Rare sequential EGFR and ALK mutations in non-small cell lung cancer: A case report and literature review

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Abstract. In non-small cell lung cancer, the two main genetic alterations are epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) rearrangements. The presence of both mutations in a single patient or genetic mutation discrepancies between primary tumors and metastases is uncommon. Therefore, at present, there are no guidelines on the optimal approach and treatment for this group of patients. This report presents the case of a 58-year-old woman with EGFR-mutated regional lung cancer who underwent surgery followed by adjuvant chemotherapy. Upon disease recurrence, the response to EGFR-tyrosine kinase inhibitor therapy was poor. Further analysis of metastatic pleural fluid revealed an ALK mutation. The patient was then treated with anti-ALK therapy, resulting in long-term disease stability. In conclusion, the coexistence of EGFR and ALK mutations in lung cancer is rare, likely due to tumor heterogeneity and prior treatments. Resistance to targeted therapies can develop through new molecular alterations during disease progression. Re-biopsies at progression are crucial for detecting these changes and optimizing treatment based on the updated molecular profile.

Introduction

According to GLOBOCAN 2022 statistics, lung cancer has the highest incidence and mortality rate in both men and women (1). Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for 80-85% of cases (2). In recent years, the advent of targeted therapies for NSCLC has significantly improved the survival of patients, with 5-year survival rates for patients with EGFR mutations reaching 30-40% and for ALK-positive patients achieving 50-60%, compared with 5-year survival rates of only 5-10% in the pre-targeted therapy era (3-5). Epidermal growth factor receptor (EGFR) has the highest proportion, occurring in 45% of Asian patients and 20% of Caucasian patients with adenocarcinoma histology (6). In these patients, EGFR-tyrosine kinase inhibitors (TKIs) are indicated as the first-line treatment. Classical activating mutations (exon 19 deletions and the L858R point mutation) account for most EGFR mutations and are strong predictors for a good response to EGFR-TKIs (7). By contrast, 10-20% of patients with NSCLC harbor uncommon or rare EGFR mutations, including G719X (Exon 18), L861Q (Exon21) and S768I (Exon 20), which have lower response rates (8). Anaplastic lymphoma kinase (ALK) rearrangement is less common than EGFR mutation and is found in ~5% of patients with NSCLC (9). ALK-TKIs are the optimal first-line treatment for individuals with ALK rearrangement. The simultaneous or sequential appearance of both mutations (EGFR and ALK) in a patient is rare, as it is considered mutually exclusive. This raises questions regarding the appropriate time and specimens for investigation, as well as optimal treatment options for these patients. In the present report, the case of a patient with simultaneous EGFR and ALK mutations is detailed.

Case report

Patient. A 58-year-old asymptomatic female patient, with no past medical history, was admitted with a left upper lung cancer with the pathology of adenocarcinoma on a routine health check in November 2017 at E Hospital (Hanoi, Vietnam). The patient underwent laparoscopic surgery to remove the left upper lobe of the lung, lymph node dissection and then 6 cycles of adjuvant chemotherapy [paclitaxel 175 mg/m^2 and carboplatin area under the curve (AUC) 5 every 21 days]. PCR combined with molecular probe hybridization of the tumor specimens was performed to detect gene mutations, revealing a G719C mutation on exon 18. The patient was then periodically monitored every 3 months.

In May 2020, the disease recurred at the left chest wall nodule and left internal mammary nodes. The patient's clinical examination was normal. The patient received chemoradiotherapy (33 fractions at 1.8 Gy) concurrent with

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paclitaxel 50 mg/m^2 and carboplatin AUC 2 (repeated weekly for 6 weeks), followed by consolidation chemotherapy of paclitaxel 200 mg/m^2 and carboplatin AUC 6 (repeated every 3 weeks for 2 cycles) at Vinmec Hospital (Hanoi, Vietnam).

