

## Case Report

# Diffuse cystic lung adenocarcinoma: a case report and literature review

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**Abstract:** Lung adenocarcinoma can exhibit a variety of radiological manifestations. However, the presence of diffuse cystic lesions in both lungs is extremely rare. Here, we report a case of a middle-aged woman with a primary lung adenocarcinoma that manifested as diffuse cystic lesions in bilateral lungs. Histopathological examination ultimately confirmed the lung adenocarcinoma. The patient was treated with the epidermal growth factor receptor (EGFR) inhibitor Gefitinib and remained stable during 18 months of follow-up. Knowledge of uncommon radiological performances of lung adenocarcinoma characterized by diffuse cystic imaging is important in suggesting the diagnosis and preventing misinterpretation.

**Keywords:** Lung adenocarcinoma, diffuse cysts, radiology, diagnosis

## Introduction

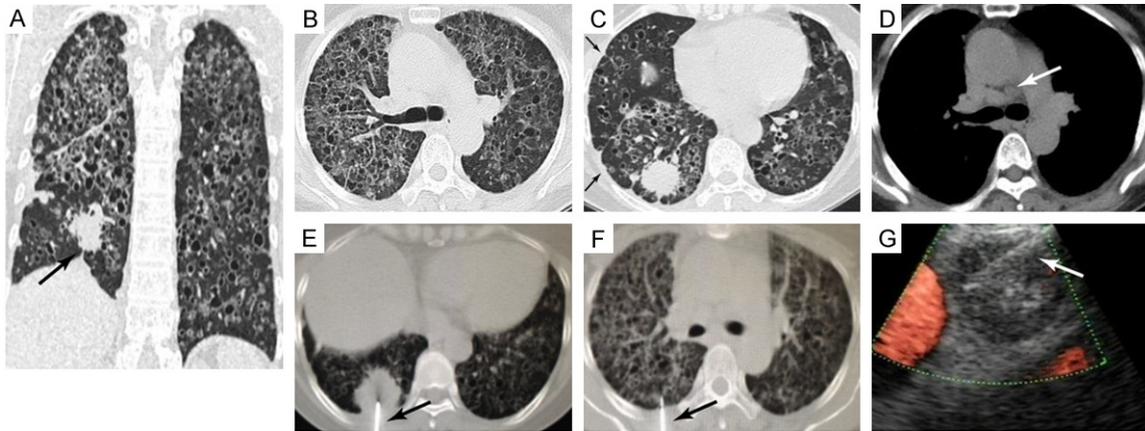
Classical radiology signs of pulmonary cystic lesions during imaging are common. However, the diagnosis is a challenging process. The presence of diffuse cysts in the lungs can be a presentation of several diseases, including pulmonary emphysema, cystic bronchiectasis, Langerhans cell histiocytosis, interstitial pulmonary fibrosis, Wegener granulomatosis, and infectious diseases. Cavities develop rarely in metastatic lung adenocarcinoma [1], and the presence of diffuse cysts is even more uncommon. Herein, we report a case of lung adenocarcinoma with diffuse cystic lesions in both lungs.

## Case report

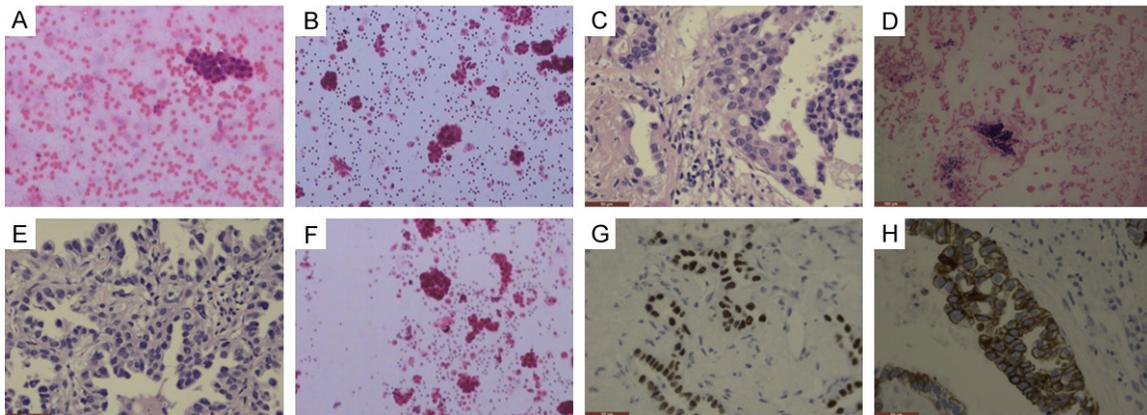
A 56-year-old female patient presented to our hospital complaining of an ongoing cough and shortness of breath lasting longer than one month. The patient's medical history was clean and there was no history of smoking. Auscultation revealed no attenuated respiratory sounds, and no signs of rales or wheezing was observed. In addition, there was no superficial node enlargement or acropachy. Laboratory

