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REVIEW

Lung cancer associated with cystic airspaces: A contemporary review

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ABSTRACT

Lung cancer associated with cystic airspaces: A contemporary review

Lung cancers associated with cystic airspaces (LCCAs) are a rare and relatively novel concept analyzed in various case reports and retrospective studies. In this review, it was our aim to investigate the morphologic, imaging, and clinicopathologic characteristics of this entity, as well as its natural course in light of the current literature. Literature search including the years 2000-2022 was conducted in PubMed. We analyzed the definition, morphological classification, pathogenesis and histopathology, imaging and clinical features, differential diagnosis and natural course and prognosis of LCCAs. LCCAs are increasingly being identified as missed or delayed diagnoses in lung cancer screening programs. Early recognition and intervention of this entity when cyst wall thickening or solid components appear can potentially improve outcomes. Nevertheless, the prognosis and survival of these patients are still poorly understood due to limited data, and further research is needed to better understand the behavior of these lesions and propose management guidelines.

Key words: *Cystic; non-small cell lung cancer; prognosis*

ÖZ

Kistik hava boşluklarıyla ilişkili akciğer kanseri: Güncel bir derleme

Kistik hava boşluklarıyla ilişkili akciğer kanserleri, çeşitli vaka raporlarında ve retrospektif çalışmalarda analiz edilen nadir ve nispeten yeni bir kavramdır. Bu derlemede, bu durumun morfolojik, görüntüleme ve klinikopatolojik özelliklerinin yanı sıra doğal seyrini güncel literatür ışığında araştırmayı amaçladık. PubMed'de 2000-2022 yıllarını kapsayan literatür taraması yapılmıştır. Kistik hava boşluklarıyla ilişkili akciğer kanserlerinin tanımını, morfolojik sınıflandırmasını, patogenezini ve histopatolojisini, görüntüleme ve klinik özelliklerini, ayırıcı tanısını, doğal seyrini ve prognozunu analiz ettik. Kistik hava boşluklarıyla ilişkili akciğer kanserleri akciğer kanseri tarama programlarında giderek daha fazla gözden kaçan veya gecikmiş tanı konulan durumlar olarak tanımlanmaktadır. Kist duvarı kalınlaşması veya katı bileşenler ortaya çıktığında bu

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varlığın erken tanınması ve müdahalesi potansiyel olarak sonuçları iyileştirebilir. Bununla birlikte, bu hastaların prognozu ve sağkalımı sınırlı veriler nedeniyle hala yeterince anlaşılmamıştır ve bu lezyonların davranışını daha iyi anlamak ve yönetim kılavuzları önermek için daha fazla araştırmaya ihtiyaç vardır.

Anahtar kelimeler: *Kistik; küçük hücreli olmayan akciğer kanseri; prognoz*

INTRODUCTION

Lung cancer typically manifests as solid masses or nodules. However, with the extensive use of computed tomography (CT) in clinical practice and with the advent of screening programs utilizing low-dose CT, lung cancer cases are identified at earlier stages. Additionally, advanced imaging technology has allowed us to identify various morphological subtypes that exhibit distinct imaging features, including pure ground-glass, part-solid, or cystic lesions. Among these various types of imaging subtypes, lung cancer associated with cystic airspaces (LCCAs) is relatively rare.

Since its initial description in the 1940s, LCCAs have been analyzed and documented in various case reports and retrospective studies (1-18). Nevertheless, there is still no widely recognized definition and nomenclature of this disease, nor an established guideline designed to address the management of these lesions. Moreover, LCCAs are increasingly being detected as missed or delayed diagnoses in non-small cell lung cancer (NSCLC) screening programs due to its similarity in appearance to pulmonary bulla or cysts. In the Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON) lung cancer screening trial, LCCAs have been found responsible for approximately 23% of missed or delayed lung cancer cases (19). This highlights the importance of recognizing the imaging features and raising awareness of this subtype of lung cancer for early detection. Thus, in light of the current literature, we aimed to investigate the morphologic, imaging, and clinicopathologic characteristics of NSCLC associated with cystic airspaces, as well as its natural course.