In September 2020, the patient was transferred to Hanoi Medical University Hospital (Hanoi, Vietnam), and a chest CT scan performed 2 months after chemoradiation showed an upper lobectomy, pleural thickening with enhanced nodule measuring 18x40 mm with no abnormal mediastinal lymph nodes and no bilateral pleural effusion (Fig. 1). The patient was further treated with a second-generation EGFR-TKI drug, afatinib (40 mg once a day, 1 h before food or 3 h after food). After 3 months of treatment, in December 2020, the patient developed rapidly increasing dyspnea and the disease progressed with a large amount of pleural effusion. A CT scan image showed irregular left pleural thickening, a large left pleural effusion of 75 mm causing passive atelectasis, a left chest wall enhancing nodule of 15x13 mm, pericardial fluid of 16 mm and no unusual mediastinal lymph nodes (Fig. 2). The patient then underwent a pleural puncture to reduce the difficulty breathing and to collect specimens for testing. The cell block from the left pleural effusion, stained with hematoxylin and eosin (H&E), revealed cells arranged in clusters resembling glandular structures. These cells displayed large, basophilic nuclei and a high nucleus-to-cytoplasm ratio, raising a strong suspicion of adenocarcinoma (Fig. 3). However, other differential diagnoses, including reactive mesothelial cells and mesothelioma, needed to be excluded. To clarify the diagnosis, additional immunohistochemical staining was performed. The tumor cells demonstrated positivity for epithelial markers such as CK7 and lung adenocarcinoma markers such as transcription termination factor 1 (TTF-1), while being negative for mesothelial markers such as calretinin. These findings confirmed the diagnosis of metastatic lung adenocarcinoma with associated pleural effusion (Fig. 4).

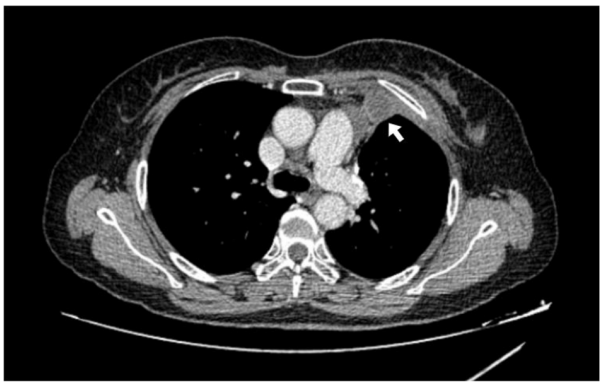

Figure 1. Chest CT scan 2 months after chemoradiation. The white arrow indicates nodular pleural thickening.

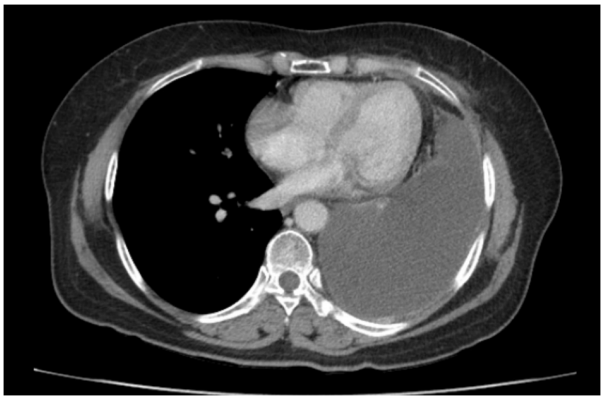

Figure 2. Chest CT scan 3 months after epidermal growth factor receptor-tyrosine kinase inhibitor therapy. A large amount of left pleural effusion was noted.

Gene mutation testing on pleural fluid specimens using the new-generation gene sequencing method (test performed by the Medical Genetics Institute using the Miseq system; Illumina, Inc.) detected the ALK-EMAP like 4 (EML4) fusion mutation. The patient was then switched to the second-generation ALK-TKI drug, ceritinib (450 mg, once a day on an empty stomach, at least 2 h before or after food), and re-evaluated every 3 months Fig. 5 shows the CT scan obtained after the first 3 months of ceritinib treatment, indicating a significant reduction in pleural effusion. During the first month of taking ceritinib, the patient had diarrhea, but it was mild and intervention was not indicated. After that, the patient tolerated the drug well, with no further side effects noted. Since then, the disease has responded well to treatment and has become stable. Fig. 6 displays the most recent follow-up CT scan after 50 months of receiving ceritinib, showing that the amount of pleural effusion has remained nearly unchanged with no evidence of disease progression. The diagnostic, treatment and response of the patient are summarized in Fig. 7.

