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EGFR, KRAS and ROS1 variants coexist in a lung adenocarcinoma patient

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ABSTRACT

The c-ros oncogene 1 (ROS1) fusion is almost mutually exclusive to epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) or Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation in non-small cell lung cancer (NSCLC), and it is not seen in the literature for patients to exhibit three mutations. The present study reported a case of a 53-year-old male diagnosed with adenocarcinoma, exhibiting combined EGFR, KRAS mutations and ROS1 rearrangement. At the first line therapy, the patient was treated with crizotinib because of the KRAS mutation that is a known resistant factor of EGFR-TKI resistance, but no responsive. At the second line therapy, EGFR-TKI Icotinib revealed a good response until now. To the best of to our knowledge, this is the first case report of a patient with concurrent EGFR, KRAS mutations and ROS1 fusion. This patient had an excellent response to Icotinib but not crizotinib, suggesting that the EGFR mutation was the oncogenic driver but ROS1 fusion and KRAS mutation not.

1. Case report

A 53-year-old Chinese man was admitted with a 2-month history of cough and chest pain. A chest computed tomography revealed an about 4 cm right lower lobe mass with right pleural effusion (Fig. 1A). Whole body bone scan showed multiple bone metastases. No metastasis was observed by abdominal ultrasound examination and magnetic resonance imaging of the brain. The patient had no smoking history. He had no family history of malignant tumor. Pathological examination of brush biopsy of electronic bronchoscopy and CT-guided percutaneous pulmonary biopsy showed lung adenocarcinoma (Fig. 1C). The patient was clinically diagnosed with stage IV lung adenocarcinoma, T4N3M1b, with Eastern Cooperative Oncology Group performance status of 1.

The biopsied specimen from this patient was tested for *epidermal growth factor receptor (EGFR), Kirsten rat sarcoma viral oncogene homolog (KRAS), and v-Raf murine sarcoma viral oncogene homolog B (BRAF)* using amplification-refractory mutation system (ARMS) assay with AmoyDx *EGFR*29 Mutations Detection Kit, AmoyDx *KRAS19* Mutations Gene Detection Kit, AmoyDx *BRAFV600E* Mutation Gene Detection Kit, and was tested for *anaplastic lymphoma kinase (ALK)*, The *c-ros oncogene 1 (ROS1)* status using reverse-transcriptase polymerase chain reaction (RT-PCR) assay with AmoyDx *EML4-ALK* Fusion Gene Detection Kit, AmoyDx *ROS1* Fusion Gene Detection Kit (Amoy Diagnostics, Xiamen, China). The findings showed that the patient was negative for *EML4-ALK* fusion and *BRAF* mutation, but was positive for *EGFR* mutations *(exon 19 deletion)*, *KRAS mutation (Gly12Ala), and ROS1* fusions (Fig. 1D–F respectively). The *ROS1* fusions were also confirmed by sequencing (Fig. 2), but the *KRAS* mutation was not found in the sequencing, maybe because the sequencing is not so sensitive like ARMS.

The treatment of the patient was initiated with docetaxel plus carboplatin in the first-line treatment setting. After two cycles of this regimen, the disease progressed. Then, we detected the gene mutation aforementioned. Because of the *KRAS* mutation, a known factor of EGFR tyrosine kinase inhibitors (EGFR-TKIs) resistance, the patient received crizotinib treatment. However, the patient had a disease progression after one month, and then we tried Icotinib treatment, and got partial response after one month (Fig. 1B). Moreover, the patient has been treated for another 8 months with stable disease now.

