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CASE REPORT

Concurrent *ROS1* gene rearrangement and *KRAS* mutation in lung adenocarcinoma: A case report and literature review

You-cai Zhu[1], Xue-ping Lin[2], Xiao-feng Li[1], Li-xin Wu[1], Hua-fei Chen[1], Wen-xian Wang[3], Chun-wei Xu[4], Jian-fa Shen[5], Jian-guo Wei[6] & Kai-qi Du[1]

1 Department of Thoracic Disease Center, Zhejiang Rongjun Hospital, Jiaxing, China
2 Department of Pathology, Jiaxing University College of Medicine, Jiaxing, China
3 Department of Chemotherapy, Zhejiang Cancer Hospital, Hangzhou, China
4 Department of Pathology, Fujian Provincial Cancer Hospital, Fujian Medical University Cancer Hospital, Fuzhou, China
5 Department of Surgery, Zhejiang Rongjun Hospital, Jiaxing, China
6 Department of Pathology, Shaoxing People's Hospital, Shaoxing, China

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Correspondence
Jian-fa Shen, Department of Surgery, Zhejiang Rongjun Hospital, No. 589 Central West Road, Jiaxing, Zhejiang Province, China.
Tel/Fax: +86 573 8288 0120
Email: 13520879463@163.com

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Abstract

Lung adenocarcinomas with gene rearrangement in the receptor tyrosine kinase *ROS1* have emerged as a rare molecular subtype. Although these lung adenocarcinomas respond to *ROS1*tyrosine kinase inhibitors, many patients ultimately acquire resistance. *ROS1*gene rearrangement is generally mutually exclusive with other driver genomic alterations, such as those in *EGFR*, *KRAS*, or *ALK*, thus multiple genomic alterations are extremely rare. Herein, we report a case of a 42-year-old man diagnosed with lung adenocarcinoma positive for a *SDC4-ROS1* fusion, who was treated with crizotinib followed by three cycles of chemotherapy. A biopsy acquired after disease progression revealed the original *SDC4-ROS1* fusion along with a *KRAS* point mutation (p.G12D).We reviewed the related literature to determine the frequency of gene mutations in non-small cell lung cancer patients. A better understanding of the molecular biology of non-small cell lung cancer with multiple driver genomic aberrations will assist in determining optimal treatment.

Introduction

Lung cancer is the leading cause of cancer-related death in men and women. Most patients present with advanced non-small cell lung cancer (NSCLC) at the time of diagnosis. Chemotherapy and radiation provide only palliative relief at this stage, thus prognosis is poor for these patients. In addition to stage, NSCLC can be categorized by the presence of specific driver mutations and genomic aberrations. Molecular targeted therapy is effective in advanced NSCLC patients with the associated gene mutations. Oncogenes such as *EGFR* and *KRAS* are common driver genes in lung adenocarcinoma. Conversely, *ROS1* rearrangement has been identified in only 1–2% of NSCLC cases.[1,2] Studies have shown that *ROS1* fusions are mutually exclusive with *EGFR*, *KRAS*, or *ALK* mutations.[3] The tyrosine kinase inhibitor (TKI), crizotinib, is effective in patients with lung cancers that harbor *ROS1* gene rearrangement.[1,2] However, most patients with *ROS1* rearrangements treated with crizotinib will eventually develop resistance.[4]

Herein, we report a rare case of a patient with a lung adenocarcinoma with a *SDC4-ROS1* fusion gene, as well as a *KRAS* p.G12D mutation. Little is known about the clinical presentation, prognostic value, prediction of effectiveness of different therapy regimens, and the genetic heterogeneity of tumors in NSCLC patients with concomitant genomic aberrations in *ROS1* and other oncogenic driver genes.

Case report

A 42-year-old male never-smoker who complained of a persistent cough was examined by computed tomography (CT), which revealed a 30 mm wide tumor in the upper region of the right lobe of the lung in July 2016 (Fig 1a).

On physical examination, space-occupying lesions were found. No significant medical history was reported. Abdominal CT, brain magnetic resonance imaging, and bone emission CT revealed no additional abnormalities. Blood laboratory testing showed carcinoembryonic antigen levels above normal limits.