Histopathological and immunohistochemical analysis protocol. The specimen consisted of 200 ml of pleural fluid (sent to the pathology laboratory) and was stored at 4˚C. The specimen was allowed to sediment naturally for 10 h, after which the supernatant was discarded and the sediment was collected. The sediment was transferred to test tubes (15x45 mm), then centrifuged for 10 min at 447 x g and room temperature. The supernatant was removed and the sediment was fixed in 10% neutral buffered formalin (NBF) at room temperature for 5 h, with a volume ratio of NBF to sediment of 10:1. Next, the sample was again centrifuged for 10 min at 447 x g and room temperature and then incubated at 55˚C for 1 h. After fixation, the specimen formed a firm pellet that was easily retrievable, which was wrapped in non-adhesive paper and placed in a cassette for routine histopathological processing and embedding within paraffin. Then, 3-5 μm-thick sections were cut from the paraffin block using a microtome and stained with H&E at room temperature for 30-45 min. Immunohistochemical staining of CK7, CK20, TTF-1 and calretinin (Table I) was also performed using the fully automated DAKO Omnis immunostaining system from Agilent Technologies, following the manufacturer's protocol, with both positive and negative controls included. The H&E and immunohistochemically stained slides were examined under a light optical microscope.

Discussion

In the present study, the patient was initially diagnosed with local regional lung cancer and underwent surgery followed by

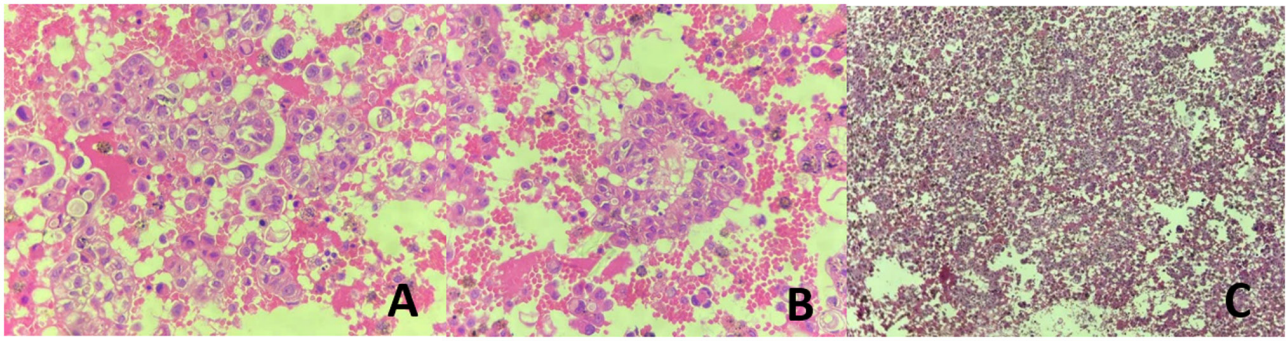

Figure 3. Hematoxylin and eosin staining of the left pleural effusion cell block. (A) High-magnification view showing clusters of malignant cells with glandular formation, large basophilic nuclei and a high nucleus-to-cytoplasm ratio (magnification, x40). (B) High-magnification field demonstrating similar cytological features (magnification, x40). (C) Low-magnification view showing the overall architecture of the cell block with tumor cell clusters in a background of fibrin and inflammatory cells (magnification, x10).

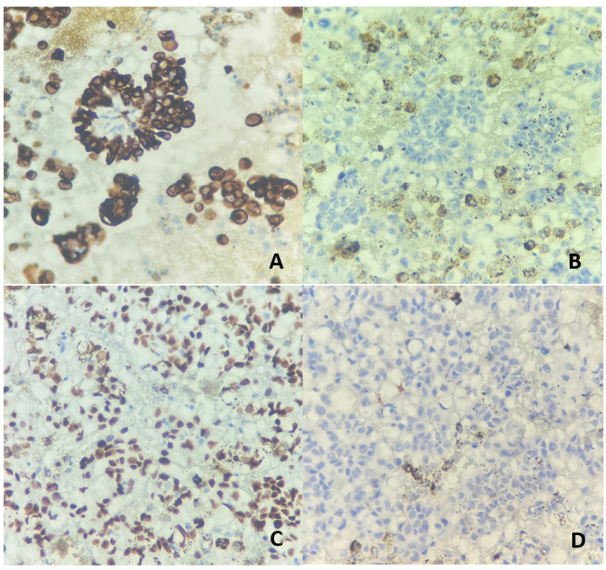

Figure 4. Immunohistochemical staining of the histological biopsy from the left pleural fluid cell block. Cells are arranged in clusters with epithelioid morphology suggesting glandular, papillary structures; the cells exhibit large, basophilic nuclei and a high nucleus-to-cytoplasm ratio. (A) Cluster tumor cells showing strong CK7 expression, confirming epithelial origin (magnification, x40). (B) Tumor cells showing a loss of CK20 expression (magnification, x40). (C) Atypical epithelioid cells exhibiting strong nuclear transcription termination factor 1 expression, indicative of lung adenocarcinoma (magnification, x40). (D) Absence of calretinin expression, ruling out mesothelial differentiation (magnification, x40).

