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CASE REPORT

Concomitant epidermal growth factor receptor mutation/c-ros oncogene 1 rearrangement in non-small cell lung cancer: A case report

Gui-Qin Peng, Hai-Chi Song, Wan-Yi Chen

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Abstract

BACKGROUND

Epidermal growth factor receptor (*EGFR*) mutation and c-ros oncogene 1 (*ROS1*) rearrangement are key genetic alterations and predictive tumor markers for non-small cell lung cancer (NSCLC) and are typically considered to be mutually exclusive. *EGFR/ROS1* co-mutation is a rare event, and the standard treatment approach for such cases is still equivocal.

CASE SUMMARY

Herein, we report the case of a 64-year-old woman diagnosed with lung adenocarcinoma, with concomitant *EGFR* L858R mutation and *ROS1* rearrangement. The patient received two cycles of chemotherapy after surgery, but the disease progressed. Following 1-month treatment with gefitinib, the disease progressed again. However, after switching to crizotinib, the lesion became stable. Currently, crizotinib has been administered for over 53 months with a remarkable treatment effect.

CONCLUSION

The efficacy of *EGFR* tyrosine kinase inhibitors and crizotinib was vastly different in this NSCLC patient with *EGFR/ROS1* co-mutation. This report will aid future treatment of such patients.

Key Words: Non-small cell lung cancer; Epidermal growth factor receptor; C-ros oncogene 1; Co-mutation; Treatment strategies; Case report

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Core Tip: Over the past two decades, molecular targeted therapies have improved clinical outcomes significantly for non-small cell lung cancer (NSCLC) patients with either epidermal growth factor receptor (*EGFR*) mutation or c-ros oncogene 1 (*ROS1*) fusion. Nevertheless, *EGFR*/*ROS1* co-mutation is a rare event in NSCLC, and the standard treatment for such cases is still equivocal. We report an *EGFR*/*ROS1* co-mutation in an NSCLC patient who remained clinically stable after 53 months of treatment with crizotinib. This is the longest progression-free survival reported in the literature. This case suggested that crizotinib may be a potential choice for NSCLC patients with such *EGFR*/*ROS1* co-mutations.

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INTRODUCTION

Lung cancer has the second-highest incidence of all cancers and the highest cancer-related death rate in the world[1]. Non-small cell lung cancer (NSCLC) accounts for about 85% of all lung cancers. Lung adenocarcinoma is the most common histopathological subtype of NSCLC, accounting for about 55% of cases. The mutation rate of epidermal growth factor receptor (*EGFR*) in Asian patients with lung adenocarcinoma is approximately 51%, and the mutation rate of c-ros oncogene 1 (*ROS1*) in NSCLC is 2%-3%[2-4]. *EGFR/ROS1* co-mutation is relatively rare, and the incidence of concomitant *EGFR* mutations in patients with *ROS1* fusion genes is less than 24%[5-7].

Early studies have shown that tyrosine kinase inhibitors (TKIs) targeting *EGFR* and *ROS1* are the first-line treatment for patients with *EGFR* mutations or *ROS1* rearrangement[8-11]. However, there is currently no consensus on the optimal management of patients with these co-mutations. This article reports the treatment of an NSCLC patient with *EGFR* and *ROS1* co-mutation to provide a reference for the treatment and management of other NSCLC patients with these co-mutations.

CASE PRESENTATION

Chief complaints

A 64-year-old Chinese woman presented on November 1, 2018 with a complaint of cough and sputum production for 1 wk.

History of present illness

Symptoms started 1 wk before presentation, with cough and sputum production.

History of past illness

An appendectomy due to appendicitis had been performed approximately 30 years prior to the presentation. Cholecystectomy due to cholelithiasis had been performed 10 years after the appendectomy.

Personal and family history

The patient denied any family history of malignant tumors. The patient also had no history of smoking.

Physical examination

On physical examination, the vital signs were as follows: Body temperature, 36.6 °C; blood pressure, 136/75 mmHg; heart rate, 74 beats per min; and respiratory rate, 20 breaths per min.

Laboratory examinations

Levels of serum tumor markers were normal. Carcinoembryonic antigen was < 0.5 ng/mL (normal range: 0-5 ng/mL), squamous cell carcinoma antigen was 0.6 ng/mL (normal range: 0-1.5 ng/mL), and cytokeratin 19 fragment was 1.57 ng/mL (normal range: 0-2.08 ng/mL). No abnormality was found in the routine blood and urine analyses.

Imaging examinations

On November 2, 2018, chest computed tomography (CT) showed a 2.8 cm × 1.8 cm patchy shadow in the inferior lobe of the right lung. The scan also showed multiple ground-glass nodules in bilateral lungs. The patient was prescribed oral anti-tuberculosis drugs. She discontinued the medication after 1 month due to intolerance. On March 25, 2019, the patient visited our hospital again. Chest CT showed a 4.0 cm × 2.7 cm shadow in the lower lobe of the right lung. Due to the significant growth, the possibility of a neoplastic lesion was considered.

