Metastatic breast cancer in primary lung cancer with compound *EGFR* mutations: A case report

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Abstract. The epidermal growth factor receptor (*EGFR*) is the most common driver gene in the development and progression of non-small cell lung cancer (NSCLC). Mutations in *EGFR* exons 18-21 are frequently observed, particularly exon 19 deletions and the exon 21 L858R point mutations. The T790M mutation in *EGFR* exon 20 was the first resistance mechanism to tyrosine kinase inhibitors (TKIs) identified in *EGFR*-mutant NSCLC. The coexistence of an exon 19 deletion and the exon 20 T790M missense mutation in *EGFR* is relatively rare, with a low incidence. The incidence of breast metastasis from primary lung cancer ranges from 0.5 to 6.0%, making it an infrequent occurrence. The present study reported a patient with primary NSCLC harboring both an *EGFR* exon 19 deletion and the exon 20 T790M missense mutations, who developed metastatic breast cancer after being progression-free for 1 month. Following the Chinese Society of Clinical Oncology and National Comprehensive Cancer Network guidelines for lung cancer, the patient was treated with furmonertinib, a third-generation targeted antitumor therapy. The present case provides notable insights for the diagnosis and treatment of NSCLC with coexisting *EGFR* exon 19 deletion and exon 20 T790M missense mutation, and a rare clinical example of breast metastasis from lung cancer.

Introduction

Lung cancer is currently one of the most common malignancies in humans, and its incidence and mortality rates ranking among the highest. The common symptoms of lung cancer are cough, dyspnea, pain and weight loss. The main risk factors of lung cancer include smoking, environmental exposure containing carcinogens and chronic obstructive pulmonary disease (1). The epidermal growth factor receptor (*EGFR*) gene is the most prevalent driver gene in patients with non-small cell lung cancer (NSCLC). Among patients with NSCLC harboring *EGFR* mutations, common mutations, such as EGFR exon 19 deletion and exon 20 T790M missense mutation, account for 75-80% of all cases. Rare *EGFR* mutations, which have an incidence rate of ~10%, are defined as mutations other than exon 19 deletions and exon 21 L858R substitutions (2).

Primary NSCLC metastasis to the breast is relatively rare, accounting for <0.5% of cases of NSCLC (3). This type of metastasis typically signifies disease progression and may be associated with drug resistance. The T790M mutation in *EGFR* exon 20 was the first resistance mechanism to tyrosine kinase inhibitors (TKIs) identified in *EGFR*-mutant NSCLC (4). Currently, *EGFR*-TKIs are considered the standard first-line treatment for patients with locally advanced or metastatic NSCLC harboring sensitizing *EGFR* mutations (5,6). The present case report mainly reports a typical case of rare gene mutation lung cancer that eventually metastasized to breast cancer, providing valuable clinical management experience and treatment ideas.

Case report

In August 2023, a 36-year-old female patient presented to a general physician in The People's Hospital of Tiantai County (Taizhou, China) with a cough and asthma that had persisted for >1 month. A lung CT scan (Fig. 1A) revealed a mass near the hilum of the right lung, suggesting a malignant tumor with partial atelectasis of the right lower lung. A thoracic puncture and drainage were performed. Cytopathology of centrifugal smears from the right pleural effusion and from bronchoalveolar lavage fluid-a diagnostic technique that analyzes fluid retrieved from the alveolar surface-revealed red blood cells, inflammatory cells and heterogeneous cell clusters, findings diagnostic for adenocarcinoma (Fig. 2). Genetic analysis (Data S1) detected an *EGFR* exon 19 deletion [c.2240$_2$254del; p.L747$_T$751del; variant allele frequency (VAF)=8.49%] and an exon 20 T790M mutation (c.2369C>T; p.T790M; VAF=10.53%). Following the Chinese Society of Clinical Oncology and National Comprehensive Cancer Network guidelines for lung cancer (7,8), the patient was

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treated with furmonertinib (80 mg once daily in the morning), a third-generation targeted antitumor therapy.

After 8 months of furmonertinib treatment (April 2024), a CT scan of the upper abdomen and pelvic cavity (Fig. 1B) indicated that the mass near the hilum of the right lung was markedly smaller compared with that at baseline, and the enlarged lymph nodes in the mediastinum were no longer detectable. Furthermore, the multiple small nodules in the right lung were reduced in size and the inflammation in both lungs had resolved. There was also notable improvement in the right lung cancer lymphadenitis, right pleural thickening and pleural effusion.