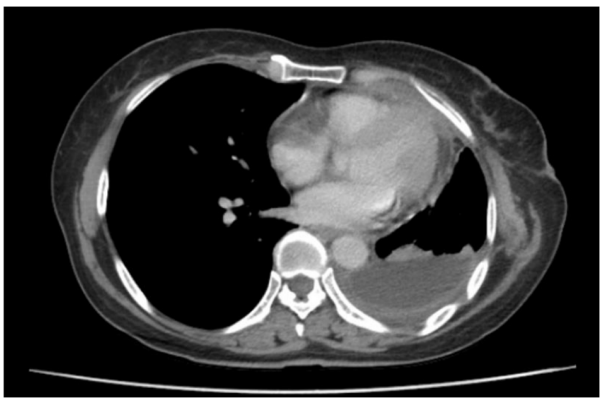

Figure 5. Chest CT scan after the first 3 months of treatment with anaplastic lymphoma kinase-tyrosine kinase inhibitor. The pleural fluid was notably decreased.

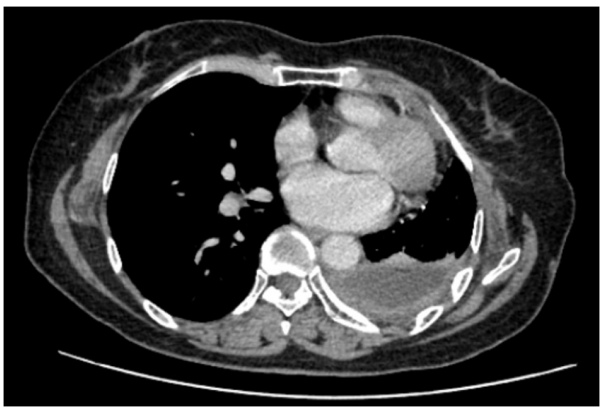

Figure 6. Chest CT scan collected February 2025 (stable disease for 50 months).

adjuvant chemotherapy. Subsequent analysis of the post-operative tumor specimen revealed an EGFR gene mutation, specifically G719C mutation, which is relatively rare compared with the more common EGFR mutations such as exon 19 deletions and L858R. The G719C mutation, along with other exon 18 mutations (such as G719S and G719A), accounts for 3-5% of all EGFR mutations in NSCLC (10). With first-generation TKIs, patients with G719C and similar exon 18 mutations exhibit response rates of 30-50%, with progression-free survival (PFS) times shorter than those typically observed in patients with exon 19 deletions or L858R mutations. Afatinib has shown improved efficacy for uncommon mutations, including G719C. Clinical data suggest that afatinib provides higher response rates and a longer PFS time for G719 mutations compared with first-generation TKIs (11-13). Although primarily used for T790M resistance mutations, some studies suggest that osimertinib may also have activity against G719C. However, afatinib tends to be the preferred option in clinical practice for this mutation, owing to more robust data on uncommon mutations (13,14). In the present study, upon disease recurrence, the response to EGFR-TKI was notably poor, marked by the development of pleural effusion within the first 3 months.

Table I. Primary antibodies used in immunohistochemistry.

Primary antibody	Clone	Supplier	Cat. no.	Dilution
CK7 (monoclonal)	OV-TL12/30	Dako (Agilent Technologies, Inc.)	M7018	1:250
CK20 (monoclonal)	K_s20.8	Dako (Agilent Technologies, Inc.)	M7019	1:250
TTF-1 (monoclonal)	8G7G3/1	Dako (Agilent Technologies, Inc.)	M3575	1:100
Calretinin (monoclonal)	DAK-Calret 1	Dako (Agilent Technologies, Inc.)	M7245	1:100

TTF-1, transcription termination factor 1.