Tumor biopsy pathology conducted on July 26, 2016, revealed that the patient had a stage IIIB ($T_2N_3M_0$) adenocarcinoma (Fig 2a). Reverse transcription-PCR was performed on a formalin-fixed, paraffin-embedded tumor specimen to identify genomic aberrations. The tumor was negative for *EGFR* and *ALK* mutations, but positive for *ROS1* gene aberrations (Fig 3). The patient was prescribed oral crizotinib in August 2016. A CT scan taken in September 2016 showed a partial response in the pulmonary lesions (Fig 1b). Unfortunately, a CT scan in November 2016 showed progression of the pulmonary lesions (Fig 1c), indicating acquired resistance to crizotinib. Three cycles of chemotherapy were administered with pemetrexed (0.8 g) and carboplatin (550 mg) between November 2016 and January 2017. Although only slow progression of the pulmonary lesions was observed, a CT scan revealed metastasis to the left adrenal gland (Fig 1d). A second lung tumor biopsy (Fig 2b) was taken and next-generation sequencing was performed to provide guidance for new therapeutic strategies. A variant of the *ROS1* translocation (*SDC4-ROS1*), a point mutation in *KRAS* (p. G12D) accompanied by a *KRAS* gene amplification, and a point mutation in *SMO* (p.L707V) were found (Geneplus, Beijing, China) (Fig 4). The patient was treated with the MEK inhibitor, selumetinib (AZD6244), combined with pemetrexed. The patient was alive at the time of article submission. The authors confirm that written informed consent for publication of case details and any accompanying images were provided by the patient.

Discussion

ROS1 fusion genes as potential oncogenic drivers in NSCLC were discovered in 2007 in a rare subset of lung adenocarcinomas.[5] *ROS1* gene rearrangement is detected in 0.9–1.7% of NSCLC patients;[1,6,7] however, the frequency of *ROS1* fusions increases to 3.9–7.4% of lung adenocarcinoma patients with wild-type *EGFR*/*KRAS*/*ALK*.[3,8] Several gene fusion partners of *ROS1* fusions have been discovered, including *CD74*, *SLC34A2*, *SDC4*, *EZR*, *FIG*, *TPM3*, *LRIG3*, and *KDELR2*. *CD74* is the most common fusion partner in NSCLC.[9] As inpatients with *ALK* fusions, patients with *ROS1* rearrangement are often younger, never-smokers, and have adenocarcinoma histology.[6,10]

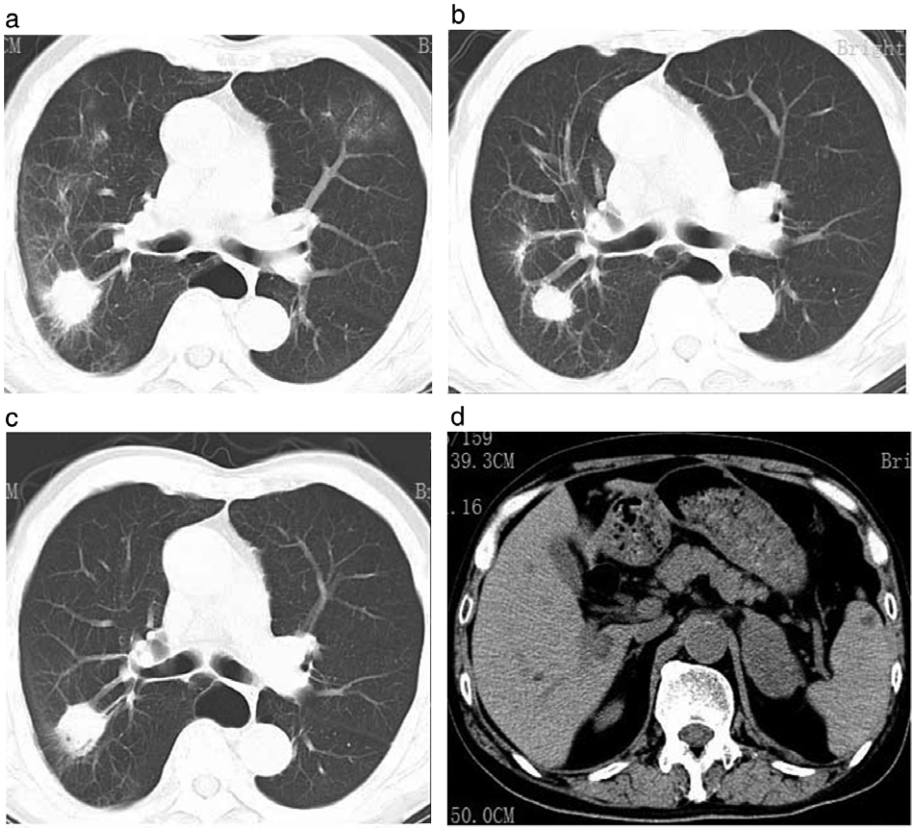

Figure 1 Lung computed tomography scans from (**a**) July 2016, (**b**) September 2016, (**c**) November 2016, and (**d**) of the left adrenal gland with tumor metastasis (red arrow).

