**Acquired** **SAMD5-RET** **Fusion-Mediated Resistance to Gefitinib in Metastatic Non-Small Cell Lung Cancer Harboring EGFR-Activating Mutation: A Case Report**

Dai S.S¹, Zhou P³, Fenq M² and Qiu Z*²

¹Center of Gerontology and Geriatrics, West China Hospital, Sichuan University, Chengdu, P.R. China
²Department of Respiratory and Critical Care Medicine, West China Hospital, Sichuan University, Chengdu, P.R. China
³Department of Pathology, West China Hospital, Sichuan University, Chengdu, P.R. China

*Corresponding author:
ZhiXin Qiu,
Department of Respiratory and Critical Care Medicine, West China Hospital, Sichuan University, Chengdu, 610041, P.R. China.
Tel: 86-2885423998,
E-mail: qiuseagull@foxmail.com

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Dai S, Zhou P and Qiu Z, these authors are contributed equally to this article.

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Abbreviations:
CCDC6 = coiled-coil domain containing 6; CT = computed tomography; EMT = endothelial-mesenchymal transition; EGFR = epidermal growth factor receptor; HER2 = human epidermal growth factor receptor-2; KIF5B = kinesin-1 heavy chain; MET = mesenchymal to epithelial transition factor; NGS = next generation sequencing; NSCLC = non-small cell lung cancer; NCOA4 = nuclear receptor coactivator 4; PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit; RET = rearrangement during transfection; PD = progressive disease; SAMD5 = sterile alpha motif domain containing 5; TKI = tyrosine kinase inhibitor; BRAF = v-raf murine viral oncogene homolog B1; TRIM24 = tripartite motif containing 24; 19del = 19 deletion

1. Abstract

1.1. Background: Patients with disease progression on first-generation tyrosine kinase inhibitors (TKIs) usually have a poor prognosis. The mechanisms of acquired resistance to epidermal growth factor receptor (EGFR)-TKIs have been widely reported; however, reports of acquired rearrangement-during-transfection (RET) fusion are rare.

1.2. Case Summary: We report a case of lung adenocarcinoma with a novel sterile alpha motif domain containing 5 (SAMD5)-RET fusion as a mechanism of resistance to the first-generation EGFR-TKI, gefitinib. She was diagnosed with stage IV A (cT3N2M1a) lung adenocarcinoma with metastases to the right lung and right pleural cavity. Capture-based next generation sequencing (NGS) on pleural tumor sample revealed a molecular alteration in exon 19 deletion (19del) of EGFR. Gefitinib treatment was initiated. Two months later, disease progression was confirmed, with enlargement of the lung tumor and increased pleural effusion, and NGS of tumor tissue revealed SAMD5-RET fusion with allelic frequency of 14.9%. Although the patient received the best supportive treatment, she died with an overall survival of 9 months.

1.3. Conclusion: This case extended the understanding of the mechanisms of acquired resistance to first-generation EGFR-TKIs. Re-biopsy and NGS may provide the basis for accurate treatment of advanced NSCLC.

2. Background

In non-small cell lung cancer (NSCLC), acquired epidermal growth factor receptor (EGFR) T790M mutation was found in almost 50%–60% of the EGFR-tyrosine kinase inhibitor (TKI) resistant cases [1], followed by human epidermal growth factor receptor-2 (HER2) amplification (8%–13%) [2], mesenchymal to...
epithelial transition factor (MET) amplification (5%–10%) [3,4], small cell lung cancer (SCLC) transformation (5%) [5], endothelial-mesenchymal transition (EMT) (5%) [5], phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit (PIK3CA) mutation (1%–2%) [5] and v-raf murine viral oncogene homolog B1 (BRAF) mutation (1%) [6]. However, some of the resistance mechanisms are still unknown [7]. Here, we present the case of an EGFR-mutated non-small cell lung cancer (NSCLC) in a patient who developed a novel rearrangement-during-transfection (RET) fusion after progression on a first-generation EGFR-TKI.

3. Case Presentation

A 47-year-old never-smoker woman was admitted on April 20, 2017 due to right chest pain, cough, and dyspnea. Right lung breath sounds decreased, percussion dullness. She was diagnosed with stage IVA (cT3N2M1a) lung adenocarcinoma with metastases to right lung and right pleural (Figure 1, 2). Capture-based next generation sequencing (NGS) on pleural tumor sample revealed a molecular alteration in exon 19 deletion (19Del) of EGFR (19 exon p. E746_A750del in-frame deletion mutation, c.2235_2249del, p. Glu746_Ala750del, allelic frequency: 63.08%). Subsequently, the patient was started on gefitinib 250 mg once a day (QD) from May 2017. After two months of treatment, the patient's cough and dyspnea worsened. Disease progression was confirmed, with enlargement of the lung tumor and increased pleural effusion. (Figure 1). Adenocarcinoma was confirmed in the rebiopsy specimen of the pleura, and NGS of tumor tissue revealed a sterile alpha motif domain containing 5 (SAMD5)-RET mutation with an allelic frequency of the 14.9%, and the absence of the EGFR mutation (Figure 3). Therefore, the treatment regimen was changed to gefitinib 250 mg QD + cabozantinib 80 mg QD, and the symptoms of chest pain and dyspnea were alleviated. The patient progressed with a progression-free survival of 6 months in January 2018. Although the patient received the best supportive treatment, she died in April 2018 with an overall survival of 9 months.

