



## CASE REPORT

# Pneumothorax triggered by EGFR-tyrosine kinase inhibitors in three microwave ablation candidates: A review of the literature

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## Keywords

Microwave ablation; non-small-cell lung cancer; pneumothorax; tyrosin kinase inhibitor.

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## Abstract

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are widely used in patients with *EGFR*-mutant lung cancer. Meanwhile, thermal ablation such as microwave ablation has been an option for selected patients. Herein, we describe three cases of pneumothorax that occurred in microwave ablation (MWA) candidates treated with EGFR-TKIs. The three patients developed pneumothorax in different periods: case 1 developed pneumothorax two months after MWA and subsequent gefitinib therapy; case 2 took osimertinib for two years and developed pneumothorax before MWA; case 3 took gefitinib for 13 months and experienced bronchopleural fistula after MWA. Although a causal relationship is uncertain, the risk of pneumothorax for these MWA candidates should be considered.

## Key points

- Microwave ablation candidates treated with epidermal growth factor receptor tyrosine kinase inhibitors are more likely to suffer pneumothorax.
- The risk of delayed pneumothorax or even bronchopleural fistula in patients pretreated with tyrosine kinase inhibitors should be taken into consideration when selecting patients and performing microwave ablations.

## Introduction

In recent years, image-guided percutaneous thermal ablation techniques including radiofrequency ablation, microwave ablation (MWA), and cryoablation, have evolved as minimally invasive treatment options for selected patients with inoperable lung cancer or those resistant to systemic therapy.<sup>1–4</sup> Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are widely used in patients with *EGFR* mutation. In this study, we reviewed three cases of pneumothorax that occurred in MWA candidates treated with EGFR-TKIs.

## Case report

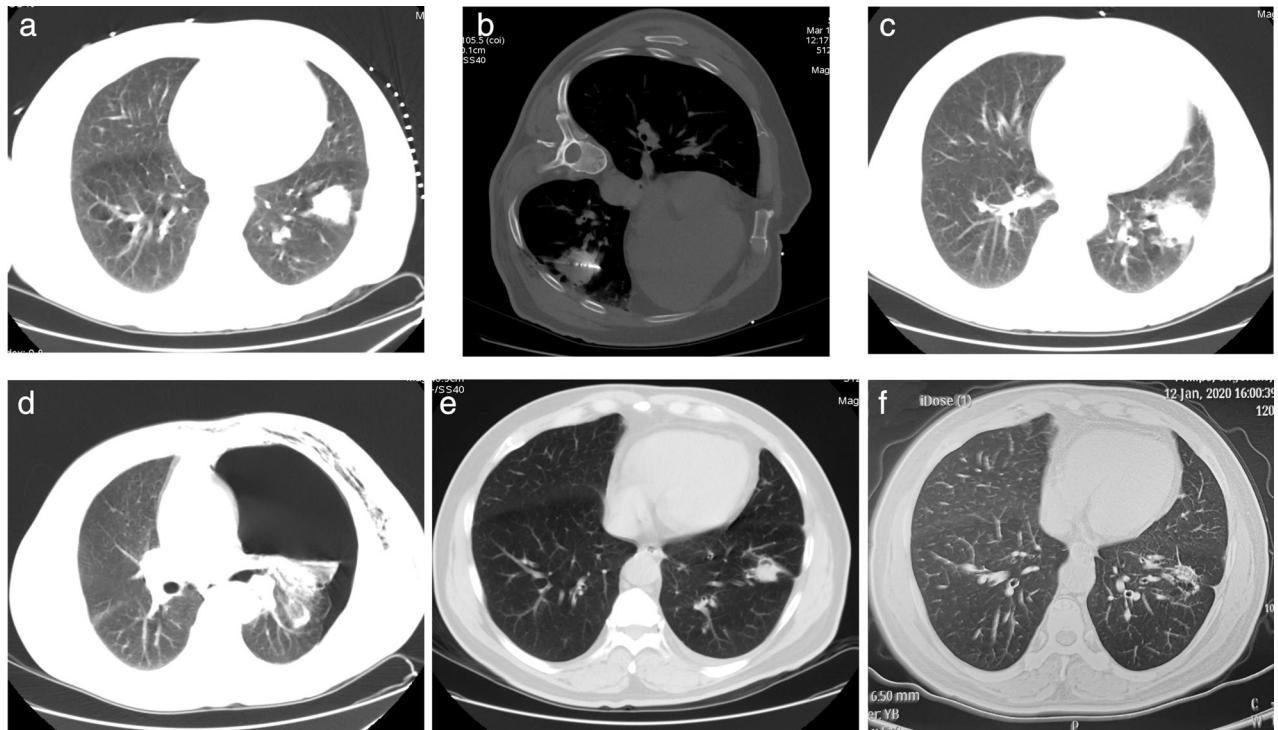
### Case 1

A 60-year-old male ex-smoker presented with an incidental left lower lobe round pulmonary nodule (3.2 × 3.0 cm)