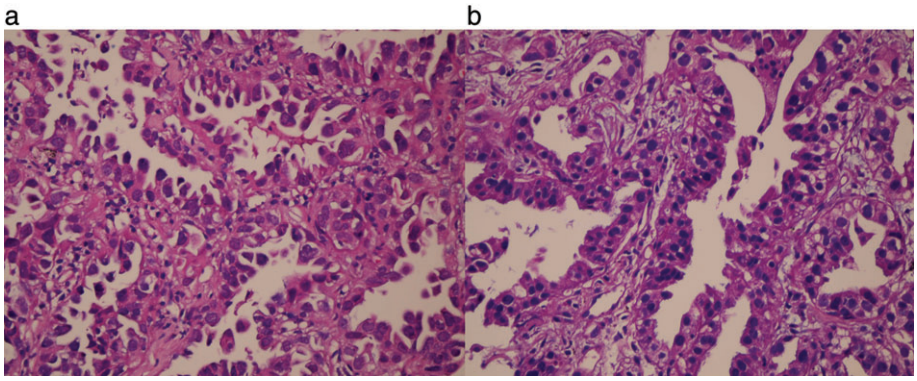

Figure 2 Hematoxylin and eosin staining revealed adenocarcinoma. The (**a**) first and (**b**) second biopsies (×400).

Patients who harbor *ROS1* gene rearrangement can benefit from treatment with TKIs. Crizotinib, a small molecule ATP-competitive ALK inhibitor, was approved for use in NSCLC patients with active *ROS1* signaling by the United States Food and Drug Administration on March 11, 2016. Crizotinib has shown to be an effective drug for improving the prognosis of NSCLC patients with *ROS1* rearrangement. A previous study reported an objective response rate of 72% and median progression-free survival of 19.2 months.[4] In Chinese NSCLC patients with *ROS1* rearrangement, crizotinib has a higher overall response rate (80.0%), disease control rate (90.0%), and longer progression-free survival (294 days) compared to pemetrexed.[11]

However, as with EGFR-TKIs and ALK-TKIs, acquired resistance to targeted therapies is inevitable. The mechanism of acquired resistance to crizotinib for NSCLC patients with *ROS1* rearrangement has not yet been identified. Molecular changes associated with acquired crizotinib resistance in *ROS1* rearrangement-positive NSCLC patients are heterogeneous, including *ROS1* tyrosine kinase mutations, EGFR activation, and epithelial-to-mesenchymal transition.[12]

KRAS is one of the most frequently mutated oncogenes in NSCLC. *KRAS* mutations account for 90% of *RAS* mutations in lung adenocarcinoma. However, debate over the prognostic role of *KRAS* mutation status in NSCLC continues. We hypothesize that changes in the expression of genes affected by *KRAS* mutation status have the most

