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Lung cancer associated with cystic airspaces: Characteristic morphological features on CT in a series of 11 cases

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ABSTRACT

Purpose: To familiarize the reader with the entity 'lung cancer associated with cystic airspaces' (LC-CAS) and create an awareness about the potential for slow progressive development of cancer within these nonaggressive appearing cystic airspaces (CAS) encountered in routine radiology practice.
Material and methods: Morphological appearances of (n = 11) LC-CAS detected during routine radiological reporting of chest CT scans were studied. Patient demographics, clinical history, characteristics of LC-CAS including location, size, wall thickening, diffuse nodularity, eccentric nodule, ground glass change, emphysema and pathology results were collected from the hospital's internal database.
Results: Patients with LC-CAS (9F/2M) were between 49 and 77 years (mean 63.18 years). All patients (n = 11) had a history of smoking. LC-CAS had a characteristic multicystic bubbly appearance. Average size of CAS at initial detection of LC was 2.52 cm (range 1.3–4 cm). Lesions were located in the RLL (n = 4), RML (n = 2), RUL (n = 1), LLL (n = 1) and LUL (n = 3) with no lobar predilection and were more commonly peripheral (n = 7) than central (n = 4). Ground glass change (n = 2), extrinsic nodules (n = 4), diffuse wall nodularity (n = 3) and intrinsic nodules (n = 2) were observed and prompted biopsy. Lesions ranged between T1a to T4. Most cancers were T1a N0 (n = 5). Adenocarcinomas formed the majority of cases (n = 9).
Conclusion: LC-CAS present as new development of diffuse nodularity, eccentric nodules or ground glass change associated with CAS. These are more commonly adenocarcinomas on histology. Recognition of CAS and appropriate malignancy workup when suspicious features are observed is essential to enable early detection of lung cancer.

1. Introduction

Incidentally detected cystic air spaces (CAS) are often overlooked on routine CT imaging due to their presumed benignity. There is growing literature describing lung carcinoma developing within the walls of benign appearing CAS. We have encountered eleven such cases during routine radiological reporting where we found biopsy proven cancer developing in association with CAS. We have observed that these spaces may have certain features indicating malignancy, that can be recognized years before the development of conventional malignant features such as tumor nodules.

This manuscript aims to familiarize the reader with the entity 'lung cancer associated with cystic airspaces' (LC-CAS) and create an awareness about the potential for slow progressive development of cancer within these nonaggressive appearing CAS encountered in routine radiology practice.

2. Material and methods

A wavier for informed consent was obtained from the institutional research ethics board for this retrospective review. Two radiologists (E.H. and N.B.) studied the morphological features on CT of (n = 11) biopsy proven lung cancers developing in cystic airspaces (LC-CAS). Imaging was performed on a 16-slice or a 64-slice CT scanner using the Low Dose CT protocol.

2.1. Review of morphology on CT

Patient demographics, characteristics of LC - CAS including lesion location (lobe and peripheral vs. central location), size of the cystic airspace, presence or absence of ground-glass change, mural nodularity, eccentric nodule, size of the eccentric nodule if present was assessed on lung window images.

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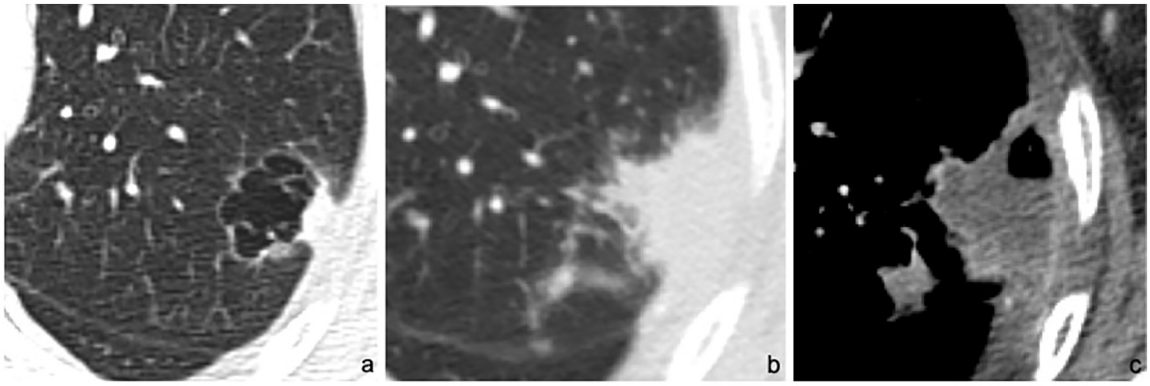