Figure 1: The main treatment processes and changes visualized on CT scans

Chest Computed tomography (CT) scan on April 22, 2017 showed irregular soft tissue shadow at the basal segment of the right lower lobe, enlarged mediastinal and right hilar lymph nodes, and right pleural effusion with pleural thickening.

Chest CT (July 11, 2017) showed massive pleural effusion in the right pleural cavity with extensive thickening of the right pleura, enlargement of the right hilar and mediastinal lymph nodes, and a small amount of pericardial effusion.

Chest CT (December 4, 2017) showed massive pleural effusion in the right pleural cavity with extensive thickening of the right pleura, and enlargement of the right hilar and mediastinal lymph nodes. The pericardium was thickened slightly with a small amount of pericardial effusion. In addition, a small thin nodular shadow under the left lung pleura and a small amount of pleural effusion on the left were observed.

A pulmonary artery vascular enhanced CT (January 16, 2018) indicated a low-density filling defect in the lumen of the pulmonary artery at the base of the left lower lobe basal segment, which suggested pulmonary thrombosis. Also, massive pericardial effusion and left pleural effusion could be observed.
Figure 2: Immunohistochemical images of pleural effusion and pleural tissue

(A) IHC results of the pleural effusion cell block were as follows: CEA (+), EC (+), Napsin A (+), TTF-1 (+), WT-1 (-), PD-L1 (+, positive proportion about 1%-2%), ALK-V (-), ROS-1 (-), which supported the diagnosis of lung adenocarcinoma.

(B) IHC results of pleural tissue were as follows: PCK (+), CK7 (+), Napsin A (+), TTF-1 (+), CR (-), WT-1 (-), PD-L1 (+, positive proportion about 3%-5%), ALK-V (-), ROS-1 (-), which supported the diagnosis of lung adenocarcinoma.
**Figure 3:** The novel gefitinib-resistant RET fusion mutation