FINAL DIAGNOSIS

Combined with the patient's medical history, the final diagnosis was determined to be NSCLC.

TREATMENT

On April 3, 2019, thoracoscopic radical resection of the lower right lung cancer and pleural adhesion cauterization was performed under general anesthesia. Postoperative pathological diagnosis was acinar adenocarcinoma grade III, micropapillary adenocarcinoma (accounting for about 5% of tumor tissue) in the local area, and tumor thrombus in the alveolar cavity (Figure 1). *ROS1* rearrangement and *EGFR* L858R mutation were detected by next-generation sequencing of 13 lung cancer driver genes. The frequency of the *EGFR* mutation found in this patient was only 1.3% (Figure 2).

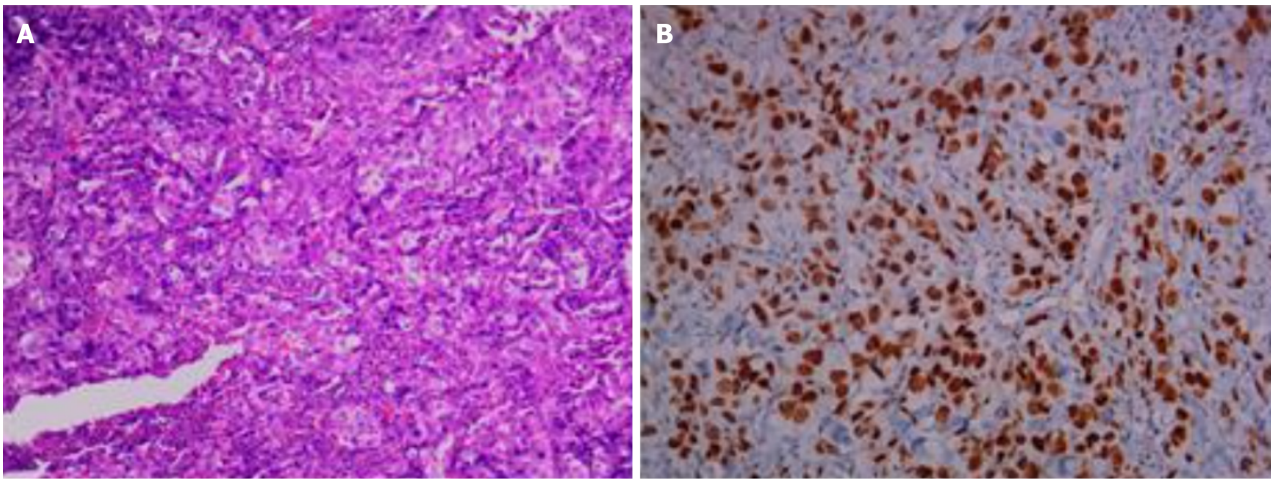


Figure 1 Histological and immunohistochemical features. A: Histology of lung biopsy; B: Expression pattern of thyroid transcription factor 1.

After thoracoscopic radical resection, the patient received two cycles of chemotherapy (pemetrexed 690 mg D1 + cisplatin 50 mg D1-2; on May 14, 2019 and June 5, 2019). Comparison of the CT film obtained on June 25, 2019 with the previous film (May 7, 2019) showed progression of the lesion. Multiple lymph nodes in the mediastinum and right hilum were also enlarged, suggesting metastasis (Figure 3).

Gefitinib was administered for 1 month starting on June 26, 2019. During this period, the patient developed drug-induced diarrhea, which improved after treatment with loperamide. Chest CT on July 30, 2019 revealed that multiple lymph nodes in the mediastinum, right cardiophrenic angle, and right hilum were enlarged, indicating progression of the disease (Figure 3).

On August 7, 2019, crizotinib was administered. The efficacy of crizotinib was evaluated after 1 month, which revealed stable disease. Since then, the patient has been treated with crizotinib for over 53 months and continues to have stable disease (Figure 3).

OUTCOME AND FOLLOW-UP

After 53 months of treatment with crizotinib, the patient is still alive.

DISCUSSION

Genetic mutations are typically considered to be mutually exclusive[12-15]. A recent study[16] demonstrated that patients with co-mutations have a poor progression-free survival. Patients with both *ROS1* fusion and *EGFR* mutations are exceedingly rare in comparison to the co-occurrence of *EGFR/PIK3CA*, *ALK/KRAS*, and *EGFR/MET* mutations[16-18]. However, using highly sensitive methods such as the amplification-refractory mutation system analysis leads to an increase in the detection rate of co-mutations of *KRAS* or *BRAF* mutations and *ALK* or *ROS1* rearrangements[13]. Studies [13-15] have shown that the incidence of concomitant gene mutations in lung adenocarcinoma was 3.8%, and *EGFR/ROS1* and *EML4-ALK* were among the mutations detected. There is no consensus on the clinical characteristics, treatment options, and prognosis of NSCLC patients with co-mutations.