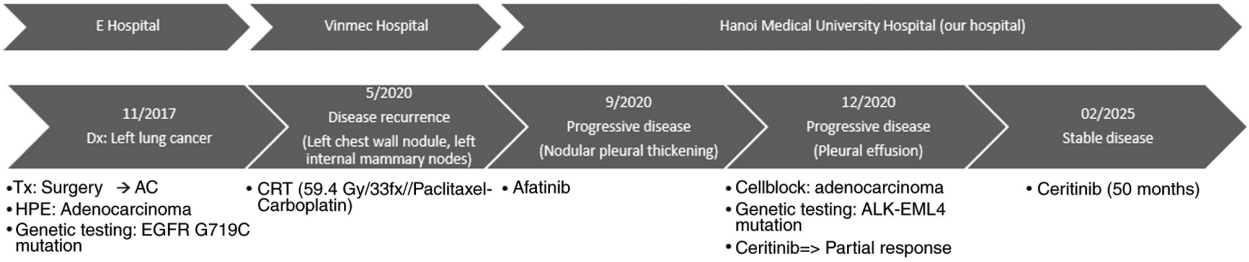

Figure 7. Clinical course of the diagnosis and treatment history of the patient. Dx, diagnosis; Tx, treatment; AC, adjuvant chemotherapy; HPE, histopathologic examination; EGFR, epidermal growth factor receptor; CRT, chemoradiotherapy; ALK, anaplastic lymphoma kinase; EML4, EMAP like 4.

This prompted the conduction of a genetic mutation test on pleural fluid specimens. Notably, EGFR gene mutations were not detected; instead, ALK mutations were identified. Based on these findings, the patient was treated with anti-ALK drugs and achieved long-term disease stability.

This change in gene mutation status at different times could be explained by the influence of chemicals on genetic mutation. In patients with advanced disease stages, it is crucial to prioritize EGFR mutation detection before initiating systemic therapy. However, the efficacy of TKI therapy as a second-line treatment appears to be inferior to that as a first-line treatment, suggesting a potential change in gene mutation status due to the influence of chemicals. A study by Bai *et al* (15) showed that chemicals (such as platinum-based chemotherapy) can initially significantly reduce the frequency of EGFR mutations in tumor tissue and plasma. Among 264 patients with advanced NSCLC, plasma EGFR mutations were found in 34.5% of samples collected before 2 chemotherapy cycles, but only in 23.1% of the post-chemotherapy plasma samples. Honda *et al* (16) also reported the case of a Japanese woman with the disappearance of an activated EGFR mutation in malignant pleural effusion after treatment with chemotherapy and TKIs. Therefore, chemotherapy and TKI treatment may have influences on gene mutation status, and thus, EGFR mutation status collected from the initial specimens might be inadequate for predicting the efficacy of TKI treatment in subsequent lines.

After failure with first- or second-generation EGFR-TKIs, clinicians typically utilize liquid biopsies to detect drug-resistant mutations, such as T790M, or identify other gene mutations with lower frequencies. Liquid biopsy, primarily through the analysis of circulating tumor DNA, offers a non-invasive approach to monitor tumor dynamics and emerging resistance mutations. For example, Iwama *et al* (17) demonstrated that an increase in EGFR-activating mutation alleles in plasma during treatment was correlated with disease progression, underscoring the value of liquid biopsy in predicting EGFR-TKI efficacy and assessing clonal evolution. Beyond detecting EGFR mutations in lung cancer, liquid biopsy has expanded to identify various other genetic alterations, including mutations in KRAS and BRAF as well as ALK rearrangements (18). Qvick *et al* (19) demonstrated that liquid biopsy could detect mutations in KRAS and BRAF, which were not identified in tumor tissue samples, highlighting its potential to uncover additional actionable mutations. In summary, liquid biopsy is a powerful tool for identifying a broad range of genetic mutations in lung cancer, such as KRAS, BRAF and ALK rearrangements, while also providing insights into epigenetic changes and copy number alterations (20,21). This broad utility enhances its role in personalized treatment strategies and monitoring therapeutic resistance.

In the early years following their discovery, the two main genetic alterations, EGFR mutations and ALK rearrangements, were previously believed to be mutually exclusive (13-15). A study indicated that ALK rearrangements were more frequently found in patients with poorly differentiated adenocarcinoma, while EGFR mutations were more typically found in well-differentiated cancer (22). Similarly, the coexistence of KRAS mutations with either of these alterations was considered nearly impossible (23,24). As a result, the initial algorithms for biomolecular characterization of non-squamous NSCLC recommended testing samples for KRAS mutations first, followed by EGFR testing only if KRAS was wild-type (24). ALK testing was reserved for cases where no alterations were detected in the prior tests. However, further studies have shown that the coexistence of EML4-ALK rearrangements and EGFR

