

## CASE REPORT

# Recurrent bilateral spontaneous pneumothorax secondary to lung adenocarcinoma with epidermal growth factor receptor mutation

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## Keywords

Epidermal growth factor receptor; lung cancer; lung cysts; pneumothorax.

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## Introduction

Cystic lung disease is characterized by multiple intrapulmonary cysts. The differential diagnosis of cystic lung disease may include lymphangiomyomatosis (LAM), pulmonary Langerhans cell histiocytosis (PLCH), lymphoid interstitial pneumonia (LIP), and cystic lung metastasis. Spontaneous pneumothorax (SP) may occur in as many as 40–80% of patients with LAM.<sup>1</sup> However, bilateral SP secondary to lung adenocarcinoma has very rarely been reported. We present a rare case of bilateral SP and thin-walled cysts as a complication of adenocarcinoma of the lung. We identified the possible mechanism of formation of these cysts, which mimics that of LAM.

## Case report

A 42-year-old female patient was admitted to our hospital for an intermittent dry cough and dyspnea on exertion that had persisted for one year. A chest radiograph approximately one

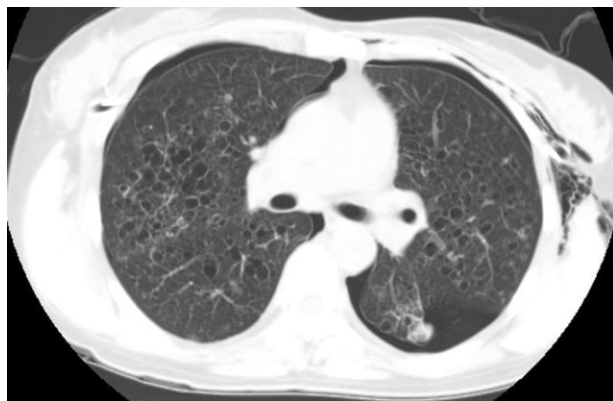
## Abstract

A 42-year-old female patient was admitted for recurrent bilateral spontaneous pneumothorax. High resolution computed tomography showed bilateral pneumothorax and numerous round and oval, thin-walled lung cysts. Microscopically, each small cyst was composed of distended subpleural alveolar spaces. Tumor cells, characteristic of acinar adenocarcinoma, obstructed and narrowed the terminal bronchioles. There was no tumor necrosis or mucin production. This suggested check-valve as a possible mechanism of the thin-walled cysts and pneumothorax. Genetic analysis suggested that the tumors were positive for epidermal growth factor receptor mutation L858R in exon 21. Bilateral spontaneous pneumothorax and thin-walled cysts in association with lung cancer is rarely reported and may be confused with cystic benign lung lesions.

year earlier had shown a left-sided pneumothorax, but as the condition was minor, the patient did not receive treatment. About two months prior to her admission, the above-mentioned symptoms had worsened, and computed tomography (CT) of the chest performed at that time showed bilateral pneumothorax and diffuse thin-walled cysts in both lungs. She experienced significant relief of her symptoms following closed thoracic drainage. However, two weeks prior to her admission, she experienced another episode of bilateral pneumothorax. The patient had no fever, chest pain, hemoptysis, or loss of weight. Her past medical history was unremarkable. She was a housewife, had never smoked, and had no family history of cancer.

Physical examination revealed no clubbing or cyanosis. There were no palpable lymph nodes. Breath sounds decreased bilaterally.

High-resolution CT (HRCT) revealed bilateral pneumothorax and numerous round and oval thin-walled lung cysts 3–10 mm in diameter. These cysts were mainly distributed in the upper and middle portions of the lung, and there were

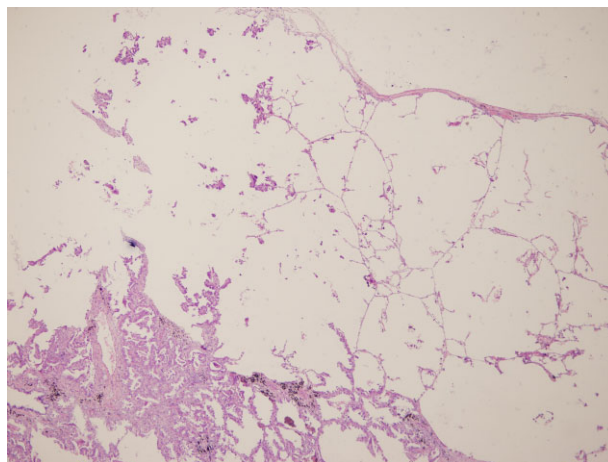


**Figure 1** Multiple thin-walled cysts in both lungs and bilateral pneumothorax.

more lesions in the right lung than in the left (Fig 1). There were some small ground-glass nodules distributed along vascular branches and in the subpleural region. A cavitory nodule 1.5 cm in diameter was also observed in the left lower lobe. A diagnosis of LAM was initially suspected. Routine blood, urine, liver and renal function tests were all within normal limits. Arterial blood gas analysis was almost normal. Analysis of tumor markers revealed an increased serum level of carcinoembryonic antigen (CEA) of 52.43 ng/mL (normal <5 ng/mL). Antinuclear antibody tests were all negative. Bronchoscopy was performed, and bronchoalveolar lavage fluid (BALF) and brush cytology found no tumor cells, while transbronchial lung biopsy (TBLB) revealed only non-specific inflammation.