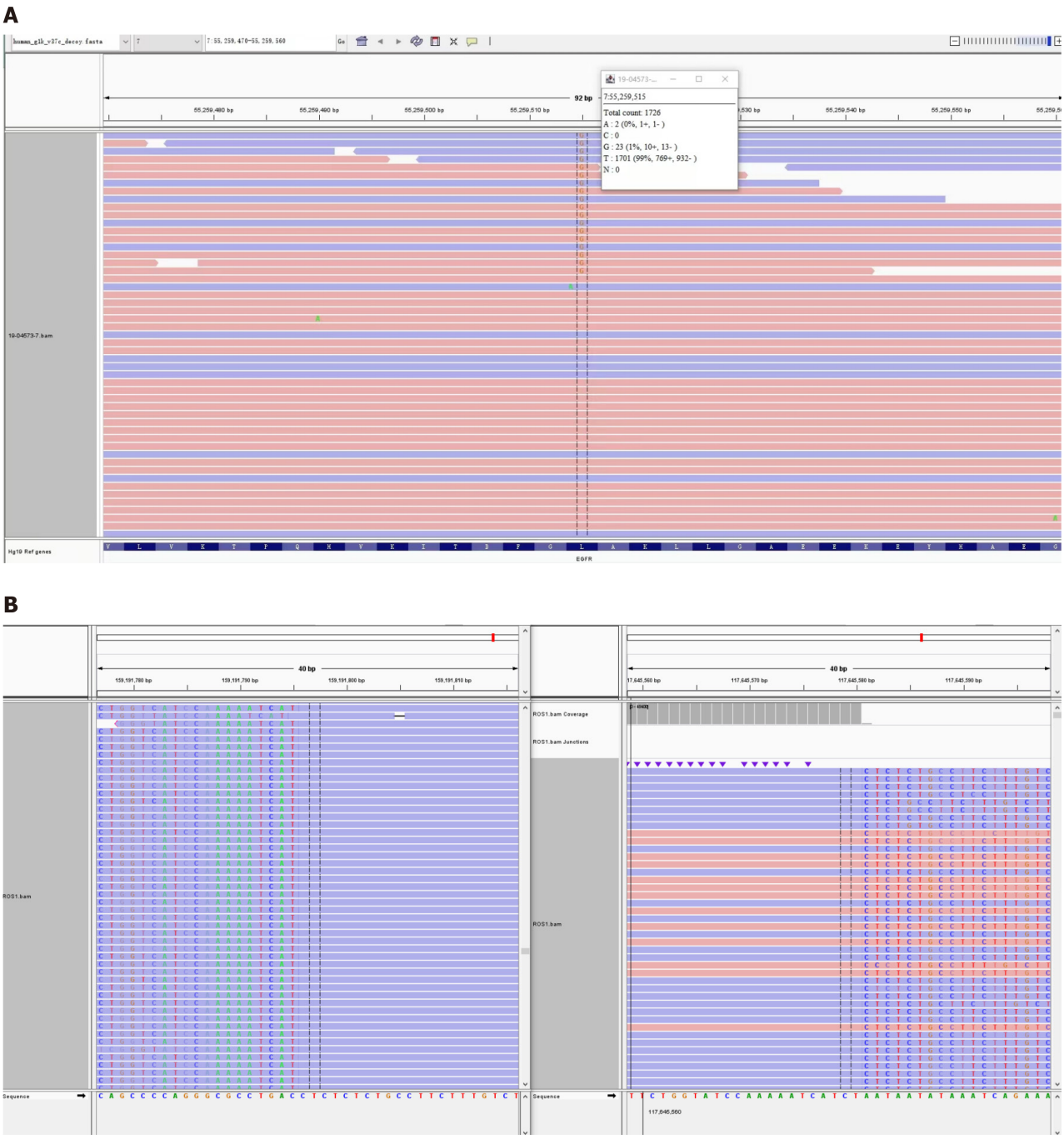
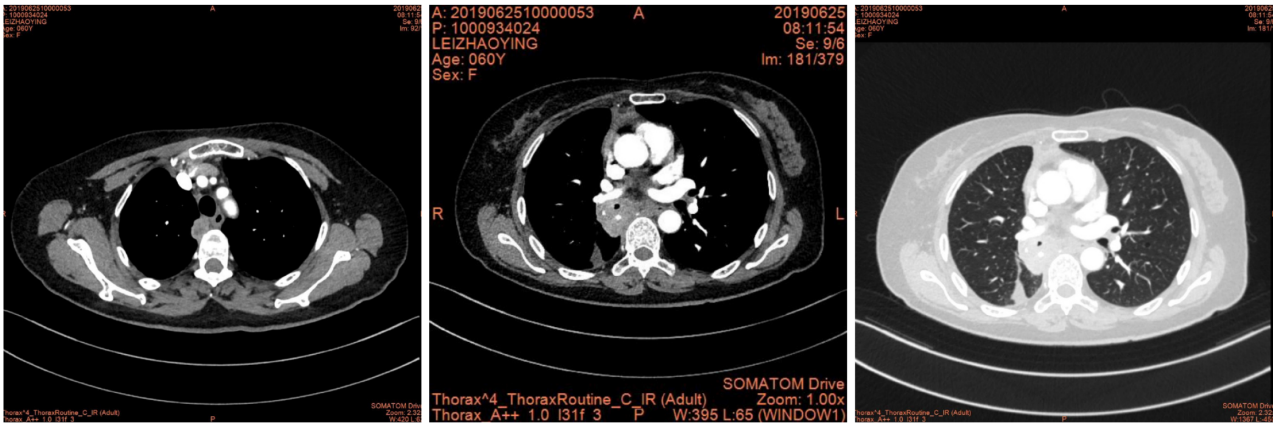