mutations, though uncommon, is possible, as is the presence of KRAS and other mutations (22,25-28). Therefore, the previously established diagnostic algorithm can no longer be the gold standard. Recent studies and reports have shown that the simultaneous appearance of both EGFR and ALK is uncommon (0.1-1.6%) (27,28). Intratumor heterogeneity, defined as the presence of sub-clonal diversities of cells within a lung tumor, may explain the occurrence of multiple genetic alterations concurrently. Nonetheless, the clinical and pathological characteristics of these patients have not been fully described, and the optimal treatment approach for this patient group is unclear. Hu *et al* (28) reported a clinical case with concomitant EGFR mutation and ALK rearrangement, progression on osimertinib and partial response to alectinib. Recently, there have been studies reporting similar cases in which 107 patients harboring both EGFR mutation and ALK rearrangement have been documented, revealing variable responses to treatment (28,29). The summary from these reports indicated a reduced overall response rate (ORR) to EGFR-TKIs, whereas patients receiving ALK-TKIs demonstrated an improved ORR. Due to the variability in response, and since there are no clinical guidelines for choosing the optimal targeted therapies in this specific group of patients, further research is required to gain an improved understanding and explore potential combination or sequential therapy strategies. Although there is no consensus in the literature, ALK-TKIs appear to be marginally more effective than EGFR-TKIs in patients with both EGFR and ALK alterations. Disease control and response has been reported as the best outcome in 69.8 and 43.4% of cases treated with EGFR-TKIs, compared with 79.5 and 51.3% of cases treated with ALK-TKIs, respectively (30,31). However, due to the limited number of evaluable patients, definitive conclusions cannot be drawn. Following a literature review of 100 cases, ALK-TKIs may be considered the preferred first-line treatment, provided no other data are available to guide the therapeutic decision (32). A potential future approach could involve investigating the safety and efficacy of dual inhibition of both ALK and EGFR, as these alterations may coexist in some patients. Designing clinical trials specifically targeting this patient subset would be a valuable step toward addressing several unanswered questions. However, due to the rarity of this condition, recruiting a sufficient number of patients would likely be a notable challenge. Assuming that there is consistency in mutation status across specimens (primary tumor and malignant pleural fluid), the transformation of EGFR gene mutations from positive to negative with the appearance of new ALK rearrangement is extremely rare. To the best of our knowledge, no other similar clinical cases have been reported. This raises questions about the appropriate time and specimens to survey genetic mutations.

Tumor heterogeneity serves a notable role in the diversity of tumor mutation status. There have been different levels of heterogeneity in cancer: Interpatient, intratumor and intertumor (28). Generally, patients with NSCLC harboring targetable driver mutations respond well to specific inhibitors. However, some patients show poor or mixed responses to targeted therapy, which may be explained by intertumor molecular heterogeneity (28,32). In the literature, several lung cancer studies have reported differences in EGFR and ALK mutational status between primary and metastatic sites (22-25). Several different models have been proposed to explain this difference in genetic profile. A classic model states that primary tumor cells have a low metastatic potential, so the accumulation of enough genetic mutations will promote metastasis (32). Besides, there can be inconsistencies between genetic testing methods, as in the present case, two gene mutation tests were performed using two different methods (32,33).

In conclusion, the simultaneous or sequential appearance of EGFR/ALK mutation in lung cancer is very rare. This can be explained by tumor heterogeneity and the effects of chemotherapy. The approach and treatment need to be individualized and remain a clinical challenge. According to reports, EGFR mutations, ALK translocations and various other biomolecular alterations can emerge during disease progression as mechanisms of acquired resistance following treatment with EGFR and ALK-TKIs (33,34). Therefore, whenever technically feasible, it is essential to perform re-biopsies in all patients with disease progression to identify any new alterations and tailor subsequent therapies based on the updated biomolecular profile.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author. The next-generation sequencing data generated in the present study are not publicly available due to ethical and confidentiality restrictions but may be requested from the corresponding author.

Authors' contributions

HVN is the clinical oncologist who treated the patient and revised the manuscript. CHD is the assistant doctor who wrote the manuscript and made contributions to the conception of the study. BTT and HLT assisted in the patient treatment, collected clinical information and assisted with the drafting of the manuscript. HVN and CHD confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent for the publication of this study was obtained from the patient.

Competing interests

The authors declare that they have no competing interests.