(Fig 1a). A computed tomography (CT)-guided biopsy confirmed *EGFR*-mutant adenocarcinoma of the lung. The patient refused pulmonary resection and then received percutaneous MWA (Fig 1b,c). He subsequently received gefitinib. Two months after MWA, he complained of a brutal chest pain and noticed a swelling of his chest. A chest CT scan identified a 70% left-sided pneumothorax (Fig 1d). An eight French loop catheter was placed. The left lung re-expanded fully under low-negative pressure within 24 hours and remained fully expanded after two weeks (Fig 1e). Gefitinib was continued throughout. Follow-up chest CT at 10 months after MWA showed a shrinking fibrotic scar (Fig 1f).

### Case 2

A 69-year-old female non-smoker presented with cough and shortness of breath. A chest CT showed a right lung primary tumor and mediastinal lymph node metastasis.



**Figure 1** Case 1, a 60-year old male patient. (a) Chest computed tomography (CT) showed a left lower lobe round pulmonary nodule. (b) CT-guided microwave ablation (MWA) was subsequently performed. (c) Chest CT scan performed immediately after MWA. (d) CT confirmed left pneumothorax at two month assessment after MWA. (e) The left lung remained fully expanded without continuous drainage after two weeks. Cavitation and tumor shrinkage were observed. (f) Chest CT at 10 months post MWA showed the fibrotic scar was shrinking.

She refused biopsy or surgery. She was clinically diagnosed with lung cancer and received icotinib. After nine months, she was commenced on osimertinib due to disease progression. Her two-year assessment showed the lesion had grown (Fig 2a). On the day of the procedure, a chest CT scan demonstrated a 80% right-sided pneumothorax (Fig 2b). Continuous catheter (12 French) drainage under low-negative pressure was utilized. Four days later, the pneumothorax was relieved and a simultaneous CT-guided biopsy and MWA of the right lower lobe pulmonary nodule (2.5 × 2.0 cm) was performed (Fig 2c,d). The pathology confirmed that it was adenocarcinoma of the lung. She received bronchial arterial chemoembolization after two months.