A right breast tumor was incidentally identified 1 month after a CT scan (June 2024). A color Doppler ultrasonography examination revealed a solid mass in the right breast, classified as Breast Imaging Reporting and Data System (BI-RADS) category 4A (Fig. 3A) (9). The right breast tumor was resected under local anesthesia. Based on postoperative pathology, immunohistochemistry (IHC) results and clinical history, the tumor was diagnosed as breast cancer secondary to a primary lung adenocarcinoma. An intravascular tumor thrombus was observed. IHC results (Data S1) demonstrated that the patient was positive for CK7, Ki-67 (~60% +), Napsin A and thyroid transcription factor 1 (TTF-1) and negative for estrogen receptor, progesterone receptor, CK5/6, Sox10, GATA binding protein 3, mammaglobin and HER2 (Fig. 4).

Asthma symptoms recurred 1 year after the first onset of illness (August 2024). Thin-layer CT and three-dimensional lung imaging (Fig. 1C) detected progressive atelectasis and a considerable right chest effusion. The right lung was not fully inflated and new inflammation was noted. Pleural fluid smears indicated cancer cells. Genetic analysis of the pleural effusion exhibited an *EGFR* exon 19 deletion and the exon 20 T790M missense mutation. The patient returned for a follow-up breast examination two months later, in August 2024. A breast color Doppler ultrasonography (August 2024) detected a solid mass of 2.25x1.12 cm in the upper quadrant of the right breast. The mass had blurred edges and was classified as BI-RADS category 5 (Fig. 3B). A physical examination indicated that the mass was hard and had poor mobility. After the patient's first diagnosis, follow-up was conducted every 2-3 months, with the last follow-up in February 2024. No other abnormalities were found during the follow-up. Therefore, based on the patient's medical history, recurrence of metastatic cancer after local resection is considered.

Discussion

The *EGFR* exon 20 T790M mutation was the first resistance mechanism to TKIs identified in *EGFR*-mutant NSCLC. In 2005, Kobayashi *et al* (4) reported a 71-year-old male patient with NSCLC treated with an *EGFR*-TKI. The patient achieved complete remission after gefitinib treatment but relapsed 2 years later. The researchers examined new biopsy samples and identified that, in addition to the *EGFR* exon deletion 19, the patient had developed an *EGFR* exon 20 T790M mutation, a C-T transformation in codon 790 in which threonine is replaced with methionine. Pao *et al* (10) analyzed samples from six patients with disease progression after *EGFR*-TKI treatment and detected the exon 20 T790M mutation in three of them. The researchers further compared the drug resistance of tumor cells with both L858R and T790M gene mutations with those with the L858R gene mutation alone. This comparison confirmed that the T790M mutation increased drug resistance by 100-fold. Among the various *EGFR* mutation types, the most common are in-frame deletions in exon 19 (19 del; ~44%), which encompass mutations such as L747 to E749 and the L858R point mutation in exon 21 (~41%) (11). Notably, tyrosine kinases exhibit reduced affinity to ATP in the presence of *EGFR* exon 19 del and L858R mutations. However, they have a relatively high affinity to *EGFR*-TKIs and, therefore, generate an antitumor effect (12). In the present case, the patient had both an *EGFR* exon 19 deletion and the exon 20 T790M missense mutation at baseline, which meant that both sensitive and drug-resistant mutations were present. A cohort study conducted by Hong *et al* (13) reported that the coexistence of these mutations negatively affected the efficacy of *EGFR*-TKIs. Their study enrolled 58 patients with advanced NSCLC and *EGFR* mutations. The mutation status in the circulating tumor DNA before TKI treatment was detected using next-generation sequencing technology. The associations between coexisting mutations and clinicopathological features, curative effects and survival time were analyzed. Their results demonstrated that the objective remission rate (44 vs. 77%), median progression-free survival (6.20 vs. 18.77 months) and median overall survival (22.70 months vs. not reached) of patients with coexisting mutations were markedly worse compared with those of patients without coexisting mutations. Coexisting mutations remained an independent prognostic predictor after multivariate analysis corrected for *EGFR* mutation subtypes and clinicopathological features (13).