References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I and Jemal A: Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 74: 229-263, 2024.
2. Zhou YJ, Zheng W, Zeng QH, Ye Y, Wang C, Fang C, Liu CJ, Niu L and Wu LM: Targeted exome sequencing identifies mutational landscape in a cohort of 1500 Chinese patients with non-small cell lung carcinoma (NSCLC). Hum Genomics 15: 21, 2021.
3. Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, Zhu J and Johnson DH; Eastern Cooperative Oncology Group: Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 346: 92-98, 2002.
4. Camidge DR, Dziadziuszko R, Peters S, Mok T, Noe J, Nowicka M, Gadgeel SM, Cheema P, Pavlakis N, de Marinis F, *et al*: Updated efficacy and safety data and impact of the EML4-ALK fusion variant on the efficacy of alectinib in untreated ALK-positive advanced non-small cell lung cancer in the global phase III ALEX study. J Thorac Oncol 14: 1233-1243, 2019.
5. Ramalingam SS, Vansteenkiste J, Planchard D, Cho BC, Gray JE, Ohe Y, Zhou C, Reungwetwattana T, Cheng Y, Chewaskulyong B, *et al*: Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. N Engl J Med 382: 41-50, 2020.
6. Zhang YL, Yuan JQ, Wang KF, Fu XH, Han XR, Threapleton D, Yang ZY, Mao C and Tang JL: The prevalence of EGFR mutation in patients with non-small cell lung cancer: A systematic review and meta-analysis. Oncotarget 7: 78985-78993, 2016.
7. Grigoriu B, Berghmans T and Meert AP: Management of EGFR mutated nonsmall cell lung carcinoma patients. Eur Respir J 45: 1132-1141, 2015.
8. Harrison PT, Vyse S, Huang PH: Rare epidermal growth factor receptor (EGFR) mutations in non-small cell lung cancer. Semin Cancer Biol 61: 167-179, 2020.
9. Jahanzeb M, Lin HM, Pan X, Yin Y, Wu Y, Nordstrom B and Socinski MA: Real-world treatment patterns and progression-free survival associated with anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor therapies for ALK+ non-small cell lung cancer. Oncologist 25: 867-877, 2020.
10. Xu H, Yang G, Li W, Li J, Hao X, Xing P, Yang Y and Wang Y: EGFR exon 18 mutations in advanced non-small cell lung cancer: A real-world study on diverse treatment patterns and clinical outcomes. Front Oncol 11: 713483, 2021.
11. Zhang T, Wan B, Zhao Y, Li C, Liu H, Lv T, Zhan P and Song Y: Treatment of uncommon EGFR mutations in non-small cell lung cancer: new evidence and treatment. Transl Lung Cancer Res 8: 302-316, 2019.
12. Heigener DF, Schumann C, Sebastian M, Sadjadian P, Stehle I, Märten A, Lüers A, Griesinger F and Scheffler M; Afatinib Compassionate Use Consortium (ACUC): Afatinib in non-small cell lung cancer harboring uncommon EGFR mutations pretreated with reversible EGFR inhibitors. Oncologist 20: 1167-1174, 2015.
13. Sehgal K, Rangachari D, VanderLaan PA, Kobayashi SS and Costa DB: Clinical benefit of tyrosine kinase inhibitors in advanced lung cancer with EGFR-G719A and other uncommon EGFR mutations. Oncologist 26: 281-287, 2021.
14. Russo A, Franchina T, Ricciardi G, Battaglia A, Picciotto M and Adamo V: Heterogeneous responses to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in patients with uncommon EGFR mutations: New Insights and future perspectives in this complex clinical scenario. Int J Mol Sci 20: 1431, 2019.
15. Bai H, Wang Z, Chen K, Zhao J, Lee JJ, Wang S, Zhou Q, Zhuo M, Mao L, An T, *et al*: Influence of chemotherapy on EGFR mutation status among patients with non-small-cell lung cancer. J Clin Oncol 30: 3077-3083, 2012.
16. Honda Y, Takigawa N, Fushimi S, Ochi N, Kubo T, Ozaki S, Tanimoto M and Kiura K: Disappearance of an activated EGFR mutation after treatment with EGFR tyrosine kinase inhibitors. Lung Cancer 78: 121-124, 2012.
17. Iwama E, Sakai K, Azuma K, Harada T, Harada D, Nosaki K, Hotta K, Ohyanagi F, Kurata T, Fukuhara T, *et al*: Monitoring of somatic mutations in circulating cell-free DNA by digital PCR and next-generation sequencing during afatinib treatment in patients with lung adenocarcinoma positive for EGFR activating mutations. Ann Oncol 28: 136-141, 2017.