Methods

In order to obtain relevant data, we conducted a literature search in PubMed using search terms "lung cancer", "cystic", "airspaces" and "cystic adenocarcinoma" including the years 2000-2022. Only case reports that provided unique and relevant data were included. In total, 36 full text papers were reviewed accordingly. However, the evidence obtained from the literature search is considered low-level evidence as almost all studies consisted of case series, and the data was heterogeneous among the studies.

Definition and Incidence

A cystic airspace (CA) is described as a well-circumscribed, air-containing lesion in the lung parenchyma that has a clear wall at the border within the normal lung tissue. This is a broad definition, and CA-related abnormalities can include emphysematous bullae, subpleural blebs, fibrotic cysts, bronchiectatic airways, congenital cysts, and distended distal airspaces (12). However, the term LCCA is not clearly defined so far. Briefly, this entity refers to a group of malignancies that present as single or multiple cystic components, with areas of ground glass or consolidation adjacent to the cyst wall or interspersed between the cystic components (13).

In recent studies, the incidence rates of LCCA have been reported to range from 1% to 9.3% (2-5). Kaneda et al. retrospectively reviewed chest CT scans of 545 patients who had undergone surgical resection for primary lung cancer and reported that 19 cases (3.5%) had cancers adjacent to a bulla (2). Farooqi et al. detected that 3.7% (26/595) of the cancer cases presented as LCCA in a screening population. Of these 26 cases, 2% were detected at baseline and 12% at annual screening (3). Fintelmann et al. conducted a review of 34.801 CT scans over a period of five-years and identified 2954 patients with NSCLC. Among these patients, 30 (1%) cases had NSCLC associated with CAs. However, the authors believe that this ratio may be an underestimation due to the exclusion of a significant number of cases (n= 325) that did not meet the observation period criterion of at least six months or lacked serial CT scans (4). In a recent study from a regional thoracic center, the incidence of LCCAs were reported to be even higher. During a three-year study period, 441 cancers were resected in 431 patients. Overall, forty-one cases (9.3%) were identified as primary lung cancers with cystic features (5).

Morphological Classification

Several classification schemes have been proposed to describe morphological appearance of LCCA (4,6-8). In the most recent classification, which was modified by Mascalchi et al., four morphologic types (Figure 1) have been described: Type I, the nodule abutting the external border of the cyst. Type II, the nodule projecting into the cystic space. Type III, cyst wall thickening, and type IV, multicystic lesion that contains areas of soft tissue attenuation (7). While the prognostic and clinical significance of this morphologic classification is unclear, it may be valuable for future research and development of management guidelines for clinical practice. Sheard et al. have emphasized the use of these classification systems to stratify the risk of malignancy. According to their experience, types I and IV are more expected to be miscategorized as benign pathologies, and types II and III have a wider range of differential diagnoses such as infection, inflammation, and cavity formation (12).

Pathogenesis and Histopathology

The pathogenesis of LCCA is not completely understood. The main theory explaining the mechanism for the development of the cystic component is considered the check-valve mechanism, in which the obstruction of the small airways by the tumor or by the fibrous depositions produced by the tumor cause dilatation of the distal airspace. This theory is reinforced by the largest studies in which the cysts increased in size as the nodular component grew in most of the cases (3,4,7). Other mechanisms of cystic space development include cystification of the tumor due to necrosis, alveolar wall destruction by the tumor, ischemic dilatation produced by occlusion of tiny capillaries supplying the bronchiole, tumor growth-particularly lepidic adenocarcinoma-along the border of preexisting cystic lesions, and genetic factors (2,3,6,7,20,21).

Although various histologic subtypes have been associated with cystic lung cancers, most cases are adenocarcinomas accounting for 70.8 to 93.3% of patients in various studies (3,4,6,7,14,16,22,23). Tan et al. have recently presented their experience with verified cystic lung tumors with a sample size of 106 cases. While the majority of the cases (87.1%) were adenocarcinomas, 7.5% were squamous carcinomas (16). The data regarding the different subtypes of adenocarcinoma is limited. Fintelman et al. have reported the lepidic-predominant adenocarcinoma (LPA) subtype in six out of 21 patients in their study (4). Squamous cell carcinoma is the second most common subtype in 4-29% of cases, while other cell types such as adenosquamous carcinoma, large cell carcinoma, lymphoma, carcinoid and poorly differentiated carcinoma have been less frequently reported in case series (3,4,12,16,23-27).