**Supplementary Table 1.** Summary of acquired RET fusions in EGFR-TKI resistant lung cancer patients.

<table>
<thead>
<tr>
<th>No.</th>
<th>Author, year</th>
<th>EGFR mutation</th>
<th>EGFR TKI(s) before RET fusion</th>
<th>RET fusion (mean allele frequency)</th>
<th>Other Mutations</th>
<th>Treatment after RET fusion</th>
<th>Response</th>
<th>Duration of response (Mo.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Wang, 2020</td>
<td>L858R, T790M</td>
<td>O + CZ</td>
<td>CCDC6-RET</td>
<td></td>
<td>O + CB</td>
<td></td>
<td>Treatment ongoing</td>
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<tr>
<td>2</td>
<td>Klempner, 2015</td>
<td>19Del</td>
<td>E</td>
<td>CCDC6-RET</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Klempner, 2015</td>
<td>19Del</td>
<td>E</td>
<td>CCDC6-RET</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Piotrowska, 2018</td>
<td>19Del</td>
<td>A</td>
<td>CCDC6–RET TP53</td>
<td>E + CB</td>
<td>SD</td>
<td>2.5</td>
<td></td>
</tr>
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<td>5</td>
<td>Piotrowska, 2018</td>
<td>19Del, T790M</td>
<td>A, O</td>
<td>CCDC6–RET</td>
<td></td>
<td>O + BLU-667</td>
<td>PR</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Schrock, 2018</td>
<td>19Del</td>
<td>E</td>
<td>CCDC6–RET</td>
<td>AKT2 amp, CCND3 amp, CCNE1 amp, BCL2L2 amp, NFKBIA amp, NFK2-1 amp, CDKN2A/B loss, TP53 Y203H, CBL Y371N, RAD51 M1β*8, SPT1 R1077H</td>
<td>O + CB</td>
<td>Treatment ongoing</td>
<td></td>
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<td>7</td>
<td>Schrock, 2018</td>
<td>19Del</td>
<td>E</td>
<td>CCDC6–RET</td>
<td>AKT2 amp, CCND1 amp, AXL amp, CCNE1 amp, CDK6 amp, FGF19/3/4 amp, CDKN2A/B loss, PARK2 splice site, TP53 K120fs<em>26, PRMB1 K416fs</em>3, SMAD4 Y133fs*8</td>
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<td></td>
<td></td>
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<td>Schrock, 2018</td>
<td>19Del</td>
<td>E</td>
<td>CCDC6–RET</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>9</td>
<td>Neal, 2016</td>
<td>NR</td>
<td>G or E</td>
<td>CCDC6–RET</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>10</td>
<td>Neal, 2016</td>
<td>NR</td>
<td>G or E</td>
<td>CCDC6–RET</td>
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<td></td>
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<tr>
<td>11</td>
<td>Xu, 2019</td>
<td>L858R</td>
<td>O</td>
<td>CCDC6–RET</td>
<td>EGFR amp</td>
<td></td>
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<tr>
<td>12</td>
<td>Oxnard, 2018</td>
<td>19Del, T790M</td>
<td>O</td>
<td>CCDC6–RET</td>
<td>TP53 F270L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Xu, 2019</td>
<td>19Del (E746_A750delA, T790M)</td>
<td>O</td>
<td>CCDC6–RET KRAS amp</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Piotrowska, 2018</td>
<td>19Del, T790M</td>
<td>E, O</td>
<td>CCDC6–RET</td>
<td>EGFR Amp, BRAF Amp, MET Amp, CKD6 Amp, CCNE1 Amp, TP53, TERT, TPM3–NTRK1</td>
<td>O</td>
<td></td>
<td></td>
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<tr>
<td>15</td>
<td>Xu, 2019</td>
<td>19Del (E746_A750delA, T790M)</td>
<td>O</td>
<td>CCDC6–RET</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Rich, 2019</td>
<td>19Del</td>
<td>E</td>
<td>CCDC6–RET (0.1%)</td>
<td>EGFR T790M, EGFR T854A, EGFR amp, MET amp</td>
<td>Pembrolizumab</td>
<td>SD</td>
<td>2</td>
</tr>
<tr>
<td>17</td>
<td>Rich, 2019</td>
<td>19Del, T790M</td>
<td>E, O</td>
<td>CCDC6–RET (0.1%)</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Rich, 2019</td>
<td>19Del</td>
<td>U</td>
<td>CCDC6–RET (0.1%)</td>
<td>EGFR T790M, EGFR amp</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Rich, 2019</td>
<td>19Del, T790M</td>
<td>A, O</td>
<td>CCDC6–RET (0.1%/0.4%)</td>
<td>O + bevacizumab</td>
<td>Progression; 10; Chemotherapy PR</td>
<td>Unknown</td>
<td></td>
</tr>
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</table>
Our patient was diagnosed with lung adenocarcinoma and harbored the EGFR 19del mutation according to targeted sequencing on initial examination. The effect was poor and the disease progressed rapidly after treatment with gefitinib. Biopsy and targeted sequencing were repeated, and interestingly, we found a novel SAMD5-RET fusion, and the original EGFR mutation was lost. We suspected whether the new mutation was induced following gefitinib treatment combined with cabozantinib, the disease progressed rapidly, indicating that broad-spectrum antitumor drugs have a poor efficacy in patients with EGFR 19del mutation or RET fusion. Previous research found that 28% of patients with RET rearrangements experienced a partial response after treatment with cabozantinib [22]. Cabozantinib alone or in combination with erlotinib has superior efficacy to erlotinib alone in EGFR wild-type advanced lung cancer patients [19]. However, caboza
tinib might have had no remarkable effect on our patient. Previous cases reported that patients with acquired RET fusion following treatment with erlotinib, icotinib, or afatinib combined with caboza
tinib achieved stable disease (SD) for only 2–7 months [9,13,15]. However, a 69-year-old male with CCDC6-RET achieved partial response after receiving osimertinib plus caboza
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4. Discussion

Our patient was diagnosed with lung adenocarcinoma and harbored the EGFR 19del mutation according to targeted sequencing on initial examination. The effect was poor and the disease progressed rapidly after treatment with gefitinib. Biopsy and targeted sequencing were repeated, and interestingly, we found a novel SAMD5-RET fusion, and the original EGFR mutation was lost. We suspected whether the new mutation was induced following gefitinib treatment combined with caboza
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http://www.acmcasereport.com/
months after completion of immunotherapy [23]. These studies also provide real clinical data supporting our treatment of patients with RET fusion.

5. Conclusion
We reported a special case of acquired RET rearrangement in an EGFR-mutated NSCLC patient whose disease progressed on first-generation EGFR-TKI, gefitinib. This case indicates that rare new mutations may be induced during treatment with EGFR-TKIs, and that the EGFR mutation itself may be suppressed after treatment. In addition, patients with RET fusion may experience rapid disease progression and may be prone to pleural, lymph node, and distant metastases. Repeated biopsies and gene tests are necessary for lung cancer patients with rapid disease progression during treatment.

6. Funding
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