The rarity and mechanism of breast metastasis secondary to a primary lung tumor have been reported in relevant literature. The incidence of breast metastasis from primary tumors outside the breast is 0.5-6.0% (14). A previous study of 6,668 patients with various malignant tumors, including lung cancer, liver cancer and kidney cancer, reported that the incidence of breast metastasis from solid malignant tumors was 0.76% (15). Of these cases, 16% were metastases from primary lung tumors. Another previous study identified 45 cases of secondary breast malignant tumor (0.56%) among 6,334 patients with breast cancer. The most common primary tumor source was lung cancer (33.3%) (16). The metastasis of cancer cells from the lungs to the breast can occur through the blood and lymph pathways (17). Huang *et al* (18) analyzed the path of lung cancer metastasis to the breast through the lymphatic system. They proposed that lung cancer cells spread onto the pleura, transferred to the axillary lymph nodes through the lymphatic system and then retrogradely transferred to the ipsilateral breast through the lymphatic vessels. Based on this hypothesis, patients may exhibit ipsilateral pleural thickening with pleural effusion, breast metastasis and axillary lymph node enlargement. This hypothesis was consistent with the characteristics of the present case. Ding *et al* (19) analyzed a case of lung cancer with contralateral breast metastasis. In such cases, tumor cells may have entered the lymphatic circulation or, through a vein, into the systemic circulation, delivering the tumor cells through the thoracic duct or blood circulation to the contralateral breast.

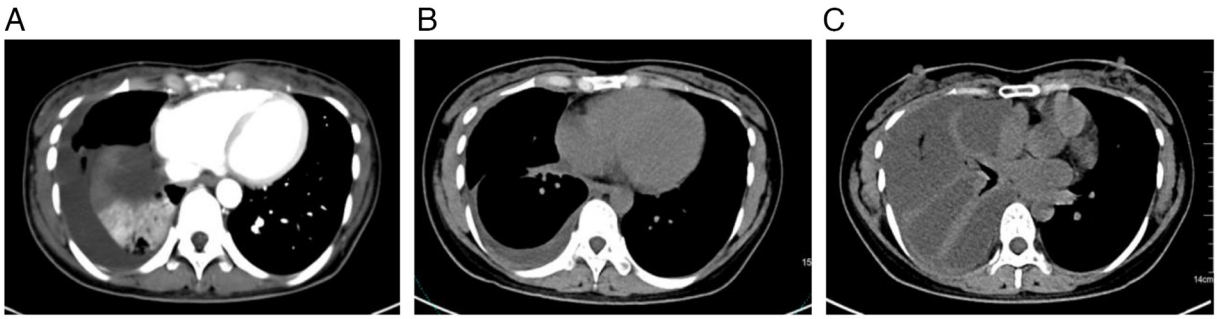

Figure 1. Imaging examination results of the disease course. (A) Baseline CT (August 2023): Mass shadow at hilum of lung, atelectasis of lower lobe of right lung, moderate effusion in right chest cavity. (B) After 8 months CT (April 2024): The mass shadow near the hilum of the right lung, the focus was markedly smaller compared with that at baseline. The multiple small nodules in the right lung were smaller compared with that at baseline and the inflammation of both lungs was basically absorbed. The right pleural thickening, pleural effusion, markedly improved compared with that at baseline. (C) CT at 1 year later (August 2024): Atelectasis is progressing and there is a lot of effusion in the right chest. The right lung is not fully inflated and the right lung is newly inflamed.

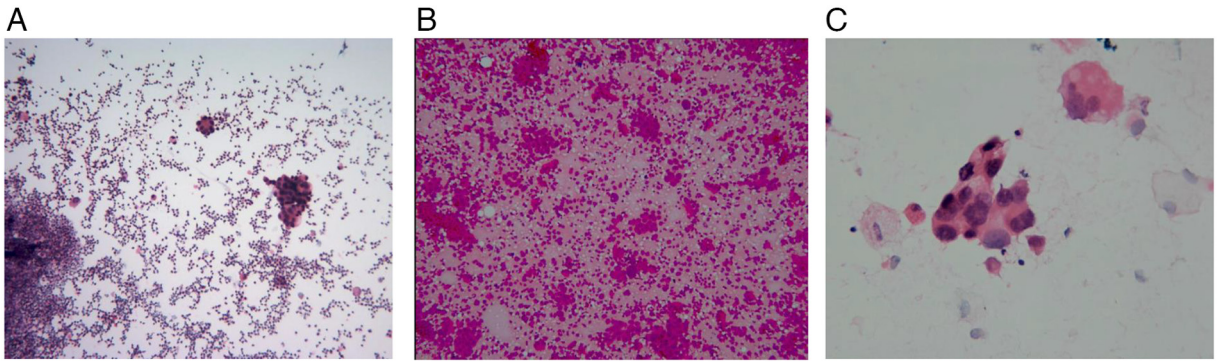

Figure 2. Cancer cells were identified in the smear of pleural effusion alveolar and lavage fluid, which tends to lung adenocarcinoma. (A) Low (magnification, x40), (B) medium (magnification, x100) and (C) high (magnification, x400).