There is limited and scarce data available on mutational analysis for cystic lung cancers. Epidermal growth factor receptor (EGFR) mutation is the most commonly reported mutation. Shen et al. have reported a 52.9% EGFR mutation rate, and Guo et al. have found an EGFR mutation rate of 37.5% (8,25). However, in two other studies by Fintelmann et al. and Snoeckx et al. Kirsten rat sarcoma virus mutation was the predominant alteration which was detected in 53.8% and 18.2% of the patients, respectively (4,14). Histopathological diagnosis and genetic alterations of LCCA among major studies are shown in Table 1.

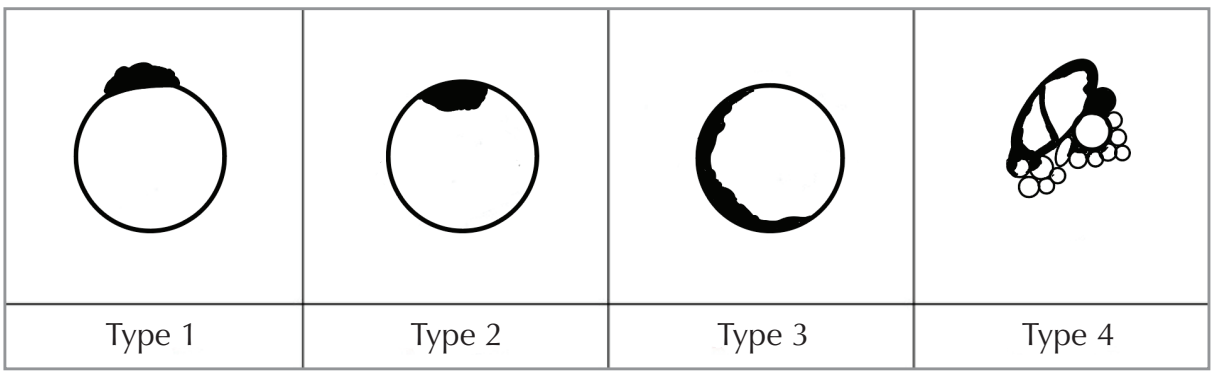

Figure 1. Morphologic classification of LCCA defined by Mascalchi el al. Type I, the nodule abutting the external border of the cyst. Type II, the nodule projecting into the cystic space. Type III, cyst wall thickening, and type IV, multicystic lesion that contains areas of soft tissue attenuation.

Table 1. Comparison of patient characteristics

1st Author (Referance)	n	Population	Age (Mean/Range)	Sex (%) F/M	Smoking status (%) S/NS	Histo	Genetic
Mendoza$^{\sigma}$ (23)	341	Asia 72% NA 13% Europe 12%	62	40/60	66/34	Adeno 88% SCC 9% Others 3%	EGFR 38% KRAS 17% No mut 42%
Byrne (CA cases) (5)	49	NA 100%	70	57/43	83/17	Adeno 80% SCC 18% Others 2%	NA
Guo (25)	15	Asia 100%	58	20/80	33/67	Adeno 73% SCC 13% Others 14%	EGFR 20% KRAS 0% No mut 47%
Zhang (27)	65	Asia 100%	33-78	32/68	38/62	Adeno 92% SCC 6% Others 2%	NA
Deng (22)	45	Asia 100%	33-78	29/71	27/73	Adeno 93% SCC 7%	NA
Byrne* (All cases) (5)	411	NA 100%	70	57/43	71/29	Adeno 71% SCC 14% Others 15%	NA

NA: North America, S/NS: Smoker/non-smoker, SCC: Squamous cell carcinoma.
*Data from the same study including all cancer cases.
$^{\sigma}$Combined data of eight studies.