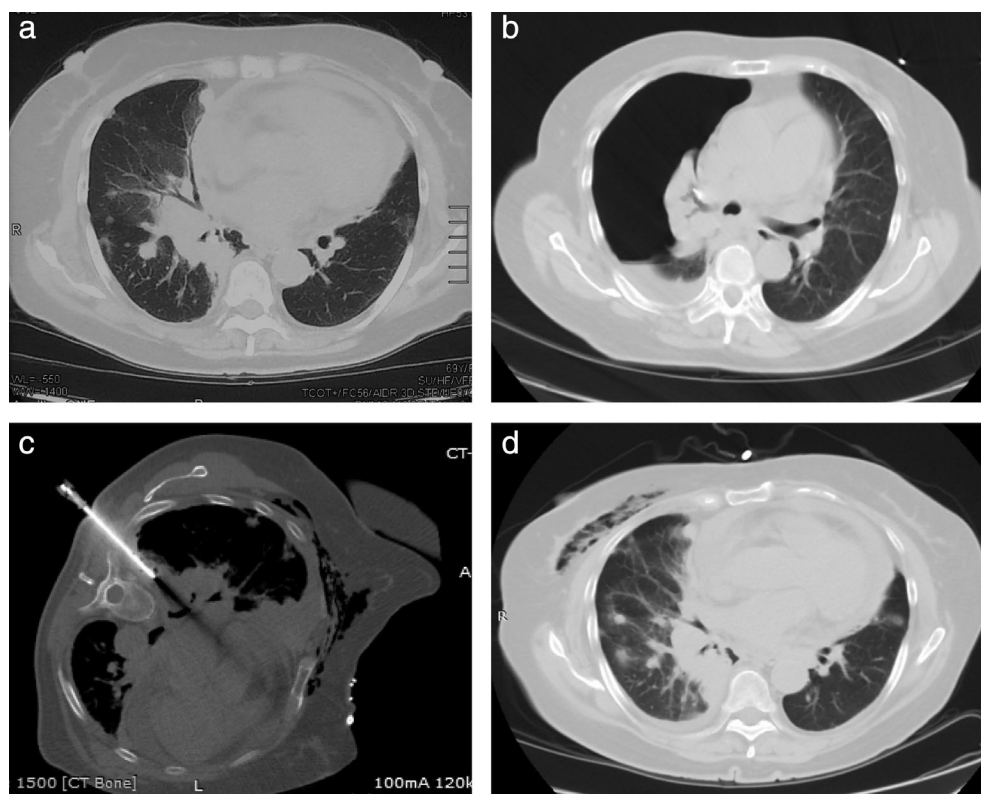
### Case 3

A 65-year-old male ex-smoker presented with complaints of facial numbness. A CT scan revealed a left pulmonary mass and two ground-glass opacities (GGOs) in the right lung. Subsequent biopsy confirmed *EGFR*-mutant adenocarcinoma of the lung. He was started on gefitinib treatment. Regular CT scans

demonstrated that the two GGOs had disappeared and that the left pulmonary lesion had shrunk and then grown after approximately 13 months (Fig 3a). The patient received simultaneous CT-guided repeat biopsy and MWA of the left pulmonary lesion (4.2 × 3.2 cm) (Fig 3b,c). The pathology confirmed that it was sarcomatoid carcinoma. After two weeks, dyspnea with fever was noted. The chest CT confirmed left pneumothorax and pleural effusion (Fig 3d). Two 10 French loop catheters were placed. CT scan showed bronchopleural fistula after 10 days (Fig 3e). Thus, one catheter was connected with water sealed bottle, and another was removed. The catheter was removed after a clamp test one month later (Fig 3f).

### Discussion

Pneumothorax is the most common complication after ablation, with an incidence of 10%–67%,<sup>4</sup> while pneumothorax as a result of response to anticancer therapy is rare in oncology and typically occurs in cases of metastatic carcinoma, especially in cases of sarcoma.<sup>5,6</sup> Although pneumothorax has been described in primary



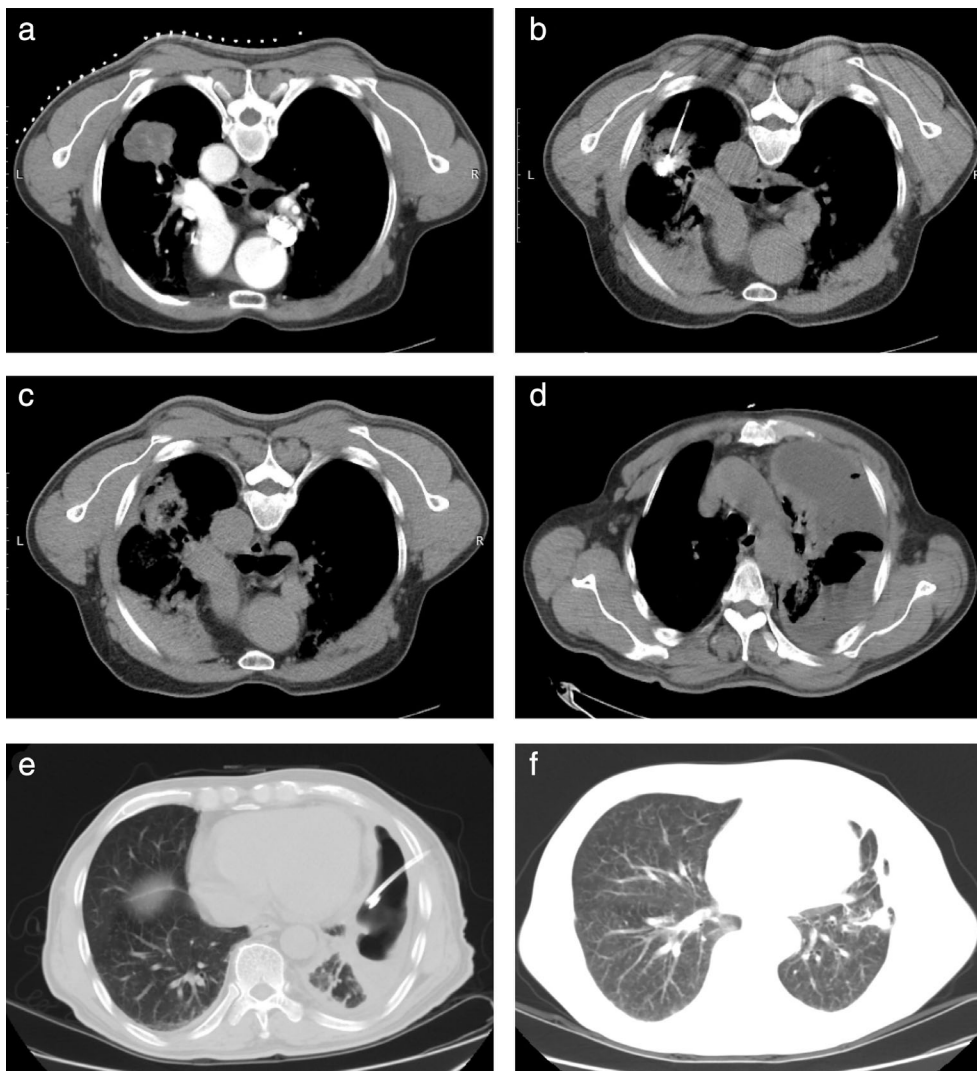
**Figure 2** Case 2, a 69-year old female patient. (a) CT scan showed that the right lung primary tumor and mediastinal lymph node metastasis had enlarged at the two-year assessment following osimertinib therapy. (b) A pneumothorax developed before MWA. (c) The pneumothorax was relieved after drainage, no cavitation or tumor progression was observed, and biopsy simultaneous with MWA was performed. (d) Catheter drainage was removed.