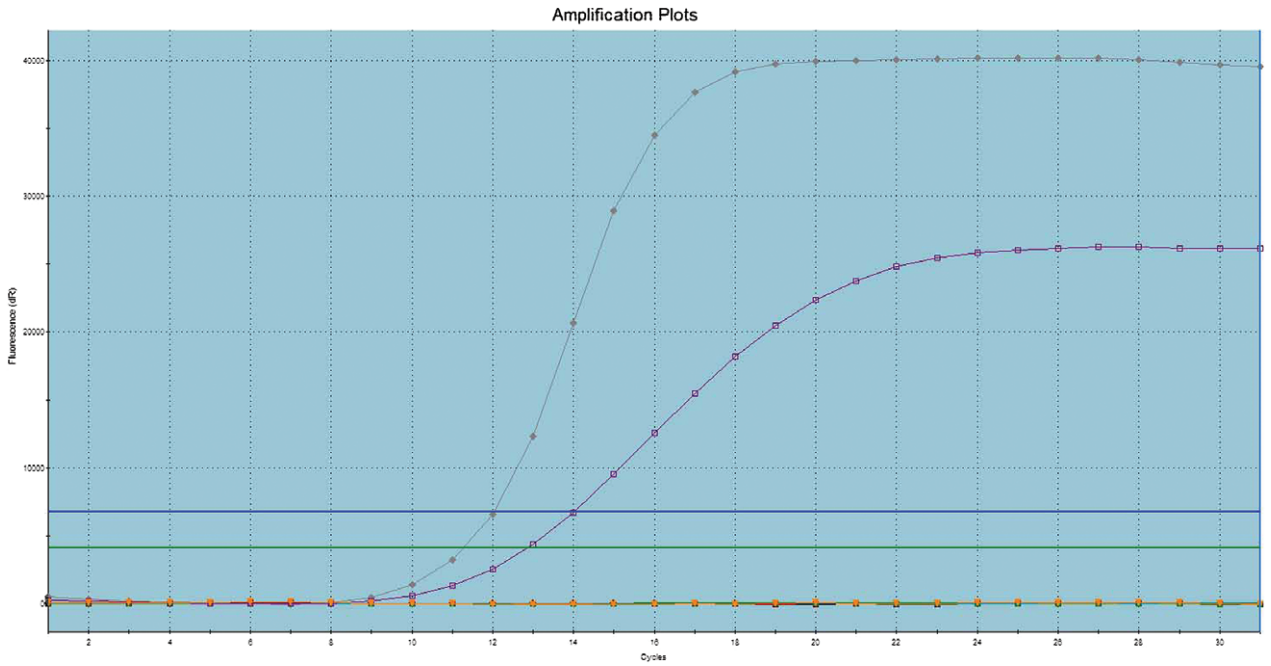

Figure 3 Schema shows tumor with drivers of *ROS1* gene positive by reverse transcription-PCR. Purple, gray, and orange represent the sample, and positive and negative controls, respectively.

