A lung adenocarcinoma patient with co-mutations of MET and EGFR exon20 insertion responded to crizotinib

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Abstract

Background: Targeted therapy has revolutionized the treatment of patients with malignancies harboring mutations in driver genes and has brought a favorable survival benefit to the population with actionable oncogenic mutations. In recent years, the MET exon14 skipping mutation has been recognized as a potentially promising therapeutic target in non-small cell lung cancer (NSCLC). These changes are mutually exclusive with molecular drivers such as EGFR, KRAS, HER-2, BRAF, ALK and ROS1. The prevalence rate of coexisting MET exon 14 mutations and EGFR sensitive mutations (L858R, exon 19 deletions) in Chinese population was reported to be 0.2% (3/1590). However, the coexistence of MET exon 14 mutations with EGFR exon 20 insertion mutations has never been reported and the management of this subtype is not identified.

Case presentation: A 69-year-old male with a right lung adenocarcinoma (T4N2M0, IIIB) was confirmed to be positive for MET exon 14 skipping (c.3028_3028+1delGGinsTT, 44.4%), MET amplification (copy number 4.4), and EGFR exon 20 insertion (p. N771_H773dup, 22.1%) mutations. After the progression of one cycle of chemotherapy (Pemetrexed 0.8 g d1), the patient was subsequently accepted treatment with Crizotinib (250 mg twice a day) and achieved an important clinical remission for six months until the development of brain metastases. Then, he was submitted to a cycle of anti-programmed cell death-1 (PD-1) therapy after failure of Crizotinib and eventually acquired resistance despite of the high expression of programmed death ligand-1 (PD-L1) and tumor mutational burden (TMB) status.

Conclusion: This case report provides treatment strategies for epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs)-untreated lung adenocarcinoma patients simultaneously carrying MET alterations and EGFR exon 20 insertion mutations. In addition, the signatures of PD-L1 or TMB expression were not the candidate for predicting the efficacy of immunotherapy in this context.

Keywords: NCSLC, MET mutation, EGFR mutation, Double mutation, Crizotinib
molecule programmed cell death-1 (PD-1) or its ligand PD-L1 may deliver co-inhibitory signaling to T cell receptors, leading an immunosuppressive microenvironment. PD-1/PD-L1 inhibitors have been an established therapy and achieved unprecedented long-term clinical effect for the capability of restoring the function of T cells to kill tumor cells [2, 3]. Mutations in EGFR, ALK, and MET indicate that patients may experience clinical benefit with the corresponding targeted drugs [4]. In recent years, the multitargeted inhibitor Crizotinib has been approved for patients with ALK/ROS1 rearrangements, MET amplification or exon14 skipping mutations [5, 6].

Although the corresponding relationship between targeted drugs and some oncogenic mutations is quite certain, the coexistence of actionable mutations in the same tumor has been little researched, and the treatment of these patients remains unclear. Dysregulation of the MET gene frequently occurs as a resistance mechanism to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) therapy. The reported frequency of concomitant MET exon 14 mutations and EGFR mutations (L858R, exon 19 deletions) in Chinese population was 0.2% (3/1590), representing a rare event in NSCLC. However, the coexistence with EGFR exon 20 insertion mutation has never been reported [7]. Here we report the first case of a non-EGFR-TKIs treated patient who harbored both EGFR exon 20 insertion and MET mutations developed lymph node enlargement after the first single-agent chemotherapy with Pemetrexed for 9 days. Subsequent attempt of Crizotinib treatment resulted in an important 6-month partial remission (PR). However, the patient ultimately failed to two-week PD-1 therapy and delivered extensive systemic metastases despite the high expression of PD-L1 and tumor mutational burden (TMB) status.

Case presentation
A 69-year-old male patient with a body mass index (BMI) of 18.4(kg/m²), presented to the Third Affiliated Hospital of Soochow University in October 2019, complaining of pulmonary lesions for 10 days, detected on radiographic follow-up imaging. The patient had a 40-pack-year smoking history with no family history of cancer. A systematic review of patients found that he had a history of microsatellite stable (MSS) sigmoid cancer (pT3N0M0, stage IIa) with wild-type KRAS/BRAF mutations and had undergone partial sigmoid cancer resection combined with mesenteric lymph node dissection in August 2018 without adjuvant chemotherapy after surgery. Postoperative pathology showed moderately differentiated moderately ulcerative adenocarcinoma (3*2.5 cm), invading the full-thickness bowel wall, with no accumulation of upper and lower resection margins, and no cancer metastasis in mesenteric lymph nodes (0/14). Immunohistochemical results showed positive results for PMS2, MSH6, MLH1, MSH2 and Ki67 (50%), as well as negative results for CerbB-2 and P53. Complete remission (CR) was achieved after 13 months of regular follow-up. However, pulmonary lesions was detected during the follow-up imaging. Pathologic examination of the bronchoscopic biopsy indicated adenocarcinoma (Fig. 1). The chest computed tomography (CT) at baseline revealed a mass in the right middle and lower lobe and enlarged lymph nodes in the right hilum and mediastinum on October 24, 2019 (Fig. 2A). Immunohistochemical staining showed positive results for thyroid transcription factor-1 (TTF-1), novel aspartie proteinase A (Napsin A), Cytokeratin 7 (CK7), cytokeratin (AE1/ AE3) and PD-L1 (approximately 50% of tumor cells), as well as negative results for cytokeratin 5/6 (CK5/6) and P40, confirming a diagnosis of right lung adenocarcinoma (T4N2M0, IIIB) according to the eighth edition of the TNM classification of lung cancer (Fig. 1).