Figure 2 Detection of epidermal growth factor receptor mutation and c-ros oncogene 1 rearrangement using high sensitivity next-generation sequencing. A: Epidermal growth factor receptor L858R mutation; B: *EZR-ROS1* E10R34 fusion.

The mechanism of *EGFR/ROS1* co-mutation remains unclear. Wu *et al*[19] hypothesized that two gene alterations can be detected within the same tumor cells in NSCLC, which might result in cancer development through co-action. Won *et al*[20] proposed that genetic instability in cancer cells leads to genetic and phenotypic heterogeneity in tumors, indicating that different genetic mutations might occur in tumor cells rather than in a single clone. Accumulating evidence shows co-existence of classical oncogenes, including *EGFR*, *ALK*, *ROS1*, and *MET*, in lung adenocarcinoma patients, especially in young females with no history of smoking[21]. In this case report, the patient was an elderly woman and the pathology suggested adenocarcinoma, which was consistent with the literature reports.

Cases of *EGFR/ROS1* co-mutation have been infrequently reported in NSCLC, creating a lack of clear treatment standards. Zhang *et al*[22] reported a patient with an *EGFR* exon 21 L858R mutation. The disease progressed after gefitinib treatment for 11 months. The gene test showed *EGFR* exon 21 L858R mutation (abundance 36.62%), *EGFR* exon 20 T790M (7.95%), and *ROS1* fusion (15.81%), as well as *EGFR*, *HER2*, and *BRAF* amplification. The second-line treatment included osimertinib, and the disease progressed after 7 months. The third-line chemotherapy included two cycles of pemetrexed and carboplatin, which did not prevent disease progression.