lung cancer on initial presentation or as a complication, they are very rarely associated with cytotoxic chemotherapy.<sup>7</sup> Tumor necrosis, check valve with compression of airway, tumor embolus, cavitary and pleural-based lung lesion, may contribute to the development of pneumothorax.<sup>8</sup> It has been suggested that cytotoxic agents and angiogenesis inhibitors may induce tumor necrosis and cavitations in lung lesions, which may be signs of clinical response but also be risk factors of rupture into the pleural cavity and the development of bronchopleural fistula during chemotherapeutic agents or EGFR-TKI treatment.<sup>9</sup> Pneumothorax during bevacizumab treatment, another angiogenesis inhibitor, is a frequent occurrence.<sup>10</sup> Moreover, pneumothorax during pazopanib, erlotinib, or crizotinib has also been reported,<sup>11</sup> with a rate of 14% among patients treated with pazopanib,<sup>12</sup> and 1% for advanced non-small cell lung cancer (NSCLC) patients treated with erlotinib.<sup>13</sup>

In our observation, the three patients had subpleural lung cancers. According to a recent study on thermal ablation for subpleural lung cancers, the rate of

pneumothorax was approximately 5%, and the tumor adjacent to pleura did not increase the risk.<sup>14</sup> However, EGFR-TKI could affect the growth and repair of epithelial cells, which may be one of the incentives. In addition, the timing or duration of EGFR-TKI therapies did not matter the results. Some patients may experience disease progression slowly during EGFR-TKI treatment and show disease-free survival benefits.<sup>15</sup> Local treatment might be an alternative option for selected patients who cannot tolerate the side-effects, afford new generation TKIs, or are resistant to current therapies. In our institution, intratumoral injection of hypertonic glucose is utilized to prevent post-procedure pneumothorax for high risk patients with neoadjuvant EGFR-TKI treatment. Hypertonic glucose can induce pleural aseptic inflammation and make two layers of pleura adhere together.<sup>16</sup>

In conclusion, here we report three cases of pneumothorax that occurred during EGFR-TKI treatment in MWA candidates with NSCLC. Although a causal relationship is uncertain, it is possible that the pneumothorax occurred due to EGFR-TKI treatment with/without



**Figure 3** Case 3, a 65-year old male patient. (a) CT scan demonstrated that a left pulmonary lesion grew after approximately 13 months of gefitinib treatment. (b) CT-guided repeat biopsy and MWA was performed. (c) Chest CT was performed immediately after MWA. (d) CT scan confirmed a left pneumothorax, pleural effusion and atelectasis after two weeks. (e) CT scan showed a bronchopleural fistula 10 days after chest drain insertion. (f) Catheter drainage was removed after one month, and the lesion gradually decreased in size.

MWA. Notably, according to our experience, the risk of pneumothorax, or even bronchopleural fistula may be higher in patients pretreated with EGFR-TKIs and this should be taken into consideration when selecting patients and performing MWA.

### Acknowledgments

Not applicable.

### Disclosure

The authors report that there are no conflicts of interest.

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