In order to make a pathological diagnosis, video-assisted thoracoscopic surgery (VATS) was subsequently performed. The lesions in the right lung were slightly more severe than those in the left. Therefore, biopsy specimens were obtained from the right lung. During VATS, diffuse changes could be observed throughout the right lung; compliance of the right lung was poor. Wedge resections were performed in all three lobes of the right lung. After lung biopsy, pleurodesis of the right pleura was performed. Microscopically, the tumor was composed of columnar cancer cells which had replaced the alveolar epithelial cells, a finding which represented lepidic predominant adenocarcinoma (LPA). Each small cyst was composed of distended subpleural alveolar spaces (Fig 2). Tumor cells, characteristic of acinar adenocarcinoma, obstructed and narrowed the terminal bronchioles. There was no tumor necrosis or mucin production. These findings suggest a check-valve mechanism of formation of the thin-walled cysts and pneumothorax. Pathological findings were the same from all three biopsied sites. There were no metastases to other organs. Thus, the final diagnosis was stage IV lung adenocarcinoma with bilateral lung metastases.

Genetic analysis suggested that the tumor was positive for epidermal growth factor receptor (EGFR) mutation L858R in



**Figure 2** Tumor cells consistent with acinar adenocarcinoma, narrowed peripheral airways, and distended subpleural alveolar spaces (hematoxylin & eosin×100).

exon 21. However, the patient could not afford the cost of small-molecule EGFR-tyrosine kinase inhibitors (TKIs). She was treated with six cycles of chemotherapy combined with pemetrexed and cisplatin. Her disease remained stable for the first 1.5 years and then progressed. Her overall survival was 2.5 years.

## Discussion

Spontaneous pneumothorax resulting from a neoplasm in the lung does not frequently occur. Pneumothorax occurs most frequently with osteosarcomas, although it has been reported in other sarcomatous tumors and in tumors with an aggressive and necrotic nature.<sup>2</sup> Metastatic pulmonary angiosarcomas, especially those arising from the scalp, frequently present with pneumothorax.<sup>3–5</sup> SP as a complication of primary lung carcinoma is rare. It is estimated that only 2% of all cases of SP coexist with malignant lung diseases, either primary or secondary.<sup>6</sup> One case of bilateral SP as a complication of lung cancer has been reported previously.<sup>7</sup>

In the present case, HRCT revealed bilateral diffuse thin-walled cysts which were initially misdiagnosed as LAM. Considerable overlap in etiology and pathophysiology exists between cavities and cysts.<sup>8</sup> Thus, the cysts in this case might also be called thin-walled cavities. Spontaneous cavitations are common in primary lung cancer; however, cavitations of secondary cancers are rare. The phenomenon occurs in only 4% of secondary lung cancers, and the cavitations are usually confused with cavity benign lesions.<sup>9</sup> The wall of a cavitated mass is generally thick and irregular, although thin-walled cavities can be found with metastases from sarcomas and adenocarcinomas.<sup>2</sup> Ten case reports of lung cancers associated with multiple thin-walled cavities have been reported.

**Table 1** Characteristics of 10 cases of lung ADC with multiple thin-walled cysts

Literature	Gender	Age	Biopsy method	Mechanism of cyst formation	Histologic diagnosis
Ohba S, <i>et al.</i> <sup>10</sup>	F	47	autopsy	necrosis and check-valve mechanism	BAC
Imai S, <i>et al.</i> <sup>11</sup>	M	70	autopsy	mucus production	mucinous BAC
Kobayashi H, <i>et al.</i> <sup>12</sup>	F	66	autopsy	mucus production	mucinous BAC
Weisbrod GL, <i>et al.</i> <sup>13</sup>	F	49	open biopsy	mucus production	mucinous BAC
	F	28	wedge biopsy	necrosis; obstructive bronchiectasis	mucinous BAC
	M	57	open biopsy		BAC
	F	82	TBLB		BAC
Kojima K, <i>et al.</i> <sup>14</sup>	F	63	TBLB	check-valve mechanism	ADC
Morimoto T, <i>et al.</i> <sup>15</sup>	F	68	TBLB	disruption of the alveolar, check-valve mechanism	BAC
Isobe K, <i>et al.</i> <sup>16</sup>	M	82	autopsy	mucus production, necrosis, and check-valve mechanism	mucinous BAC

ADC, adenocarcinoma; BAC, bronchioloalveolar carcinoma; TBLB, transbronchial lung biopsy.

All of these cases were reported before 2009; therefore, the term “bronchioloalveolar carcinoma” (BAC) had not yet been created. The histological diagnosis in nine of the cases was BAC, including five cases of mucinous BAC. The other case was diagnosed as moderately differentiated adenocarcinoma. The mechanisms of cyst formation included tumor necrosis, mucus production, check-valve mechanism, and obstructive bronchiectasis.<sup>10–16</sup> Most of the literature came from Japan. The characteristics of the 10 cases are listed in Table 1. In the current case, histological examination of the resected specimens from the three lobes of the right lung assisted us in determining the possible mechanism leading to the thin-walled cysts and pneumothorax. When small airways are narrowed by cancer invasion and act as a check-valve, distal alveolar spaces become dilated by air trapping and eventually rupture. This strongly suggests a check-valve mechanism as the cause of the thin-walled cysts and pneumothorax in this case.

Genetic analysis suggested that the tumor was positive for EGFR mutation L858R in exon 21. Chung *et al.* reported that EGFR mutations were common in multiple lung adenocarcinomas.<sup>17</sup> Kaneda *et al.* suggested that the specific EGFR mutation L858R in exon 21 might be the main factor contributing to lung carcinogenesis in multiple lung cancers.<sup>18</sup> To our knowledge, this is the first report of EGFR mutation status in a patient with recurrent SP and thin-walled cysts associated with lung adenocarcinoma.

## Conclusion

The combination of bilateral SP and thin-walled cysts in association with lung cancer is rarely seen. Pneumothorax can be the first sign of lung cancer. These thin-walled cysts, with SP, may be confused with cystic benign lesions, such as LAM, PLCH, and bullae.

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## Disclosure

No authors report any conflict of interest.

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