Imaging Features

LCCA refers to a group of lesions that exhibit significant morphological diversity. As a result, the imaging features linked to this entity are heterogeneous within various studies. Briefly, two main imaging features have been consistently reported: The presence of a cystic component (unilocular, multilocular, thick or thin-walled) and a nodular component (solid, part solid, or ground-glass). The cystic component can be misleading for radiologists and may suggest a benign cause (inflammatory changes or infection), making early diagnosis challenging due to various appearances it can present. Therefore, it is important to pay special attention to certain imaging features such as wall thickening (focal or diffuse) consolidation or ground glass opacities that are adjacent to or within cystic airspaces.

In major studies, the distribution of LCCA throughout the lung parenchyma has been found to be uniform, with no predilection for any lobe. However, they are more commonly observed in the peripheral/subpleural regions rather than central regions (3,4,6,7,23,25). This is an expected situation since the majority of LCCAs are adenocarcinomas and these are prone to be located in the lung periphery.

To date, the relation between radiologic characteristics and pathological invasiveness of the lesion has only been reported in a single study (8). In that study, Shen et al. have categorized adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), and LPA as the well-differentiated group and defined acinar, papillary, micropapillary, and mucinous adenocarcinomas as moderately/poorly (M/P) differentiated group. The study demonstrated that the type III morphological pattern was independently associated with a higher likelihood of M/P-differentiated group [odds ratio (OR), 6.451; 95% confidence interval (CI), 1.145–36.353; p= 0.035] when compared to type I LCCA. Additionally, the presence of part-solid and solid components in the wall was strongly associated with a higher likelihood of M/P-differentiated histological subtypes (OR, 27.178; 95% CI, 5.614-131.566; p< 0.001 and OR, 614.576; 95% CI, 36.428-10368.608; p< 0.001, respectively), as compared to the ground-glass component in wall. Moreover, an irregular inner surface of the cyst was also found to be an independent risk factor for M/P-differentiated histological subtypes (OR, 7.008; 95% CI, 1.873-26.216; p= 0.004) (8).

For proper classification and accurate follow-up of LCCAs, it is recommended to use a CT protocol with thin-section images (preferably 1.0 mm) and multiplanar reconstructions to examine the cystic and non-cystic parts of the tumor. Obtaining ideal pathological tissue is challenging in LCCAs due to the cystic nature of the lesions. However, CT three-dimensional reconstruction can provide a clear display of the microstructures both inside and outside the wall of cystic airspaces and help the evaluation of lesion morphology, identification of suspicious features. The presence of non-uniform cyst walls, septations within cyst, wall nodule or nodules, ground glass opacities around the cyst and irregular margins are suspicious findings for a malignant pathology (16). Since morphological changes during follow-up can be subtle, it is essential to archive the CT images to ensure accurate tracking of disease progression (13). Accessing previous images is therefore critical for achieving an accurate and timely diagnosis.

Although flourodeoxyglucose positron emission tomography (FDG-PET) is effective in the diagnosis and staging of lung cancer, its utility in patients with LCCAs is not well established due to lack of evidence. Thin-walled cystic lesions and small mural nodules may not exhibit flourodeoxyglucose (FDG) uptake, which may limit the diagnostic value of FDG-PET in such cases. Cystic airspaces, particularly type IV subtypes, may lower the whole density of active cells, potentially reducing the sensitivity of FDG-PET scans. Furthermore, the majority of LCCAs are of the adenocarcinoma type, which includes subsolid lesions such as LPA, MIA, and AIS subtypes. These tumors are relatively slow-growing tumors, making them more challenging to assess with FDG-PET due to their low rate of metabolic activity (12,28). In the Fintelmann study, solely mural nodules greater than 8 mm exhibit FDG uptake. In thick-walled cases without mural nodules, only solid and greater than 8 mm lesions showed FDG uptake (4). Similarly, Haider et al. reported that the smallest nodule showing FDG uptake was 7 mm in size (6). In the Mascalchi study, adenocarcinomas with predominant morphology of type I and II did not show FDG uptake. On the other hand, patients who had manifest uptake were all type III and IV predominant subtypes (9).

Based on the limited available data, FDG-PET may be useful for characterizing patients who had solid lesions greater than 7 mm in size. However, it is important to note that even in the absence of FDG-uptake, cystic lesions with increasing soft tissue on CT should be regarded as highly suspicious for malignancy. While the absence of FDG-uptake does not necessarily exclude the possibility of a tumor, a high FDG-uptake on PET scans can also be seen in benign conditions, such as infection or inflammation. Therefore, the results of FDG-PET scans should always be interpreted in conjunction with other diagnostic tests and clinical information to accurately diagnose and manage LCCA.