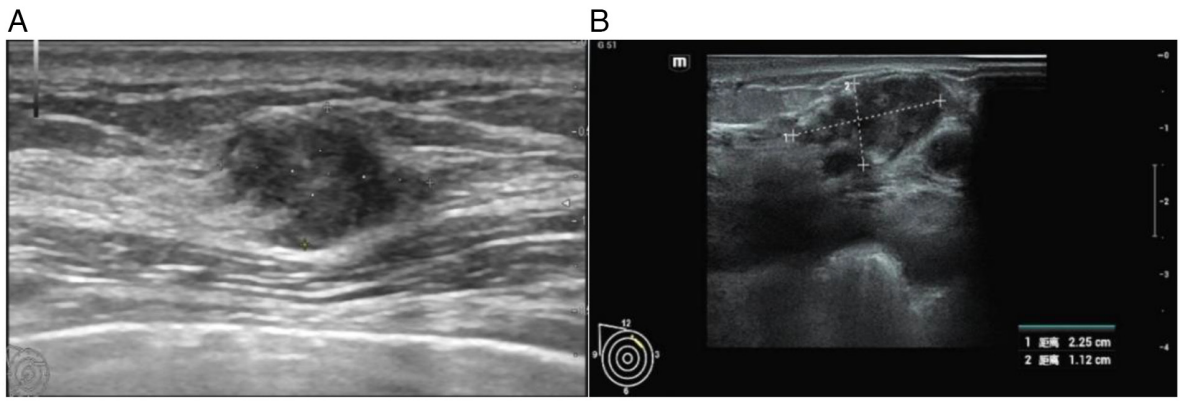

Figure 3. Color Doppler ultrasound results. (A) June 2024 Breast color Doppler ultrasound: Hypoechoic area of right breast, with unclear boundary and irregular shape. (B) August 2024 Breast color Doppler ultrasound: Blurred edge, irregular shape, blood flow signals around.

Regarding the differentiation between primary and secondary breast tumors, primary breast cancer often has fibrous connective tissue hyperplasia in the tumor area, while metastatic lesions lack this proliferative reaction. As a result, their size recorded during clinical examination is often similar to that observed in breast radiographs or ultrasonography (20). Metastatic tumors are more likely to occur in superficial positions than primary breast lesions and often do not cause clinical manifestations such as skin depression, possibly because metastatic tumors are often located outside the ductal system (21). These tumors often manifest as a palpable, painless, rapidly-growth mass with a clear boundary, mostly in the upper outer quadrant (22).

Radiologically, secondary breast metastasis lacks the structural distortion, burr and microcalcification observed in primary breast tumors. It also lacks the smooth outline of benign masses (for example, fibroadenoma or cyst) (23). The absence of carcinoma *in situ* is another characteristic of metastatic lesions (24). Histologically, almost all neuroendocrine tumors that have metastasized to the breast are