With informed consent, paired tumor-normal targeted next generation sequencing of 1021 cancer-related genes (Geneplus- Beijing Ltd, Beijing, China) was performed on DNA derived from bronchoscopic biopsy tissue and leukocytes on November 6, 2019. In total 29 somatic mutations were identified, including actionable targets such as MET exon14 skipping (c.3028_3028+1delGGinsTT, 44.4%) (Fig. 3A), MET amplification (copy number 4.4),

![Fig. 1 Hematoxylin and eosin staining for lung adenocarcinoma. The sample was formalin-fixed, paraffin-embedded, and then stained with eosin. Hematoxylin and eosin staining (H&E) showed very few atypia cells showing adenoid differentiation (x40). Microscopy was performed using an Olympus BX5 microscope (Japan) and Guangzhou Mingmei MD30 camera (China) with no filter, acquisition software was MicroShot basic, Mingmei MD30 cellsens Entry camera system with a resolution of 1000 (W) x 563(H) pixels and no downstream processing. Scale bar: 100 μm](image)
EGFR exon 20 insertion (p.N771_H773dup, 22.1%) (Fig. 3B), NF1 IVS41(c.6365-2A>C, 9.3%), and CCND1 amplification (copy number 3.4). Table 1 lists all of the identified somatic mutations, including single-nucleotide variations, small insertions/deletions, copy number variations, and rearrangements. The TMB and microsatellite instability (MSI) were calculated as previously described [8, 9], and the results were TMB-H (28.2 Muts/Mb>20 Muts/Mb) and MSS.
According to the National Comprehensive Cancer Network clinical practice guidelines for NSCLC (2019, Version 4), the patient should receive 6 cycles of Pemetrexed (500 mg/kg) and Carboplatin (AUC 6.0 mg/mL/min) administered at 21-day intervals as first-line therapy. The patient refused platinum-based chemotherapy for being informed of the gastrointestinal adverse reactions. Therefore, one cycle of chemotherapy (Pemetrexed monotherapy 0.8 g d1) was first given on November 18, 2019. After the first round of chemotherapy, he developed chest tightness and fatigue symptoms with a poor general condition. Subsequently, the first evaluation by CT showed progressed of disease with enlarged lymph nodes in the right hilum and mediastinum on November 27, 2019 (Fig. 2B). Considering the alteration of MET (Exon 14 skipping and amplification), Crizotinib was initiated at a dose of 250 mg twice a day. After 1 month of treatment, a significant decrease in tumor size was achieved with improvements in the patient's symptoms and functional

Table 1 List of all identified somatic mutations, including single-nucleotide variations, small insertions/deletions, copy number variations, and rearrangements