Fig. 1. Characteristic bubbly cystic airspace in the left upper lobe in a 69-year-old male, smoker in July 2011 (Panel a). Note the eccentric nodular soft tissue thickening along its lateral margin. Complete replacement of the cystic airspace with soft tissue was seen in February 2013 (Panel b). This demonstrated internal necrosis (Panel c), chest wall and rib erosion. A left upper lobectomy was performed. Histology revealed squamous cell carcinoma (T4a, N0).

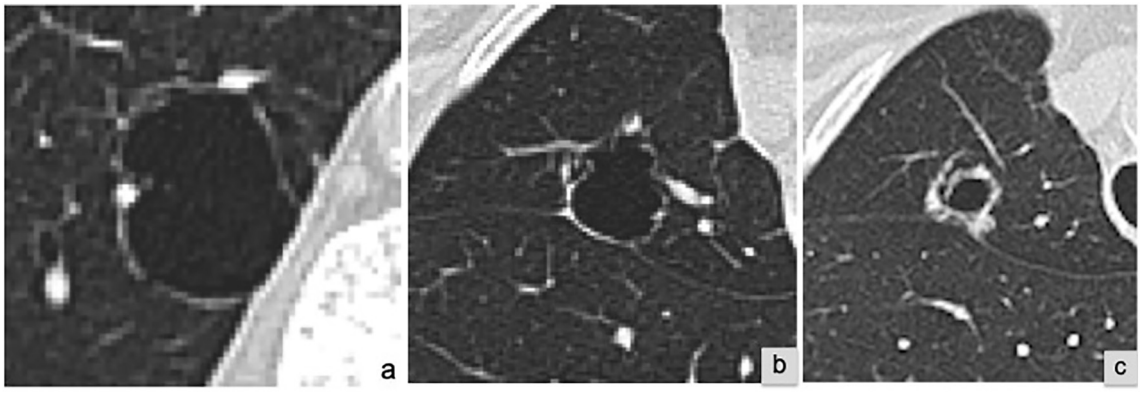

Fig. 2. Two separate cystic airspaces in a 49-year-old woman in the right lower lobe (Panel a) and middle lobe (Panels b and c) who had a previous right upper lobectomy for an adenocarcinoma. Note the diffuse nodularity surrounding the wall of the cystic air space (Panel c) with no discrete large nodule. Middle lobectomy revealed a T2a No adenocarcinoma.

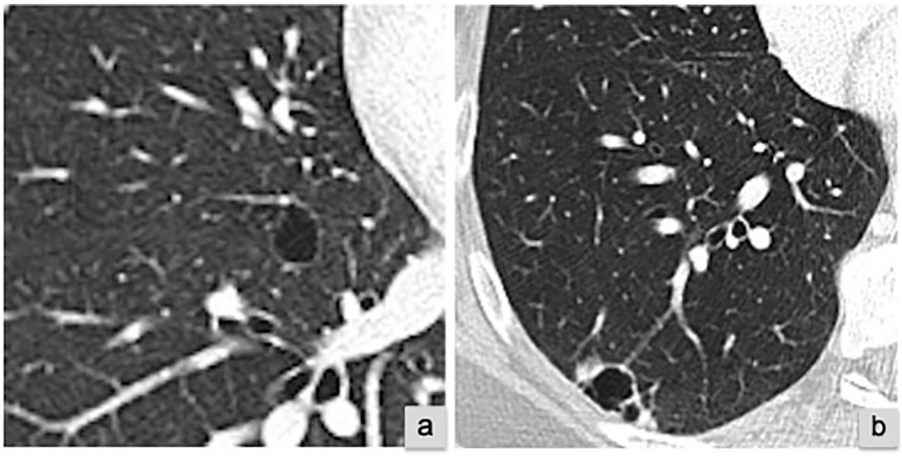

Fig. 3. Two cystic airspaces (Panels a and b) in a 54-year-old woman. The cystic airspace in the right lower lobe (Panel b) demonstrates an extrinsic 7 mm nodule outside the cyst wall along its medial margin and extrinsic nodular wall thickening along its lateral margin. A right lower lobectomy was performed. Histology revealed a T1b No adenocarcinoma.