Clinical Features

The clinical presentation of patients with LCCAs is found to be similar to other types of lung cancer and can vary depending on the stage of the disease. In a recent meta-analysis, Mendoza et al. have summarized the clinicopathologic characteristics of LCCA in 341 patients from eight major studies (23). Most of the patients had stage I disease (61.8%), while stage II (12.4%), stage III (11.5%), and stage IV (14.3%) were less frequent. Approximately 35% of the patients were symptomatic, and the most common presenting symptoms were cough (30.5%), chest pain (10.2%), hemoptysis (9.3%), fever (3.4%), malaise (0.8%), and pneumothorax (0.8%) (23). Several studies have reported a higher incidence of LCCA among smokers and individuals with emphysema (3,4,6,7,23). On the contrary, Deng and Tan have reported a higher proportion of nonsmokers, with a ratio of 72.5% and 53.8%, respectively (16,22). Mascalchi et al. have reported that 17 out of 24 patients with LCCA also had emphysema, and two of these 17 patients had combined pulmonary fibrosis and emphysema (7). Farooqi et al. have found that 11 of 26 patients with pericystic lung cancer also had emphysema (3). The comparison of patient characteristics among the major studies are shown in Table 1.

Differential Diagnosis

Diagnosing LCCAs can be challenging since there are various benign causes that can mimic its radiologic features. Inflammatory conditions such as infections, granulomatous diseases, and benign cysts can all exhibit features such as bulla wall thickening, irregular cysts, and cavities with associated nodular components, making it difficult to differentiate from LCCAs. Additionally, fungal infections may manifest as cystic airspace, nodular wall thickening, or large lesions in the form of mycetomas and mimic type II LCCA lesions (12,13).

Growth rate and multiplicity of lesions, medical history, and clinical findings are the main sources that may help us to discriminate between benign and malignant lesions. The presence of acute infection signs and symptoms associated with radiological indicators of parenchymal inflammation and multifocal presentation of cystic lesions can be regarded as diagnostic of an infectious etiology. Additional parenchymal findings resembling nodules or consolidations are also suggestive of an underlying infectious disease. Conversely, the absence of these findings with no significant previous medical history may point out a high likelihood of malignancy. Reviewing previous imaging studies may reveal the presence of underlying cavitary or cystic diseases, or demonstrate a rapid progression of findings, both of which can suggest an infective or inflammatory process. Lesions that respond to therapy or heal over time are considered to be indicative of a benign condition.

Benign pulmonary cysts may also mimic LCCAs. Araki et al. have shown that 8% of patients over 40 years of age have benign cysts. They are generally solitary and positioned on the periphery of the lower lobe, and they tend to remain steady or slightly expand in size over time. On the contrary, LCCAs occur throughout the lung, almost always peripherally, and may present as multiple cystic lesions (29). Uncommon causes of cystic parenchymal lesions include amyloidosis, vasculitis, bronchogenic cysts, pulmonary infarction, and less common infectious processes like Nocardia infections (12,13).

Based on our experience, cystic lesions exhibiting wall thickening and/or associated nodule require close monitoring and interventional procedures if deemed necessary. It is important to note that a negative PET-CT scan does not necessarily exclude the presence of a malignancy in persistent suspicious nodules. Additionally, LCCAs are typically located in peripheral areas of the lung, making diagnosis through bronchoscopic methods challenging. In many cases, percutaneous needle biopsy of solid or subsolid components may eventually be required. However, due to the thin cystic wall of LCCAs, CT-guided percutaneous biopsy can easily cause pneumothorax and may result in difficulty obtaining ideal pathological tissue. A multidisciplinary approach is crucial for the optimal management of cystic lesions that persist, grow, or demonstrate morphological changes, taking the patient's preferences into consideration.