A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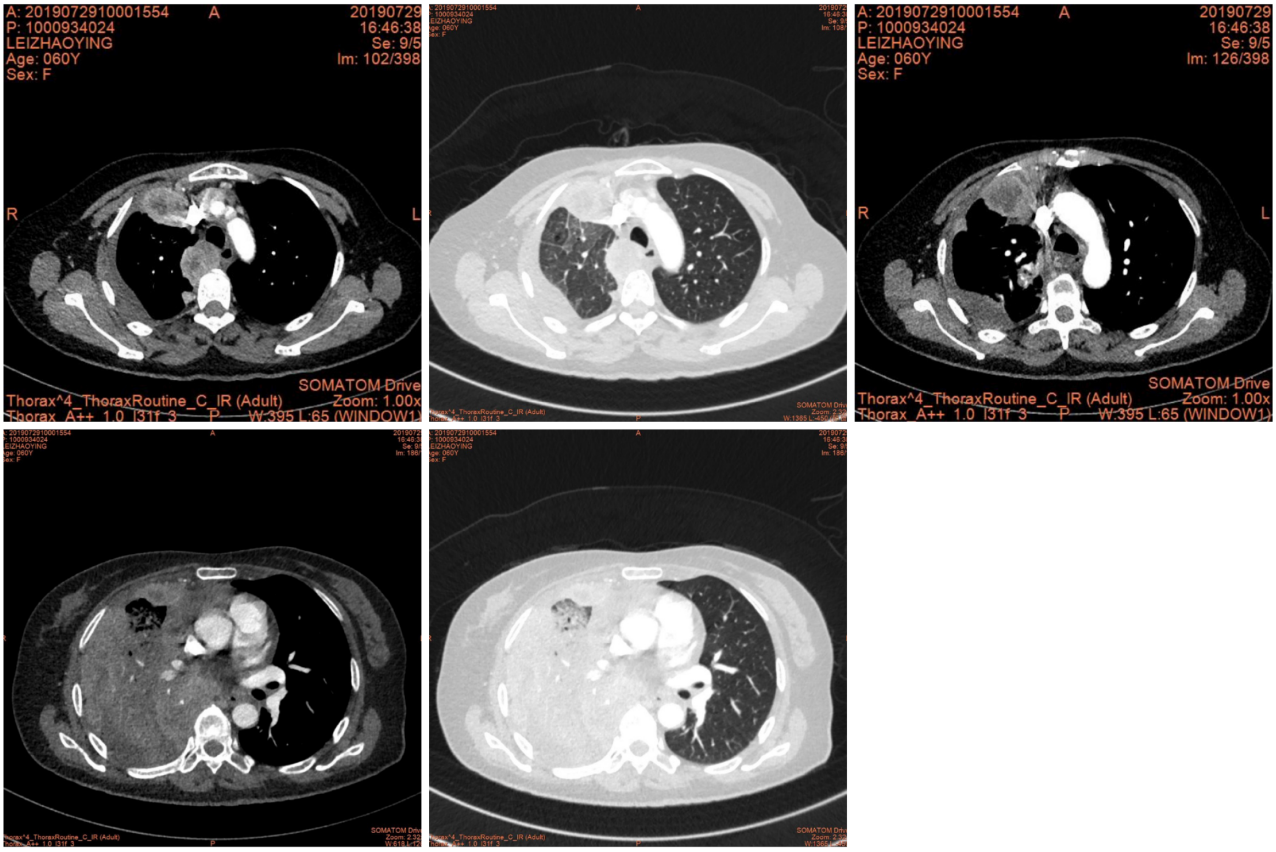
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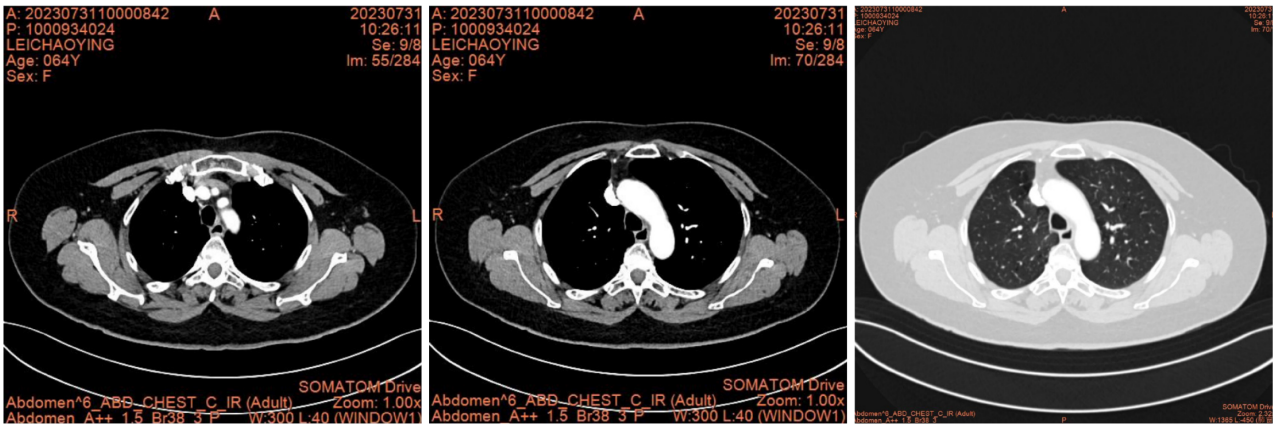
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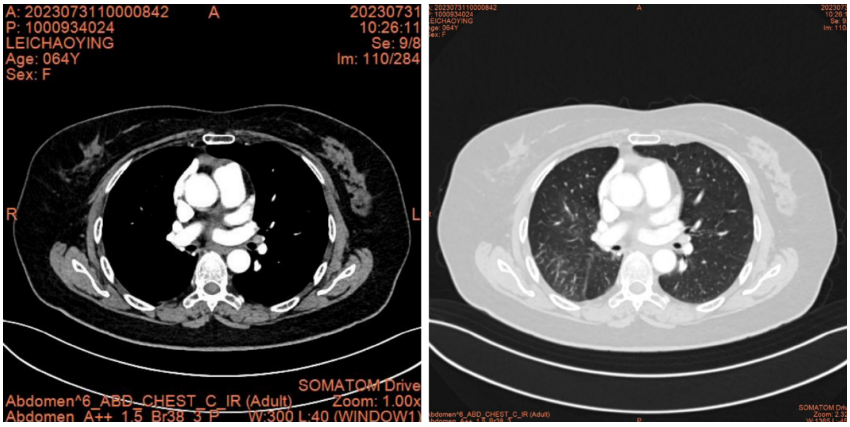

Figure 3 Serial computed tomography images. A: Computed tomography (CT) after postoperative recurrence; B: CT after 1 month of gefitinib therapy. Progressive disease of the lung was detected; C: CT after 53 months of crizotinib therapy. Stable disease was detected.

Another study reported the cases of three stage IA NSCLC patients with *EGFR/ROS1* co-mutation who received chemotherapy (regimen not reported) for 3 months after surgery[23]. During the 12-month follow-up, one patient developed relapse and the other two were in stable condition. In another case report, a 53-year-old man was diagnosed with lung adenocarcinoma with concomitant *EGFR* and *KRAS* mutations and *ROS1* rearrangement[24]. He was treated with crizotinib as the first-line treatment, but the disease progressed after 1 month. After icotinib was administered for 1 month, a partial curative effect was observed. The condition of that patient was stable after 8 months of maintenance treatment.