2.2. Histology results and staging

Pathology results from biopsy or from surgical specimens when surgery was performed were documented. Presence or absence of emphysema in the surrounding lung parenchyma was noted. Final TNM staging of the lung cancer was also noted from the pathology report and clinical notes in the hospitals internal database.

3. Results

3.1. Patient demographics

A total of (n = 11) cases were reviewed. The average age of patients with LC-CAS was 63.18 years (range 49–77). The gender ratio was (F: M = 9:2). A history of smoking was present in all (n = 11) patients.

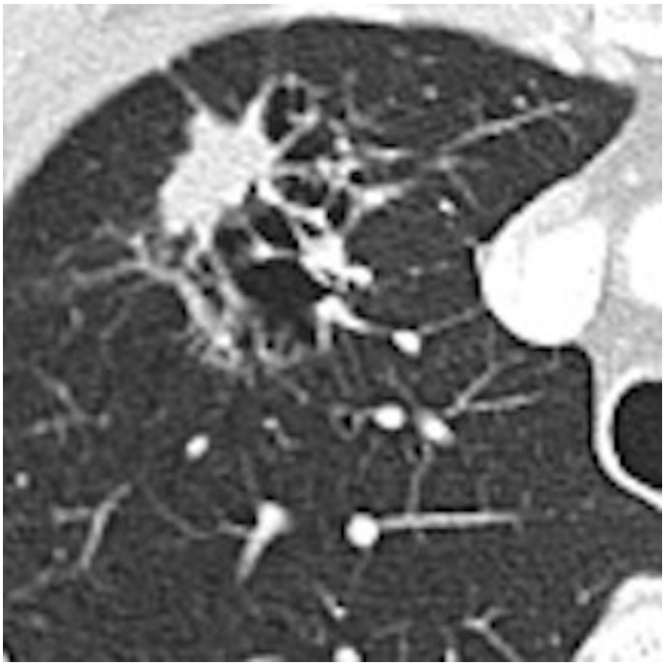

Fig. 4. Characteristic multicystic bubbly appearance of a cystic-airspace with lobulated margins and multiple internal septations in a 63-year-old woman. The airspace demonstrates an eccentric nodule. This was a T2a No adenocarcinoma.

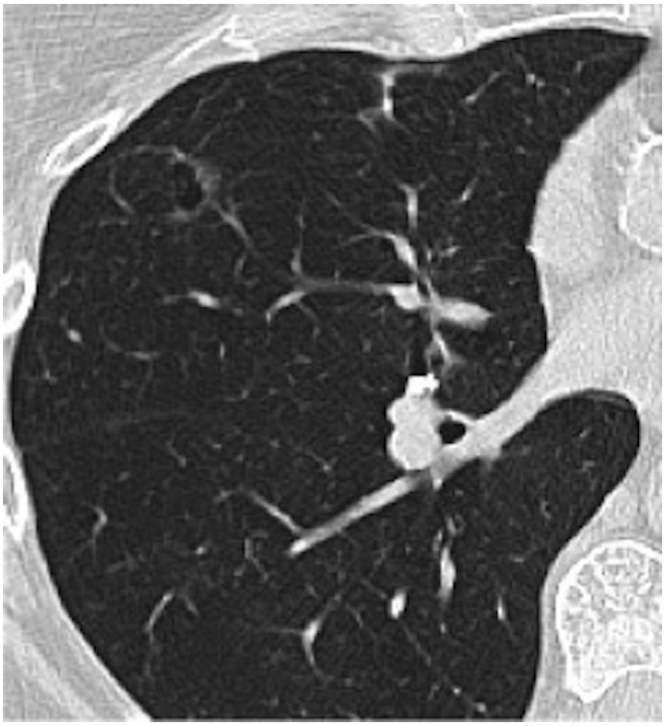

Fig. 5. Ground glass change located eccentrically along the margin of a cystic-airspace in a 66 year-old-woman. Middle lobe resection revealed a T1a No adenocarcinoma.