investigations were as follows: hemoglobin level: 121 g/L, platelet count:  $320 \times 10^9/L$ . Carcinoembryonic antigen: 345.84 ng/ml (normal reference: 0-5 ng/ml), Carbohydrate antigen (CA) 125: 40.7 IU/ml (normal reference: <35 IU/ml), CA 153: 60.3 IU/ml (normal reference: <31.3 IU/ml). Levels of cytokeratin 19 fragment, squamous cell carcinoma antigen, and CA 199 were in the normal range. Levels of autoantibody spectrum, vasculitis-related autoantibody spectrum, immunoglobulin (Ig) series (IgA, IgG, IgM and IgE), complement component C3, complement component C4, serum kappa chain, serum lambda chain, urine lambda chain, rheumatoid factor, anti-O antibody, anti-cyclic citrullinated peptide, anti-double stranded DNA, allergen assay, human immunodeficiency virus antibody test, arterial blood gas analysis, and sputum culture were unremarkable. A computed tomography (CT) (Siemens, Germany) scan of the chest showed diffuse cystic lesions in bilateral lungs with a  $3.7 \times 3.6$  cm lung mass in the right lower lung (**Figure 1A, 1B**), multiple nodules in the right subpleural area (**Figure 1C**), and a small amount of pleural effusion on the right side of the chest. Also noted were enlarged mediastinal nodes (**Figure 1D**). Using abdominal CT scans, cranial mag-

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**Figure 1.** Radiological appearances and needle aspiration biopsy. (A) Posteroanterior radiograph shows bilateral diffuse air-cysts and a 3.7 × 3.6 cm right lower lung mass (arrow). (B) Axial chest CT shows diffuse cystic lesions in both lungs. (C) Ground-glass nodules, subpleural multiple nodules and (D, arrow) mediastinal lymph nodes. (E) TTNA biopsy of right lower lung mass and (F) right upper lung cystic lesions. (G) EBUS-TBNA at mediastinal lymph nodes.



**Figure 2.** Histocytological features and immunohistochemical staining. (A) Branchofibroscopic brush-off cytological features and (B) thinprep cytological test in BALF. (C) Histological features of right lower lung mass and (D, E) right upper lung diffuse cystic lesions. (F) Cytological features of 4R group lymph nodes. (G) Immunohistochemical staining shows positive expression of TTF-1 and (H) CK7 in the tumor cells from lung (A: H&E × 100; B: H&E × 100; C: H&E × 400; D: H&E × 100; E: H&E × 400; F: H&E × 100; G: × 400; H: × 400).

netic resonance scans, and bone Single-Photon Emission CT (SPECT) scans, no abnormalities were found. To form a definite diagnosis of the disease, additional studies were performed. This included a BF-XP260F ultrathin bronchoscopy (Olympus, Japan) that revealed right lower lobe basal segment bronchial lumen stenosis. Adenocarcinoma cells were detected in both branchofibroscopic brush-off cytological examination and thinprep cytologic testing of bronchoalveolar lavage fluid (BALF) (**Figure 2A, 2B**). Subsequently, CT-guided transthoracic needle aspiration (TTNA) biopsy (**Figure 1E, 1F**) and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) (**Figure 1G**) we-

re performed. Pathological examination revealed that the right lower lung mass, right upper lung cystic tissue, and 4R group lymph nodes were indeed adenocarcinoma (**Figure 2C-F**). In addition, immunohistochemical analysis revealed that tumor cells derived from lung tissue were positive for thyroid transcription factor-1 (TTF-1) and cytokeratin 7 (CK7) (**Figure 2G, 2H**). Histopathological diagnosis was consistent with right lower lung adenocarcinoma and metastasis of mediastinal lymph nodes (T2aN3M1a, stage IV). The patient, who had an epidermal growth factor receptor (EGFR) exon 21 L858R point mutation, had been treated with Gefitinib (Iressa, ZD1839). The condition of the patient

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**Table 1.** Cases of lung adenocarcinoma with lungs diffuse cystic lesions

Case	Sex/Age (years)	Clinical presentations	Lesions and metastatic sites	Treatment	Follow-up
Sabloff et al. [4]	F/29	Chronic cough, shortness of breath with exertion	Lungs	NA	NA
Huang et al. [5]	F/46	Shortness of breath, cough, pneumothorax	Lungs, right hilar lymph nodes	NA	NA
Wang et al.	F/56	Cough, shortness of breath with exertion	Lungs, mediastinal lymph nodes, pleura	Gefitinib	PFS more than 18 months

NA, Not available; PFS, Progress free survival.

remained stable during 18 months of follow-up.