According to Zhuang *et al*[21], the progression-free survival of patients with an *EGFR* co-mutation treated with first-line TKIs was better than that of patients treated with first-line chemotherapy. A recent study described the case of a 48-year-old woman diagnosed with NSCLC with an *EGFR* 19 deletion/*ROS1* rearrangement who achieved a favorable outcome[19]. Following 1 month of treatment with a combination of almonertinib and crizotinib, there was a significant reduction in the primary mass and all lymph nodes. Almonertinib was subsequently replaced by furmonertinib due to elevated levels of creatine kinase. The patient received furmonertinib and crizotinib treatment for 7 months, and stable disease was achieved throughout the follow-up period.

It appears that the clinical efficacy of *EGFR* TKIs and crizotinib treatment is quite different based on these clinical reports and our experience. The best choice for first-line treatment remains unclear. It has been reported, though, that the efficacy of TKIs can be predicted by the phosphorylation levels of EGFR and ALK in patients with *EGFR/ALK* co-mutation[25].

Nevertheless, there are still several challenges in predicting the efficacy of treatment in patients with *EGFR/ROS1* co-mutations. First, current genetic testing is unable to determine the dominant oncogene aberration in a single tumor cell. Second, there is limited research on the relationship between the abundance of a *ROS1* mutation and lung cancer prognosis. Finally, there have been no reports on whether EGFR phosphorylation levels and *ROS1* mutation abundance can predict the effectiveness of TKIs. In our report, we found that the patient had a very low *EGFR* mutation frequency (1.3%), which may explain the poor response to the gefitinib treatment. Therefore, it is possible that low EGFR phosphorylation levels could be associated with a poorer prognosis when treated with TKI therapy.

Liu *et al*[26] observed that TKI combination therapy was more effective than single TKI treatment in patients with *EGFR/ALK* co-mutations. Wu *et al*[19] demonstrated similar outcome in one patient with an *EFGR* 19 deletion/*ROS1* rearrangement upon treatment with a combination of third-generation EGFR TKIs and crizotinib. Combination therapy appears to exhibit a favorable efficacy. However, not all patients are able to tolerate the toxicity associated with TKI combination therapy. Therefore, further investigation is required to determine the necessity of combination therapy.

There is no overall survival difference between patients with single *EGFR* mutations and those with concomitant *ALK/ROS1* mutations (21.0 months *vs* 23.0 months, respectively, $P = 0.196$)[27]. However, concomitant *EGFR* mutation and *ALK/ROS1* mutation reduced the therapeutic effect of EGFR TKIs in patients. Patients with co-mutations had a significantly shorter progression-free survival than those with a single *EGFR* mutation (6.6 months *vs* 10.7 months, respectively, $P = 0.004$)[27]. In our report, the patient remained stable after 53 months of crizotinib treatment, which is the longest reported progression-free survival of a patient with an *EGFR/ROS1* co-mutation.

CONCLUSION

EGFR/ROS1 co-mutation is rare in patients with NSCLC. Due to its rarity, the best treatment approach is unclear. TKI therapy can be used as the first-line option, but the clinical efficacy of EGFR-TKIs and crizotinib therapy appears to vary significantly between patients. The level of *EGFR* phosphorylation may play a crucial role in the selection of therapeutic drugs. Further investigation is required to examine the correlation between *ROS1* mutation frequency and the prognosis of lung cancer.

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REFERENCES

1 **Sung H**, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021; **71**: 209-249 [PMID: 33538338 DOI: 10.3322/caac.21660]

2 **Shi Y**, Au JS, Thongprasert S, Srinivasan S, Tsai CM, Khoa MT, Heeroma K, Itoh Y, Cornelio G, Yang PC. A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER). *J Thorac Oncol* 2014; **9**: 154-162 [PMID: 24419411 DOI: 10.1097/JTO.0000000000000033]

3 **Han B**, Tjulandin S, Hagiwara K, Normanno N, Wulandari L, Laktionov K, Hudoyo A, He Y, Zhang YP, Wang MZ, Liu CY, Ratcliffe M, McCormack R, Reck M. EGFR mutation prevalence in Asia-Pacific and Russian patients with advanced NSCLC of adenocarcinoma and non-adenocarcinoma histology: The IGNITE study. *Lung Cancer* 2017; **113**: 37-44 [PMID: 29110846 DOI: 10.1016/j.lungcan.2017.08.021]

4 **Kohno T**, Nakaoku T, Tsuta K, Tsuchihara K, Matsumoto S, Yoh K, Goto K. Beyond ALK-RET, ROS1 and other oncogene fusions in lung cancer. *Transl Lung Cancer Res* 2015; **4**: 156-164 [PMID: 25870798 DOI: 10.3978/j.issn.2218-6751.2014.11.11]

5 **Lin JJ**, Ritterhouse LL, Ali SM, Bailey M, Schrock AB, Gainor JF, Ferris LA, Mino-Kenudson M, Miller VA, Iafrate AJ, Lennerz JK, Shaw AT. ROS1 Fusions Rarely Overlap with Other Oncogenic Drivers in Non-Small Cell Lung Cancer. *J Thorac Oncol* 2017; **12**: 872-877 [PMID: 28088512 DOI: 10.1016/j.jtho.2017.01.004]