3.2. Imaging characteristics on CT

The cystic airspaces in LC-CAS were round to oval in shape and ranged in appearance from simple cyst (n = 1) to cysts with slightly irregular walls and a few thin internal septations (n = 6) to multicystic bubbly CAS with lobulated margins (n = 4) and multiple internal complete and incomplete septations. Ground-glass change associated with CAS (n = 2), extrinsic nodule (n = 4), diffuse wall nodularity (n = 3) and intrinsic nodules (n = 2) were observed and prompted biopsy. Average size of CAS at initial detection of LC was 2.52 cm (range 1.3–4 cm). Lesions were located in the RLL (n = 4), RML (n = 2), RUL (n = 1), LLL (n = 1) and LUL (n = 3) with no lobar predilection. Lesions were more often peripheral (n = 7) in location as against central (n = 4). Multiple CAS were seen in (n = 5) cases. Emphysema within the surrounding lung parenchyma was seen in (n = 5) patients on imaging. Staging PET scanning was performed in (n = 7) patients, of which (n = 2) lesions were PET negative. SUV uptake among PET positive lesions ranged between 1.5 and 10.3 (average 6.54 SUV).

3.3. Histology and staging

Excision was performed and a specimen report was available in (n = 9) (81.8%) cases while only biopsy results were available in (n = 2) (18.2%) cases. Lesions ranged between (T1a to T4) however were most commonly T1a (n = 5) followed by T2b (n = 3) and T1b (n = 2). Size of the tumor on pathology ranged between 1.1 cm–9 cm (average = 2.9 cm). None of the lesions were associated with lymph node or distant metastasis. Similar to prior series adenocarcinomas formed the majority of cases (n = 9) with squamous cell carcinoma (n = 2) forming the remainder. Emphysema or cystic change was present in the background lung parenchyma in all (n = 9) of the excised tumors.

3.4. Follow-up interval

The time interval between the first examination when the lesion was detected, and when the biopsy/excision was performed ranged between 1 and 64 months (average 24.5 months).

4. Discussion

We have described the spectrum of morphological appearances on CT (Figs. 1–10) of lung cancer associated with cystic air spaces (LC-CAS). We observed that, morphologically CAS range from simple lung cysts (Fig. 6), lung cysts with slightly irregular walls (Fig. 2) to characteristic multicystic bubbly air spaces with internal complete and incomplete septations (Figs. 1, 4, 7, 8). Early signs of lung cancer (LC) development include appearance of wall nodularity (Figs. 1, 2), eccentric nodules (Figs. 3, 4, 9, 10) or ground glass change along the margins of the CAS (Figs. 5, 6) along with increase in complexity of the CAS. The presence of these features should warrant close follow-up of the LC-CAS ultimately leading to biopsy and histological diagnosis.

Cystic air spaces have been seen to be associated with 1% cases of non-small cell lung cancer [1]. The earliest documentation of LC-CAS was in 1954 when six cases of carcinoma of the bronchus with the radiological appearance of thin walled cysts or cavities were described [2]. These did not have distinguishing imaging characteristics from benign entities however they differed from the appearance of solid neoplasms breaking down [2]. Different types of cystic airspaces including multiloculated cystic lesions [3], congenital lung cysts and emphysematous bullae [4,5] have been described in association with lung cancer.

4.1. Mechanism of association of lung cancer with cystic air spaces

The most commonly proposed mechanism for the development of LC-CAS is a check- valve mechanism wherein intermittent obstruction of the bronchiole by the tumor causes dilatation of the airspace distal to it [2,3,6]. Other mechanisms described previously include necrosis and cystification within a tumor, alveolar wall destruction by tumor cells or by mucus retention, adenocarcinoma growing along the wall of pre-existing cystic lesions such as bullae and lung cysts, lipedic growth of

Fig. 6. Simple cystic-air-space in the left upper lobe with subtle ground glass change along the lateral margin of the cyst wall (Panel a) in May 2010 in a 64 year-old-woman. Complete replacement of the cyst with a solid nodule was seen (Panel b) in September 2015. This demonstrated an SUV of 5.4 on PET imaging (Panel c). Biopsy showed adenocarcinoma. This was treated with stereotactic radiation therapy.