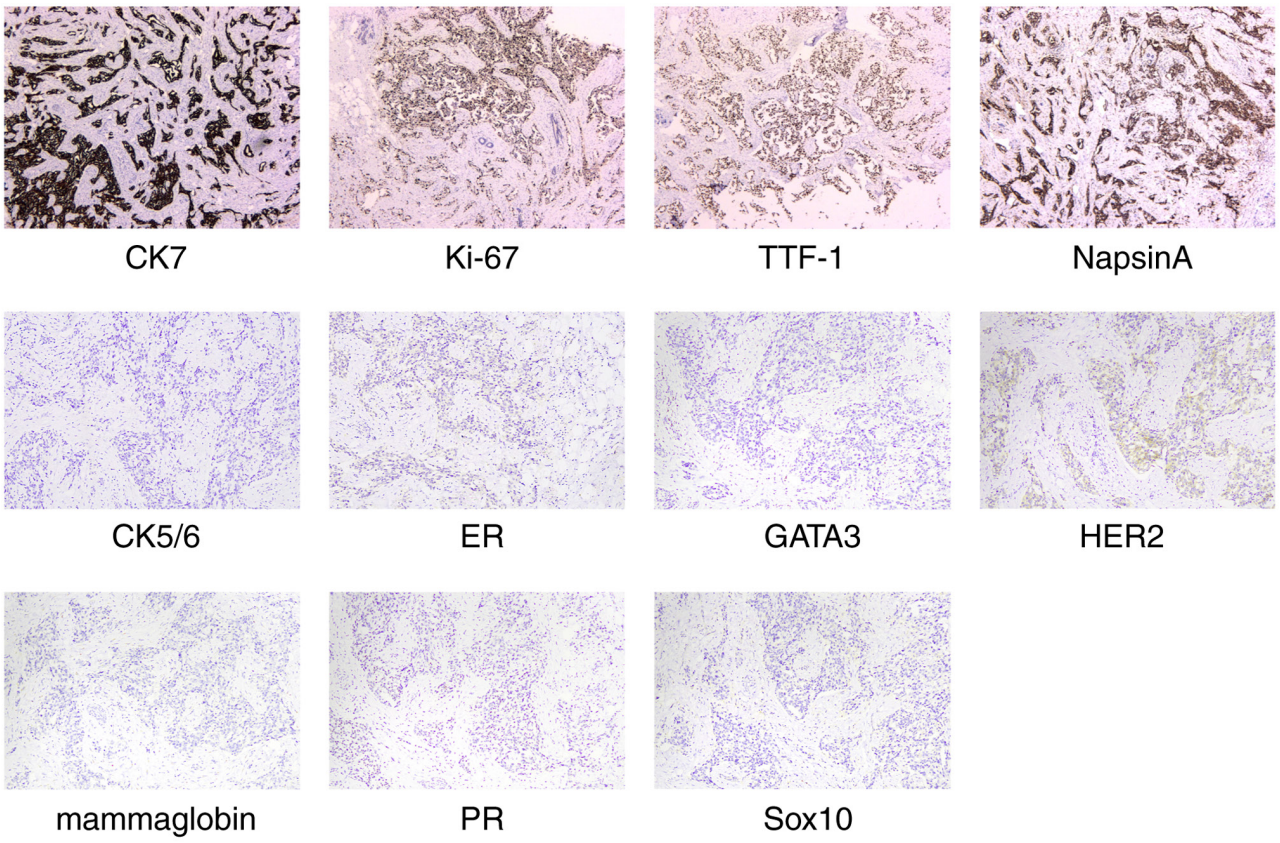

Figure 4. Immunohistochemical results: Positive for CK7, Ki-67 (~60%+), Napsin A and TTF-1 and negative for ER, PR, CK5/6, Sox10, GATA3, mammaglobin and HER2 (magnification, x200). ER, estrogen receptor; PR, progesterone receptor; GATA3, GATA binding protein 3; TTF-1, thyroid transcription factor 1.

strongly and diffusely positive for the neuroendocrine markers synaptophysin and chromaffin (25). Neuroendocrine metastases to the breast are often positive for TTF-1, while primary breast cancer is negative for TTF-1 (26). However, certain studies have reported TTF-1^{+} primary breast cancer. For example, previous studies summarizing the expression of TTF-1 in breast metastases of primary lung cancer identified 22 positive and four negative cases (27,28). These findings demonstrated that TTF-1 is a notable biomarker of lung cancer metastasis to the breast. In previous studies, increasing evidence has demonstrated that even metastatic carcinomas derived from the same primary tumor may exhibit divergent immunohistochemical profiles, largely attributable to tissue heterogeneity and potential alterations in receptor expression during metastatic progression (29-31). In the present case, the positivity for TTF-1 and Napsin A, both highly specific markers of pulmonary origin, along with the absence of breast-specific markers, markedly supports a lung origin for the breast lesions (32). Therefore, TTF-1 immunoreactivity should not be ignored in the pathological examination of breast lesions from patients with a known history of lung cancer.

In conclusion, although breast metastasis of lung cancer is rare, accurate diagnosis, clear staging and a correct treatment plan are of notable clinical significance. If breast nodules are identified in patients with malignant lung tumors, screening is suggested to avoid misdiagnosis. It is particularly key to identify the source of tumors by combining medical imaging and IHC results.

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Availability of data and materials

All data related to gene sequencing can be found in the Mendeley Data database (doi: 10.17632/wpw7mstpp8.1) at the following URL: https://data.mendeley.com/datasets/wpw7mstpp8/1. The rest of the data generated in the present study may be requested from the corresponding author.

Authors' contributions

FW conceptualized the present case report. XL devised the methodology. GC performed the follow-up collection of the patient data and validated the data. TY conducted the formal analysis. YX conducted the patient follow-up and wrote the original draft. All authors read and approved the final manuscript. TY and FW confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The present study was approved by Ethics Committee of Tiantai Hospital [approval no. Ethical Review 2025 Other No.

(014); Taizhou, China]. The patient in the present case report agreed to participate in the present study.

Patient consent for publication

The patient in the present case report provided written informed consent for publication of the present study.

Competing interests

The authors declare that they have no competing interests.

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