6 **Scheffler M**, Schultheis A, Teixido C, Michels S, Morales-Espinosa D, Viteri S, Hartmann W, Merkelbach-Bruse S, Fischer R, Schildhaus HU, Fassunke J, Sebastian M, Serke M, Kaminsky B, Randerath W, Gerigk U, Ko YD, Krüger S, Schnell R, Rothe A, Kropf-Sanchen C, Heukamp L, Rosell R, Büttner R, Wolf J. ROS1 rearrangements in lung adenocarcinoma: prognostic impact, therapeutic options and genetic variability. *Oncotarget* 2015; **6**: 10577-10585 [PMID: 25868855 DOI: 10.18632/oncotarget.3387]

7 **Wiesweg M**, Eberhardt WEE, Reis H, Ting S, Savvidou N, Skiba C, Herold T, Christoph DC, Meiler J, Worm K, Kasper S, Theegarten D, Hense J, Hager T, Darwiche K, Oezkan F, Aigner C, Welter S, Kühl H, Stuschke M, Schmid KW, Schuler M. High Prevalence of Concomitant Oncogene Mutations in Prospectively Identified Patients with ROS1-Positive Metastatic Lung Cancer. *J Thorac Oncol* 2017; **12**: 54-64 [PMID: 27575422 DOI: 10.1016/j.jtho.2016.08.137]

8 **Mok TS**, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, Sunpaweravong P, Han B, Margono B, Ichinose Y, Nishiwaki Y, Ohe Y, Yang JJ, Chewaskulyong B, Jiang H, Duffield EL, Watkins CL, Armour AA, Fukuoka M. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009; **361**: 947-957 [PMID: 19692680 DOI: 10.1056/NEJMoa0810699]

9 **Zhou C**, Wu YL, Chen G, Feng J, Liu XQ, Wang C, Zhang S, Wang J, Zhou S, Ren S, Lu S, Zhang L, Hu C, Hu C, Luo Y, Chen L, Ye M, Huang J, Zhi X, Zhang Y, Xiu Q, Ma J, Zhang L, You C. Erlotinib *versus* chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol* 2011; **12**: 735-742 [PMID: 21783417 DOI: 10.1016/S1470-2045(11)70184-X]

10 **Shaw AT**, Ou SH, Bang YJ, Camidge DR, Solomon BJ, Salgia R, Riely GJ, Varella-Garcia M, Shapiro GI, Costa DB, Doebele RC, Le LP, Zheng Z, Tan W, Stephenson P, Shreeve SM, Tye LM, Christensen JG, Wilner KD, Clark JW, Iafrate AJ. Crizotinib in ROS1-rearranged non-small-cell lung cancer. *N Engl J Med* 2014; **371**: 1963-1971 [PMID: 25264305 DOI: 10.1056/NEJMoa1406766]

11 **Soria JC**, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, Dechaphunkul A, Imamura F, Nogami N, Kurata T, Okamoto I, Zhou C, Cho BC, Cheng Y, Cho EK, Voon PJ, Planchard D, Su WC, Gray JE, Lee SM, Hodge R, Marotti M, Rukazenkov Y, Ramalingam SS; FLAURA Investigators. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. *N Engl J Med* 2018; **378**: 113-125 [PMID: 29151359 DOI: 10.1056/NEJMoa1713137]

12 **Cardarella S**, Ortiz TM, Joshi VA, Butaney M, Jackman DM, Kwiatkowski DJ, Yeap BY, Jänne PA, Lindeman NI, Johnson BE. The introduction of systematic genomic testing for patients with non-small-cell lung cancer. *J Thorac Oncol* 2012; **7**: 1767-1774 [PMID: 23154547 DOI: 10.1097/JTO.0b013e3182745bcb]

13 **Takeuchi K**, Soda M, Togashi Y, Suzuki R, Sakata S, Hatano S, Asaka R, Hamanaka W, Ninomiya H, Uehara H, Lim Choi Y, Satoh Y, Okumura S, Nakagawa K, Mano H, Ishikawa Y. RET, ROS1 and ALK fusions in lung cancer. *Nat Med* 2012; **18**: 378-381 [PMID: 22327623 DOI: 10.1038/nm.2658]

14 **Sun Y**, Ren Y, Fang Z, Li C, Fang R, Gao B, Han X, Tian W, Pao W, Chen H, Ji H. Lung adenocarcinoma from East Asian never-smokers is a disease largely defined by targetable oncogenic mutant kinases. *J Clin Oncol* 2010; **28**: 4616-4620 [PMID: 20855837 DOI: 10.1200/JCO.2010.29.6038]

15 **Yoshida A**, Kohno T, Tsuta K, Wakai S, Arai Y, Shimada Y, Asamura H, Furuta K, Shibata T, Tsuda H. ROS1-rearranged lung cancer: a clinicopathologic and molecular study of 15 surgical cases. *Am J Surg Pathol* 2013; **37**: 554-562 [PMID: 23426121 DOI: 10.1097/PAS.0b013e3182758fe6]