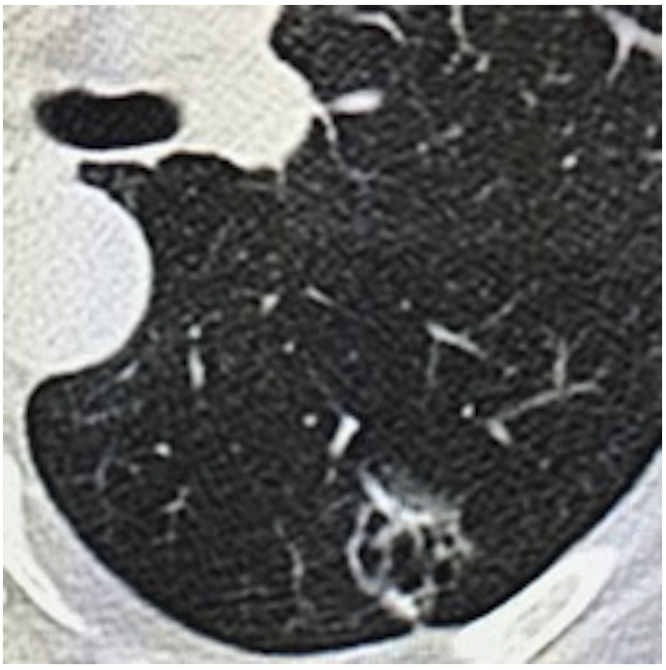

Fig. 7. Characteristic multicystic bubbly appearance of a cystic-airspace with lobulated margins and multiple internal complete and incomplete septations in a 67-year-old woman who had prior right upper and middle lobe resections. The airspace demonstrates subtle eccentric ground glass change anteriorly and nodular wall thickening along its posterior margin. Left lower lobe wedge resection revealed a T1b N0 adenocarcinoma.

adenocarcinoma in an area of emphysema and elastic traction by surrounding lung tissue as a mechanism for cyst formation [2,3,7–9].

4.2. Histology of lung cancer associated with cystic air spaces

Adenocarcinomas with lipedic, papillary and acinar predominant patterns were found in nine of our patients (81.8% cases), while two of our patients demonstrated squamous cell carcinomas on histology. This distribution is similar to prior series where adenocarcinomas formed the majority of cases ranging from 70.8 to 88% [1,8,9]. Squamous cell [10], large call [4] and small cell carcinomas have been reported less frequently.

4.3. Association of LC-CAS with smoking and emphysema

Emphysema and smoking are closely associated and are independent risk factors for lung carcinoma. The presence of diffuse lung changes such as emphysema in turn makes interpretation of pericystic changes in LC-CAS more challenging [11]. Emphysema has been seen in 70.8% to 85% [8,9] of LC-CAS. In the present series, emphysema within the surrounding lung parenchyma was present in six of the nine patients that had lung resection. Two patients had subpleural bullae and cystic change and one had organizing pneumonia that may have obscured emphysematous or cystic change. Similar to prior observations [1,8], a history of smoking was present in all our patients.

4.4. PET CT imaging in LC-CAS

Staging with FDG PET (Fig. 6) was performed in seven of our patients. Two LC-CAS did not demonstrate FDG uptake. These included a 1.5 cm bubbly cystic airspace (T1a N0 adenocarcinoma) with no solid nodule and a 2.3 cm cystic airspace with wall nodularity without a discrete nodule. Five LC-CAS demonstrated FDG uptake that ranged between 1.5 and 10.3 SUV with a mean uptake of 6.52 SUV. It has been noted that increasing growth and invasiveness of the tumor associated with increasing metabolic demand increases FDG uptake [8]. The smallest nodule that demonstrated uptake in our series measured 7 mm. FDG characterization was helpful when nodules measured > 8 mm in size [1] in other larger series. Absence of uptake on PET dose not preclude malignancy [9] especially in the absence of a sizeable component (> 10 mm) [11] and irrespective of FDG uptake, CAS with increasing soft tissue on CT should be considered suspicious for lung cancer.