Natural Course and Prognosis

While it is widely recognized that the imaging characteristics of lung cancer can evolve over time, there is less information regarding the natural course of LCCAs. The natural progression of CA is highly unpredictable, as it can either increase or decrease in size, or remain stable over time. Furthermore, the morphological type of the lesion may also change. Under surveillance, many untreated lesions of adenocarcinoma with CAs may ultimately progress to solid tumors. This natural evaluation of the lesions suggests that the number of lung cancers that begin as cystic lesions may be underestimated as presented in a patient in Figure 2. A 72-year-old male patient with lung cancer in solid morphology admitted to our clinic with neurological symptoms is presented. Intracranial mass was resected, and histopathological diagnosis was undifferentiated carcinoma metastasis. Analysis of previous thoracic CT images revealed that the solid mass lesion located in the right lower lobe was a cystic lesion three years earlier. PET-CT imaging showed high FDG uptakes at the borders of the mass, resembling a cyst wall, as well as bulky mediastinal lymphadenopathies. As the patient passed away shortly after the intracranial operation, biopsy of the primary mass or mediastinal lymphadenopathies could not be performed.

Mendoza et al. performed a meta-analysis to investigate the natural progression of LCCAs. Their findings indicated that in the majority of patients (68.5%), the nodular component developed or enlarged. Cyst wall thickening occurred in nearly half of the patients (48.3%). In 12% of the patients, the lesion completely evolved into a solid mass or nodule, resulting in a loss of the cystic component. The lesion remained stable in 4.5% of the patients. Regarding the cystic component, it increased in 40.4% of the patients, decreased in 31.5% of the patients, and remained stable in 27% of the patients (23). Cysts can be present for up to six years in certain cases from screening trials before the onset of wall thickening or a solid component. Farooqi et al. reported that thickening of the cyst wall or emergence of a nodule was observed at a median of 35 months (3). Similarly, Fintelmann et al. described hat the development of a nodular component in a CA required a mean of 25 months (4). These findings suggest that long-term follow-up is crucial for patients with LCCAs.

