of cavitation in lung tumors has been associated with a poor prognosis,30 and more than 80% of cavity-forming pulmonary tumors associated with epidermal growth factor receptor overexpression exhibit rapid growth.³¹ Non-small cell carcinoma, especially squamous cell carcinoma, is the most common histologic type of cavity forming tumor, whereas small cell carcinoma has never been reported to cavitate.³² Rarely, cavitation or multiloculated cystic changes have been reported in lung adenocarcinoma.33 The most common origin of cavitating pulmonary metastases is squamous cell carcinoma of the head and neck,34 while the second most common form is metastatic adenocarcinoma. Hematologic or mesenchymal malignancies occur less frequently as cystic and cavitary pulmonary lesions, including metastasizing leiomyoma (Fig. 2I, J), leiomyosarcoma, synovial sarcoma, epithelioid sarcoma, endometrial stromal sarcoma, malignant lymphoma, angiosarcoma, and Kaposi's sarcoma.^{1,35-38} In particular, immunocompromised patients, such as human immunodeficiency virus (HIV)-infected or post-transplant recipients, have more diverse cavity-forming etiologies than do immunocompetent individuals. Kaposi's sarcoma, which has a histology of anastomosing vascular channels, appears as peribronchovascular interstitial thickening. Pulmonary non-Hodgkin's lymphoma is rare, and may manifest as cavitating nodules in immunocompromised patients.³⁹ In one study of HIV-infected patients with primary pulmonary lymphoma, 5 of 12 (41.7%) patients presented with a pulmonary cavitary lesion.⁴⁰ Primary pulmonary lymphoma is a rare entity usually formed of B-cells, and is usually low-grade lymphoma composed of mucosal-bronchial-associated lymphoid tissue.⁴¹ Highgrade primary pulmonary lymphomas often occur in immunodeficient patients, which mostly appear as multiple nodular masses with cavitation.⁴² Lymphomatoid granulomatosis associated with Epstein-Barr virus infection frequently presents with pulmonary cavities, and rarely, bronchioloalveolar carcinoma manifests as cystic or cavitary disease.^{2,43} Among infections, Pneumocystis carinii infection is a common problem in HIV-infected individuals and infrequently manifests as a cavitary infiltrate.44 Mycobacterium, histoplasmosis, and cryptococcal pneumonitis are uncommon causes of cavitary infections, and viral infections caused by cytomegalovirus or influenza viruses can appear as cavitary lung lesions at a delayed stage in these immunocompromised groups.45

OTHER UNCOMMON CYSTIC OR CAVITARY PULMONARY LESIONS

Various uncommon non-infectious etiology of cavitary lesions is pulmonary embolism, especially in adults.² Traumatic pulmonary pseudocysts, formed after blunt thoracic trauma that causes tearing or laceration of the lung parenchyma, are also a rare cause of cavitary pulmonary lesions,8 but obtaining the history of the patient usually facilitates an early diagnosis. Systemic diseases, such as connective tissue disease, Behcet's disease, and systemic autoimmune vasculitis such as Wegener's granulomatosis, which affects arteries and veins of all sizes, can involve lung parenchyma, the pulmonary artery, or large vessels (Fig. 2K, L).^{10,46} Pulmonary Behcet's disease can present as hemorrhage, infarction, or multifocal cavitary lesions. Cystic and cavitary lesions are rare in sarcoidosis, and therefore can be confusing in the manifestations of sarcoidosis, especially in active and severe sarcoidosis.⁴⁷ Both lymphangioleiomyomatosis (LAM) and Langerhans cell histiocytosis (LCH) involve all lobes of both

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Table 2. Cavitary pulmonary lesions mainly related to age

Neonates and children	
Aneurymal dilation of pulmonary small muscular arteries	
Sequestration/bronchopulmonary foregut malformations	
Diffuse cystic and cavitary lung diseases such as pulmonary Langerhans cell histiocytosi	S
Adults	
Infectious causes of pulmonary cavities	Neoplasm including malignancy
Cavitating granulomas such as tuberculosis	Squamous cell carcinoma
Invasive aspergillosis; fungus ball in cavitated infarct	Adenocarcinoma
Blastomycosis	Lymphoma
Non-tuberculous Mycobacterium	Metastasizing leiomyoma
Cryptococcosis	Kaposi's sarcoma
Actinomycosis	Metastasis
Mucormycosis	Sarcomas such as synovial sarcoma, leiomyosarcoma,
Obstructive pneumonia and abscess cavity	angiosarcoma, etc.
	Squamous cell carcinoma of head and neck origin
Cavitation within the consolidated lung diseases	Diffuse cystic and cavitary lung disease
Pulmonary embolism; bland infarct	Pulmonary lymphangioleiomyomatosis
Pulmonary vasculitides, e.g., Behcet's disease	Pulmonary Langerhans cell histiocytosis
Autoimmune diseases, e.g., Wegener's granulomatosis and rheumatoid arthritis	Honeycomb lung
Septic emboli, multiple nodule with various stages of cavitation, subpleural wedge	Idiopathic pulmonary fibrosis
shaped infiltrates	Connective tissue disease-related pulmonary fibrosis
Pulmonary massive fibrosis in pneumoconiosis	Asbestosis
Aneurymal dilation of pulmonary small muscular arteries	Chronic hypersensitivity pneumonia
	Advanced sarcoidosis
	Bronchiectasis, diffuse

Modified from Ryu JH, Swensen SJ.¹ Cystic and cavitary lung diseases: focal and diffuse. Mayo Clin Proc 2003; 78: 744-52.

lungs, and therefore appear as diffuse cystic and cavitary lesions, though there is radiologic preponderance of the lower lung. Pulmonary LCH and LAM predominantly affect adults.48 Pathologically, LAM is characterized by peribronchial, perivascular, and perilymphatic proliferation of myoid cells resulting in vascular and airway obstructions as well as cyst formation (Fig. 2M, N). Pulmonary LCH may appear as cystic with nodules, and Erdheim-Chester disease (ECD) shares pathologic features, such as xanthogranulomatous inflammation with foamy macrophages (Fig. 2O, P), and radiologically can present as symmetric, diffuse, interstitial lung disease with interlobular septal thickening.⁴⁹ Pulmonary involvement of LCH is much common in adults, but occurs in nearly half of young children with multisystem LCH. LCH can be differentiated from ECD based on an immunohistochemical profile of CD68+, Langerin-, CD1a-, and S-100 protein+/-. Bronchocentric granulomatosis may be present in the nodule, which attests to the likelihood of an infectious etiology.⁵⁰ Examples of these lesions are listed in Table 2.

CONCLUSION

In summary, we have reviewed diverse etiologies of pathologic entities showing cystic and cavitary pulmonary lesions in adults and children. The distribution of the diseases showed a slightly

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different pattern in the two groups. Identification of pathologic findings that correlate with radiologic findings, clinical progression, and location is important in the evaluation of cystic and cavitary lung lesions in order to avoid unnecessary procedure or delayed treatment.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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