16 **Li W**, Chang F, Zhang H, Meng F, Ke Z, Zhang Y. Clinical Pathological Characteristics and Prognosis of Multigene Co-Mutations in Elderly Patients With Non-Small Cell Lung Cancer: A Retrospective Analysis. *Clin Med Insights Oncol* 2023; **17**: 11795549231211505 [PMID: 38033742 DOI: 10.1177/11795549231211505]

17 **Sakamoto T**, Matsubara T, Takahama T, Yokoyama T, Nakamura A, Tokito T, Okamoto T, Akamatsu H, Oki M, Sato Y, Tobino K, Ikeda S, Mori M, Mimura C, Maeno K, Miura S, Harada T, Nishimura K, Hiraoka M, Kenmotsu H, Fujimoto J, Shimokawa M, Yamamoto N, Nakagawa K. Biomarker Testing in Patients With Unresectable Advanced or Recurrent Non-Small Cell Lung Cancer. *JAMA Netw Open* 2023; **6**: e2347700 [PMID: 38100106 DOI: 10.1001/jamanetworkopen.2023.47700]

18 **Chen H**, Liu M, Dai Z, Li S, Luo Y, Wang Y, Su W, Cai W, Yang D, Huang J, Yang Z. Concomitant genetic alterations are associated with response to EGFR targeted therapy in patients with lung adenocarcinoma. *Transl Lung Cancer Res* 2020; **9**: 1225-1234 [PMID: 32953500 DOI: 10.21037/tlcr-20-679]

19 **Wu Z**, Zhang Z, Zhang D, Li Z. Remarkable response to third-generation EGFR-TKI plus crizotinib in a patient with pulmonary adenocarcinoma harboring EGFR and ROS1 co-mutation: a case report. *Front Oncol* 2024; **14**: 1357230 [PMID: 38476366 DOI: 10.3389/fonc.2024.1357230]

20 **Won JK**, Keam B, Koh J, Cho HJ, Jeon YK, Kim TM, Lee SH, Lee DS, Kim DW, Chung DH. Concomitant ALK translocation and EGFR mutation in lung cancer: a comparison of direct sequencing and sensitive assays and the impact on responsiveness to tyrosine kinase inhibitor. *Ann Oncol* 2015; **26**: 348-354 [PMID: 25403583 DOI: 10.1093/annonc/mdu530]

21 **Zhuang X**, Zhao C, Li J, Su C, Chen X, Ren S, Li X, Zhou C. Clinical features and therapeutic options in non-small cell lung cancer patients with concomitant mutations of EGFR, ALK, ROS1, KRAS or BRAF. *Cancer Med* 2019; **8**: 2858-2866 [PMID: 31016879 DOI: 10.1002/cam4.2183]

22 **Zhang S**, Xu Z, Zhang W. OPRM1-ROS1 Fusion Detected by Next-Generation Sequencing with Circulating DNA in a Patient with EGFR Mutated Advanced NSCLC: A Case Report. *Case Rep Oncol* 2022; **15**: 700-704 [PMID: 36157687 DOI: 10.1159/000507980]

23 **Zhang X**, Jiang Y, Yu H, Xia H, Wang X. A comprehensive study on the oncogenic mutation and molecular pathology in Chinese lung adenocarcinoma patients. *World J Surg Oncol* 2020; **18**: 172 [PMID: 32677962 DOI: 10.1186/s12957-020-01947-z]

24 **Ju L**, Han M, Zhao C, Li X. EGFR, KRAS and ROS1 variants coexist in a lung adenocarcinoma patient. *Lung Cancer* 2016; **95**: 94-97 [PMID: 27040858 DOI: 10.1016/j.lungcan.2016.03.005]

25 **Yang JJ**, Zhang XC, Su J, Xu CR, Zhou Q, Tian HX, Xie Z, Chen HJ, Huang YS, Jiang BY, Wang Z, Wang BC, Yang XN, Zhong WZ, Nie Q, Liao RQ, Mok TS, Wu YL. Lung cancers with concomitant EGFR mutations and ALK rearrangements: diverse responses to EGFR-TKI and crizotinib in relation to diverse receptors phosphorylation. *Clin Cancer Res* 2014; **20**: 1383-1392 [PMID: 24443522 DOI: 10.1158/1078-0432.CCR-13-0699]

26 **Liu J**, Mu Z, Liu L, Li K, Jiang R, Chen P, Zhou Q, Jin M, Ma Y, Xie Y, Xiang J, Li B, Ma Y, Mao X, Zhang L, Zhang T, Wu D. Frequency, clinical features and differential response to therapy of concurrent ALK/EGFR alterations in Chinese lung cancer patients. *Drug Des Devel Ther* 2019; **13**: 1809-1817 [PMID: 31213769 DOI: 10.2147/DDDT.S196189]

27 **Mao Y**, Wu S. ALK and ROS1 concurrent with EGFR mutation in patients with lung adenocarcinoma. *Onco Targets Ther* 2017; **10**: 3399-3404 [PMID: 28744144 DOI: 10.2147/OTT.S133349]

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