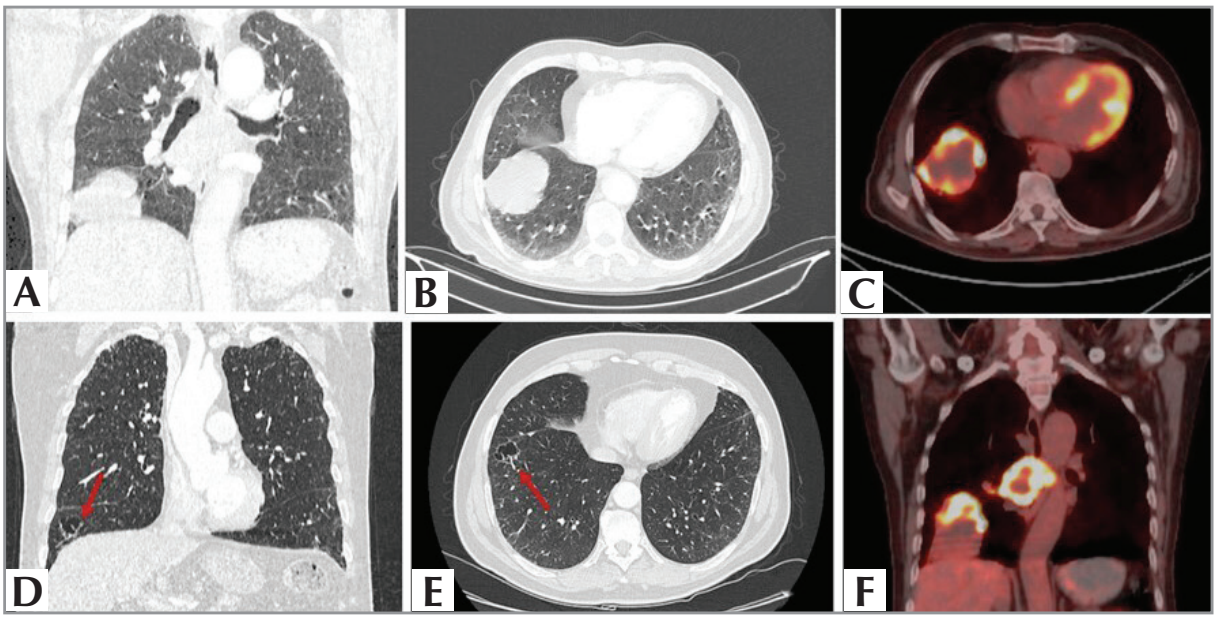

Figure 2. A 72-year-old male patient admitted with neurological symptoms. Intracranial mass was resected and histopathological diagnosis was an undifferentiated carcinoma metastasis. There was a solid mass lesion located at right lower lobe **(A,B)**; analysis of previous thoracic CT images revealed that the solid mass lesion was a cystic lesion three years prior (indicated with red arrows in **D** and **E**. PET-CT imaging showed high FDG uptakes at the borders of the mass, resembling a cyst wall, as well as bulky mediastinal lymphadenopathies **(C,F)**.

Jung et al. have recently developed a stepwise disease progression model by analyzing ninety-eight serial CT scans of 27 patients diagnosed with subsolid adenocarcinoma with cystic airspaces and investigated the link between the clinical course, clinicopathologic features, and disease progression in these patients. Their model comprises four phases. Phase I: Appearance of a CA in the middle of a non-solid nodule, phase II: CA expansion as the thickness of the ground glass opacity wall surrounding the CA remains constant or falls, phase III: Appearance of solid components on the boundary of CAs, and phase IV: The CA is surrounded by a solid wall and begins to shrink. The histopathological representation of the model demonstrated that in phase II, a fibrotic thin wall lined the borders of the CAs. In phase III, the fibrotic wall became thicker and was lined by adenocarcinoma cells (lepidic predominant). Finally, in phase IV, the region was penetrated by invasive adenocarcinoma cells (solid or micropapillary patterns), and the CAs were surrounded by a thick fibrotic wall. The model correlated well with many clinicopathologic characteristics. As the LCCAs progressed through its phases, the levels of carcinoembryonic antigen and maximum standardized uptake values (SUV_{max}) increased. Their model was also able to accurately distinguish the five-year recurrence-free survival (RFS) and overall survival (OS) rates. The five-year RFS rates were 100%, 56%, and 16% in phases II, III, and IV, respectively ($p< 0.001$). The five-year OS rates were 100%, 70%, and 48%, respectively ($p< 0.001$). The adjusted HR for recurrence in phase IV was found to be 12.38 (95% CI 1.04-1777.95, $p= 0.045$) (30). The authors proposed that frequent vascular invasion or the presence of carcinogens remaining in the CA could be responsible for the poor prognosis observed in patients with adenocarcinoma with CAs.

Despite having a unique morphology, its staging and management are currently almost identical to that of other types of lung cancer. However, due to its rarity, conducting large-scale studies may be challenging. Thus, there is still much to uncover regarding this type of lung cancer. There is very limited data on the prognosis and survival of patients with LCCA. Even though LCCAs are more likely to be diagnosed late, there is no evidence that their outcomes are poorer than those of people who do not have bullae-associated lung cancer. A prior study found that, despite the apparent more aggressive pathologic characteristics of LCCAs, the overall prognosis was comparable to that of individuals with lung cancer

not accompanied by bullae (31). In their retrospective study, Kaneda et al. observed that patients who underwent surgery for "primary lung cancer adjoining pulmonary bulla" had a significantly worse survival rate compared to the non-bullous group, but only in the advanced stages. However, it is important to note that only 10.5% of cases in their study were adenocarcinoma, which contrasts with other studies (2). Thus, more outcome data from screening studies are required on this subject.

CONCLUSION

In conclusion, untreated LCCAs have the potential to progress to solid tumors. However, diagnosing LCCA can be challenging since there are various benign inflammatory causes that can mimic its radiologic features. However, early recognition of LCCA and intervention when cyst wall thickening or solid components appear can improve outcomes. Meanwhile, the prognosis and survival of these patients are still poorly understood due to limited data. Further research is required to gain a more comprehensive understanding of the behavior of these lesions to recommend appropriate management protocols.

CONFLICT of INTREST

The authors declare that they have no conflict of intrest.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: UK, DK

Analys/Interpretation: UK, DK, SU

Data acqusition: UK, DK, YY

Writing: UK, DK, BA

Clinical Revision: UK, DK

Final Approval: All of authors

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