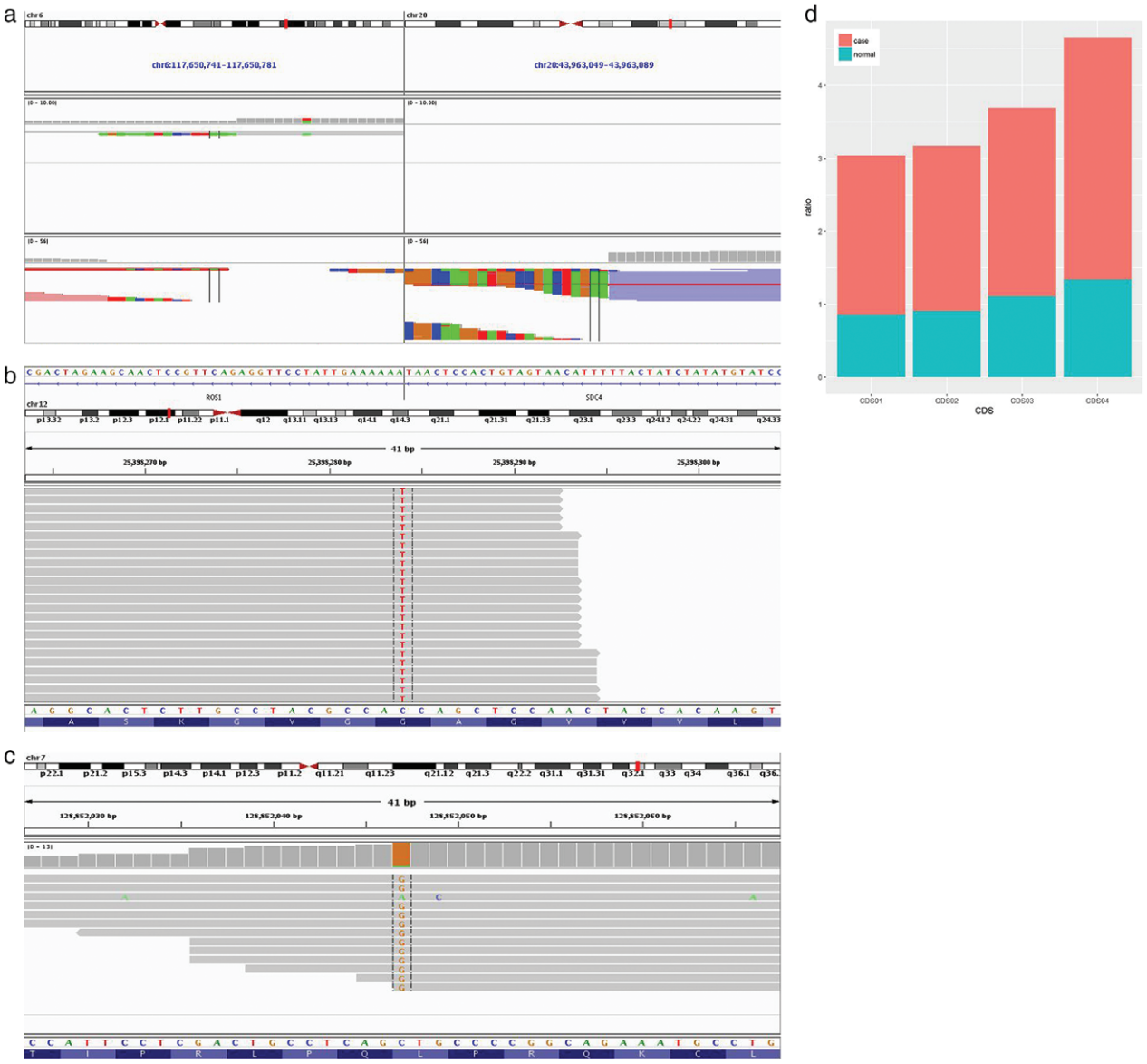

Figure 4 Schema shows tumor with dual drivers of the *SDC4-ROS1* fusion gene. (**a**) *KRAS* p.G12D, (**b**) *SMO* p.L707V, (**c**) point mutation, and (**d**) *KRAS* gene amplification by next-generation sequencing.

prominent effect and could be used as a prognostic signature in lung cancer.

Most NSCLC *KRAS* mutant cases present single point mutations at codon 12, while mutations in others positions are relatively rare (in codons 13 and 61).[13] Within codon 12, the most frequent point mutations are G12C (42%), G12V (21%), G12D (17%), and G12A (7%).[14] Mutations in *KRAS*, *NRAS*, and *HRAS* are commonly observed in various tumor types, including NSCLC.

Chemotherapy and TKI treatments in NSCLC patients with *KRAS* mutations yield inferior outcomes and are associated with negative prognosis and shorter survival.[15–17] No successful targeted therapies, such as EGFR-TKIs or ALK-TKIs, have been developed against *KRAS* mutations thus far. However, several MEK inhibitors have been developed, such as selumetinib (AZD6244). A randomized phase II trial of docetaxel with and without selumetinib revealed that patients treated with the combination had superior overall survival and a statistically significant improvement in progression-free survival and objective response rate; however, there is no drastically effective treatment for patients with these types of tumors.[18]

Some 15–30% of patients with NSCLC exhibit a gain-of-function mutation in the *KRAS* gene, resulting in a failure to respond to EGFR-TKI treatment. This phenomenon may occur in patients receiving ROS1-TKI treatment.

KRAS activation leads to ERK1/2 overexpression via the RAF/MEK/ERK signaling pathway. Therefore, inhibiting the RAF/MEK/ERK signaling pathway may result in an improvement in patients with TKI-acquired resistance.[19] Some studies have shown that gefitinib combined with selumetinib is effective in overcoming acquired EGFR-TKI resistance in lung cancer cells. The combination treatment may be beneficial to NSCLC patients who have both *EGFR* and *KRAS* mutations.

ROS1 rearrangements rarely overlap with alterations in *EGFR*, *KRAS*, *ALK*, or other targetable oncogenes in NSCLC. In a study of 62 patients with *ROS1*-rearranged NSCLC, none harbored concurrent *ALK* fusions (0%) or *EGFR* activating mutations (0%). *KRAS* mutations were detected in two cases (3.2%).[20]

Point mutations of the *KRAS* oncogene may interfere with otherwise intact ROS1 signaling, leading to a lack of response to crizotinib, and are consequently correlated with poor response to ROS1-targeted therapies. Therefore, knowledge of the *ROS1* and *KRAS* mutation status of a tumor is likely to provide a potential strategy to select patients who are likely to benefit from ROS1-targeted therapies.

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Disclosure

No authors report any conflict of interest.

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