18. Nagasaka M, Uddin MH, Al-Hallak MN, Rahman S, Balasubramanian S, Sukari A and Azmi AS: Liquid biopsy for therapy monitoring in early-stage non-small cell lung cancer. Mol Cancer 20: 82, 2021.
19. Qvick A, Stenmark B, Carlsson J, Isaksson J, Karlsson C and Helenius G: Liquid biopsy as an option for predictive testing and prognosis in patients with lung cancer. Mol Med 27: 68, 2021.
20. Rolfo C, Mack PC, Scagliotti GV, Baas P, Barlesi F, Bivona TG, Herbst RS, Mok TS, Peled N, Pirker R, *et al*: Liquid biopsy for advanced non-small cell lung cancer (NSCLC): A statement paper from the IASLC. J Thorac Oncol 13: 1248-1268, 2018.
21. Ansari J, Yun JW, Kompelli AR, Moufarrej YE, Alexander JS, Herrera GA and Shackelford RE: The liquid biopsy in lung cancer. Genes Cancer 7: 355-367, 2016.
22. Gainor JF, Varghese AM, Ou SH, Kabraji S, Awad MM, Katayama R, Pawlak A, Mino-Kenudson M, Yeap BY, Riely GJ, *et al*: ALK rearrangements are mutually exclusive with mutations in EGFR or KRAS: An analysis of 1,683 patients with non-small cell lung cancer. Clin Cancer Res 19: :4273-4281, 2013.
23. Shaw AT, Yeap BY, Mino-Kenudson M, Digumarthy SR, Costa DB, Heist RS, Solomon B, Stubbs H, Admane S, McDermott U, *et al*: Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. J Clin Oncol 27: 4247-4253, 2009.
24. Horn L and Pao W: EML4-ALK: Honing in on a new target in non-small-cell lung cancer. J Clin Oncol 27: 4232-4235, 2009.
25. Xu L, Lei J, Wang QZ, Li J and Wu L: Clinical characteristics of patients with non-small cell lung cancers harboring anaplastic lymphoma kinase rearrangements and primary lung adenocarcinoma harboring epidermal growth factor receptor mutations. Genet Mol Res 14: 12973-12983, 2015.
26. Pao W, Wang TY, Riely GJ, Miller VA, Pan Q, Ladanyi M, Zakowski MF, Heelan RT, Kris MG and Varmus HE: KRAS mutations and primary resistance of lung adenocarcinomas to gefitinib or erlotinib. PLoS Med 2: e17, 2005.
27. Thomas D, Maloney ME and Raval G: Concomitant EGFR mutations and ALK rearrangements in lung adenocarcinoma treated with osimertinib. Cureus 15: e48122, 2023.
28. Hu H, Tan S, Xie M, Guo P, Yu Q, Xiao J, Zhao K, Liao Q and Wang Y: Case report: Concomitant EGFR mutation and ALK rearrangement in non-small cell lung cancer. Front Pharmacol 14: 1167959, 2023.
29. Santelmo C, Ravaioli A, Barzotti E, Papi M, Poggi B, Drudi F, Mangianti M, Salvi M and Crinò L: Coexistence of EGFR mutation and ALK translocation in NSCLC: Literature review and case report of response to gefitinib. Lung Cancer 81: 294-296, 2013.
30. Zito Marino F, Ronchi A, Accardo M and Franco R: Concomitant ALK/KRAS and ALK/EGFR mutations in non small cell lung cancer: Different profile of response to target therapies. Transl Cancer Res 6 (Suppl 3): S457-S460, 2017.
31. Zhao N, Zheng SY, Yang JJ, Zhang XC, Xie Z, Xie B, Su J, Chen ZH, Chen SL, Zhang N, *et al*: Lung adenocarcinoma harboring concomitant EGFR mutation and EML4-ALK fusion that benefits from three kinds of tyrosine kinase inhibitors: A case report and literature review. Clin Lung Cancer 16: e5-e9, 2015.
32. Lo Russo G, Imbimbo M, Corrao G, Proto C, Signorelli D, Vitali M, Ganzinelli M, Botta L, Zilembo N, de Braud F and Garassino MC: Concomitant EML4-ALK rearrangement and EGFR mutation in non-small cell lung cancer patients: A literature review of 100 cases. Oncotarget 8: 59889-59900, 2017.
33. Zito Marino F, Bianco R, Accardo M, Ronchi A, Cozzolino I, Morgillo F, Rossi G and Franco R: Molecular heterogeneity in lung cancer: From mechanisms of origin to clinical implications. Int J Med Sci 16: 981-989, 2019.
34. Chen ZY, Zhong WZ, Zhang XC, Su J, Yang XN, Chen ZH, Yang JJ, Zhou Q, Yan HH, An SJ, *et al*: EGFR mutation heterogeneity and the mixed response to EGFR tyrosine kinase inhibitors of lung adenocarcinomas. Oncologist 17: 978-985, 2012.