4.5. Distribution and morphology of LC-CAS

Similar to prior series [1], LC-CAS were uniformly distributed throughout the lung parenchyma with no lobar predilection and were more commonly peripheral as compared to central [1]. Four morphological patterns of LC-CAS have been described i) solid nodule protruding externally or ii) internally from the cyst wall, iii) circumferential thickening of the cyst wall, and iv) tissue intermixed with a cluster of cysts [8,11]. We observed an additional morphological pattern with ground glass change along the margin of the CAS (Figs. 5, 6) in two of our patients. This ground glass change was diffuse and was not measurable as a discrete ground glass or part solid nodule. Of note, the walls of these cystic airspaces are initially very thin, usually 1 mm [9], when they can be differentiated from other lesions of infectious etiology such as lung abscesses where the cavity wall is usually thick and irregular. In LC-CAS, the wall of the airspace may progressively become thicker when it may be difficult to differentiate from a lung abscess or necrotic tumor (Fig. 1c). Correlation with clinical findings, and assessing response to treatment may help differentiate between these [11]. It

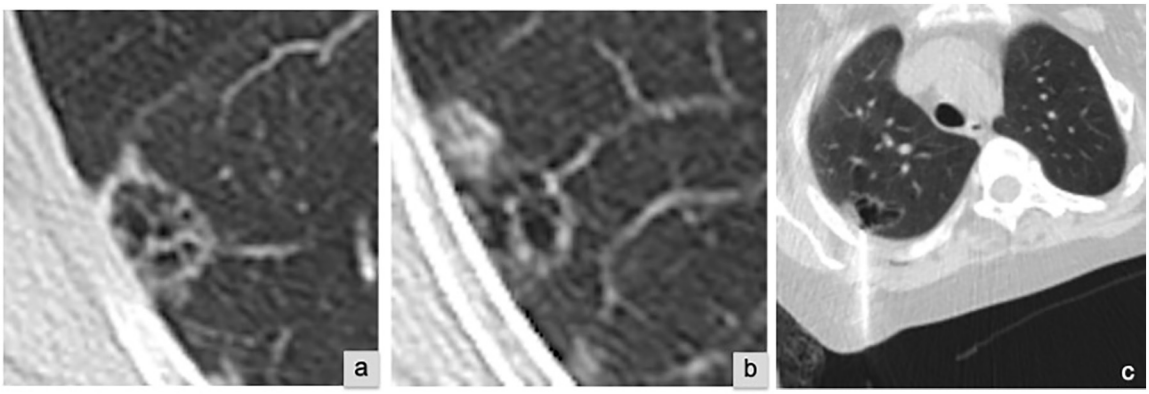

Fig. 8. Multicystic bubbly cystic airspace in the right lower lobe (Panels a and b) in a 60-year-old woman. Note eccentric wall thickening along its lateral aspect. She had a prior right upper lobectomy for an adenocarcinoma that presented as a cystic air space with an eccentric nodule (Panel c), note the biopsy needle targeting the solid component located eccentrically along the cystic air space.

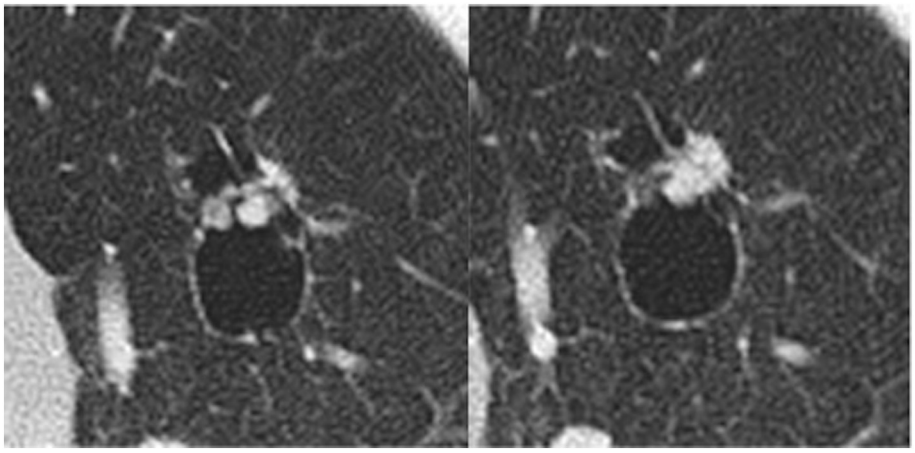

Fig. 9. Cystic airspace with intrinsic and extrinsic nodules along the walls of the air space in a 70-year-old male. Biopsy revealed adenocarcinoma. This was treated with stereotactic radiation therapy.