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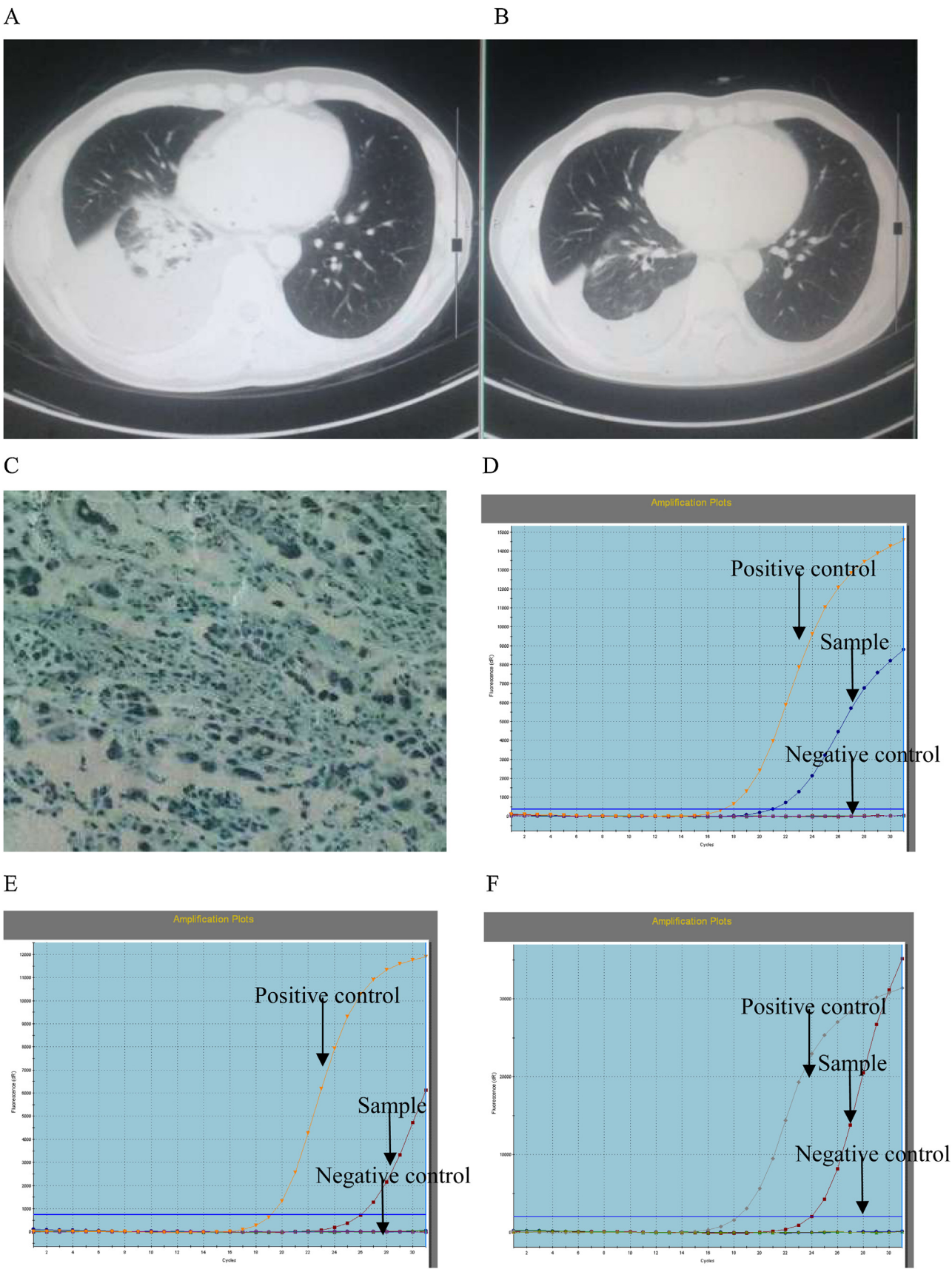

Fig. 1. Imaging, pathological and molecular examinations of the case. (A) Chest computed tomography revealed an about 4-cm right lower lobe mass with right pleural effusion. (B) Chest computed tomography showed that the patient got partial remission after one-month treatment of gefitinib. (C) Pathological examination of brush biopsy of electronic bronchoscopy revealed adenocarcinoma. (D) Amplification-refractory mutation system assay showed EGFR exon 19 deletion. (E) Amplification-refractory mutation system assay showed KRAS mutation (Gly12Ala). F, RT-PCR assay showed positive ROS1 fusion.