### Discussion

Pulmonary adenocarcinoma is a common histological form of lung cancer. Because of its complex biological characteristics, lung adenocarcinoma is shown to have a diverse appearance during CT imaging. Lung adenocarcinoma was characterized as peripheral tumor mass or ground-glass nodules using imaging techniques. Common presentations when using the radiology approach include signs of lobulation, burr, angiograms, pleural indentation, open bronchus, and bronchus encapsulated air. In addition, a small amount of studies [2, 3] demonstrated that metastatic lung adenocarcinoma presented as solitary or multiple thin-walled cavities. Primary lung adenocarcinoma which metastasis in the lungs is presented as diffuse cystic changes in imaging is very rare. To the best of our knowledge, only two cases that focus on this phenomenon have been reported. One of which was a study performed in America, the other case was reported in China. The first case was described by Sabloff et al. [4] in 2005, and focused on a 29-year-old Hispanic woman with a 10-month history of cough and mild shortness of breath, who was initially misdiagnosed as having pneumonia. The patient had been treated for over 6 months with antibiotics with no improvement of symptoms. CT imaging was non-conclusive, and TTNA biopsy ultimately concluded bronchioloalveolar cell carcinoma. Five years later, Huang et al. [5] reported another case of primary lung adenocarcinoma with the appearance of diffuse cystic lesions in the lungs. The patient, with recurrent left lung spontaneous pneumothorax and shortness of breath with exertion, was also initially misdiagnosed as having tuberculosis and was therefore subjected to anti-tuberculosis treatment for a duration of 2 months. Similar to the two cases described above, we report on a third case, also a female patient, whose previous

medical history was unremarkable. This patient had never undergone a radiological examination until clinical symptoms were identified. In addition to a mass was found in the right lower lung, uncommon manifestations of diffuse cystic lesions were identified during CT scanning, which characterized by thin-walls with clear borders, did not communicate with the bronchus. Other combined radiological performances included diverse sizes of ground-glass nodules, multiple nodules in the subpleural area, and a small amount of pleural effusion on the right side of the chest. The diagnosis of this patient was controversial until TTNA biopsy and pathology examination were performed.

Given the rarity of the reported cases of primary lung cancer with diffuse cystic lesions in both lungs, the disease can very easily be misdiagnosed. The radiological differential diagnosis of diffuse lung lesions characterized by multiple cysts or cavities includes pulmonary emphysema, bronchiectasis, desquamative interstitial pneumonia, usual interstitial pneumonia/idiopathic pulmonary fibrosis, lymphocytic interstitial pneumonia, lymphangioleiomyomatosis, Langerhans cell histiocytosis, pulmonary paragonimiasis, Wegener granulomatosis, pneumocystis carinii pneumonia, pulmonary cystic metastasis and Birt-Hogg-Dubé Syndrome [1, 6-8]. Histological and immunohistochemical features are fundamental in establishing the diagnosis of the radiologically indistinguishable primary lung adenocarcinoma. The possible mechanisms of cystic lesions in lung cancer include: tumor center necrosis, destruction of the alveolar wall by tumor cells, a tumor with preexisting cysts, bullae or honeycomb, tumor cells secrete mucus in the alveoli cavity caused by alveolar wall rupture, tumor cell autophagy, and the cystic growth behavior of the tumor [5].

There are striking similarities among these three cases (Table 1). All were female, non-smoker, presented as shortness of breath in the clinic, and minimal surgical opportunities

due to extensive lesions in the lungs. Thus, the treatment options for all three patients were limited. The treatment and follow-up data were not available in the first two cases. The patient in our study, had a sufficient response to Gefitinib, indicating that specific inhibition of EGFR tyrosine kinase activity may be a promising therapeutic option for lung adenocarcinoma patients who are radiologically characterized by diffuse cysts, which seem to have prevalence in women compared to men.

### Conclusions

In summary, we report a case of lung adenocarcinoma with a rare radiographical manifestation of diffuse cystic lesions within both lungs. This case, combined with two other cases discussed in this study, indicates that the possibility of lung cancer should be considered when the disease is manifested as diffuse cystic imaging of the lungs. In addition, performing timely pathological examination is important to establish a diagnosis and to prevent misinterpretation.

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### Disclosure of conflict of interest

None.

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