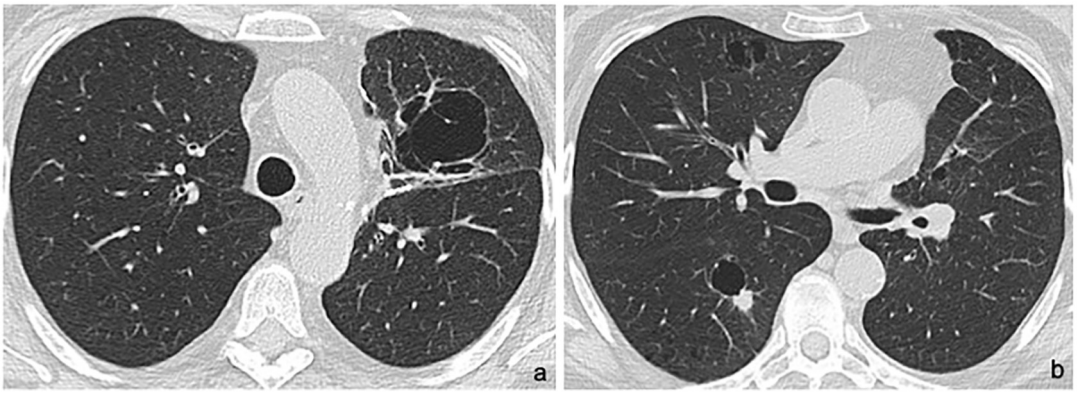

Fig. 10. Several cystic air spaces in a 77-year-old woman (Panels a and b). The cystic air space in the right lower lobe (Panel b) demonstrates an extrinsic nodule (Panel b). This was a squamous cell carcinoma (T1a N0) on histology. She has had a prior left upper lobe resection for a T1b N0 adenocarcinoma.

was also interesting to note that a simple appearing cyst (Fig. 6) with very subtle ground glass change was completely replaced by a solid nodule over an interval of 5 years in one of our cases.

4.6. Evolution of LC-CAS

It has been observed that nodules preceded the appearance of CAS in (50%) cases where CT was available, whereas CAS preceded nodules in the remaining cases [1] suggesting the possibility of multifactorial mechanisms in the development of LC-CAS. Thickening of the wall or emergence of a nodule became apparent at 12–118 months (median, 35 months) [9] indicating the need for long-term follow-up. Similarly, a mean of 25 months were required for the development of a nodule within a cystic air space [1]. An increase, decrease or no change in size of the cystic component of the airspace [8,9] or increase in the size of the solid component [11] was seen over time. In our series, the time interval between detection of CAS and biopsy ranged between 1 and 64 months (mean 20.5 months) compared to 25.5 months in larger

series [1]. We were able to follow the temporal evolution of CAS in two of our patients (Figs. 1, 6) where we saw increase in the size of the CAS as well as associated nodule. Shared et al. observed that chance in the morphology of a cyst or peri-cystic nodule should raise suspicion for cancer. [11] Bearing a low threshold for biopsy of suspicious LC-CAS lesions, three of our lesions were biopsied within 4 months of detection of LC-CAS.

4.7. Multiplicity of LC-CAS

Five patients in our series had additional CAS and three patients had prior resections for lung carcinoma suggesting the propensity for development of multiple lesions over time. One patient, a 49 year-old woman in our series with Fanconi anemia, with a T2a N0 adenocarcinoma (Fig. 2) had two additional CAS and a prior lobectomy for lung carcinoma. The genetic susceptibility of patients with Fanconi anemia to lung adenocarcinoma has been investigated [12]. Multiplicity of LC-CAS has been described in 23% [1] in a prior series.

5. Limitations

This is a small series of 11 cases of LC-CAS encountered in routine radiology practice. The aim of this manuscript is to illustrate the spectrum of morphological appearances of LC-CAS in order to create an awareness of this entity and urge appropriate management when these are encountered.

6. Conclusion

Cystic airspaces with wall irregularity, nodularity or a characteristic multicystic bubbly appearance may develop lung carcinoma over a period of time and hence require close attention and follow-up with low dose CT. Presence of emphysema in the background lung parenchyma, multiplicity of cystic airspaces and a history of smoking are common. Interval development of ground-glass change along the margins, diffuse wall nodularity, eccentric nodule or increasing complexity within a cystic airspace are indicators of malignancy and should prompt cancer assessment and workup including biopsy.

Recognition of the characteristic appearance of cystic airspaces, appropriate follow-up and malignancy workup when suspicious features are observed is essential to enable early detection of lung carcinoma.

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