| Gene   | Transcript | Nucleic acid changes | Amino acid changes | Functional area | Frequency/copy number |
|--------|------------|----------------------|--------------------|-----------------|-----------------------|
| MET    | NM_000245.2 | c.3028_3028+1delGGinsTT | -                  | EX14-IVS14      | 44.4%                 |
| MLL3   | NM_170606.2 | c.7151G>[2>1]         | p.Q238SR6*67       | EX37            | 38.4%                 |
| SERPINB4 | NM_002974.2 | c.964G>C              | p.G322R            | EX8             | 25.7%                 |
| CDC73  | NM_024529.4 | c.1590A>T             | p.R53OS            | EX17            | 24.4%                 |
| EGFR   | NM_005228.3 | c.2311_2319dupAAACCCCAAC | p.N771_H773dup     | EX20            | 22.1%                 |
| TP53   | NM_000546.5 | c.548C>A              | p.S183*            | EX5             | 17.9%                 |
| TBX3   | NM_016569.3 | c.97GT                | p.V33L             | EX1             | 15.9%                 |
| RNF43  | NM_017763.4 | c.625A>G              | p.I209V            | EX6             | 14.3%                 |
| TP53   | NM_000546.5 | c.461G>T              | p.G154V            | EX5             | 12.3%                 |
| ATRX   | NM_000489.3 | c.5594G>A             | p.R1865K           | EX23            | 11.4%                 |
| LRP1B  | NM_018557.2 | c.11063T>C            | p.L3688P           | EX72            | 10.7%                 |
| NF1    | NM_000267.3 | c.6365-2A>C           | -                  | IVS41           | 9.3%                  |
| BCR    | NM_001123385.1 | c.2965A>T              | p.S989C            | EX4             | 9.1%                  |
| KDM5C  | NM_004187.3 | c.2953G>C             | p.E985Q            | EX19            | 8.6%                  |
| STAT3  | NM_139276.2 | c.1002C>A             | p.D334E            | EX10            | 8.4%                  |
| TBX3   | NM_016569.3 | c.1565C>A             | p.P522H            | EX7             | 8.1%                  |
| FANC2D | NM_033084.3 | c.1767-1G>C           | -                  | IVS19           | 5.0%                  |
| PALB2  | NM_024675.3 | c.129G>C              | p.K43N             | EX3             | 4.8%                  |
| TP73   | NM_005427.3 | c.806G>T              | p.R269L            | EX7             | 4.7%                  |
| OR4C6  | NM_001004704.1 | c.220G>C              | p.V74L             | EX1             | 4.5%                  |
| KDR    | NM_002523.2 | c.3625G>T             | p.D1209Y           | EX27            | 4.3%                  |
| MLL3   | NM_170606.2 | c.1429G>C             | p.K4764N           | EX55            | 3.9%                  |
| MLL    | NM_001197104.1 | c.3690G>C              | p.E1230D           | EX7             | 3.9%                  |
| ABL2   | NM_007314.3 | c.125C>T              | p.T42I             | EX1             | 3.7%                  |
| ARID1A | NM_006015.4 | c.2369A>G             | p.Q790R            | EX7             | 3.5%                  |
| MLL3   | NM_170606.2 | c.14035C>T             | p.P4679S           | EX54            | 3.5%                  |
| U2AF1  | NM_006758.2 | c.255G>A              | p.D799N            | EX4             | 3.4%                  |
| CDKN2A | NM_000077.4 | c.164G>T              | p.G555V            | EX2             | 3.3%                  |
| MLL3   | NM_170606.2 | c.7322G>T             | p.G2441V           | EX37            | 3.2%                  |
| NOTCH1 | NM_017617.3 | c.4501A>T             | p.S1501C           | EX25            | 3.0%                  |
| GRM3   | NM_000840.2 | c.1037A>T             | p.H346L            | EX3             | 2.6%                  |
| FAT1   | NM_005245.3 | c.7421G>T             | p.S2471I           | EX10            | 1.9%                  |
| AKT2   | NM_001626.4 | Amplification          | -                  | All exon        | 2.2                    |
| MET    | NM_000245.2 | Amplification          | -                  | All exon        | 2.2                    |
| CCND1  | NM_053056.2 | Amplification          | -                  | All exon        | 1.7                    |

*–* means undetectable. Variant gene frequencies are defined as fractions of variant versus total sequencing read count expressed as percentages.
status. According to the Response Evaluation Criteria In Solid Tumors v1.1, PR was achieved (Fig. 2C).

Approximately six months later (June 2020), the patient was admitted to our hospital suffering from weakness of both upper limbs and back pain. Follow-up CT scan of the chest and abdomen showed progression of the lung lesions with postobstructive pneumonia and metastatic nodules in the right pleura with associated malignant pleural effusions (Fig. 2D). Brain magnetic resonance imaging (MRI) demonstrated multiple brain metastases in bilateral cerebral hemispheres (Fig. 2E). All of these symptoms indicated that the tumor had progressed despite Crizotinib therapy. Considering high level of PD-L1 expression (about 50%), the patient received a third-line treatment of Camrelizumab (200 mg) combined with Bevacizumab (300 mg) in June 2020. During treatment, the patient suffered from fatigue and weight loss. The diseases progressed further after one cycle of combined therapy. On June 16, 2020, whole-brain radiotherapy was administered because of the widespread brain metastases. Informed consent was obtained from the patient prior to treatment. In an attempt to improve tolerance to treatment, palliative intensity modulated radiation therapy (IMRT) was used. The patient received a dose of 30 Gy to the whole brain tissue, 52 Gy to left parietal lesion, and 30 Gy to right parietal lobe, right occipital lobe, and left temporal lobe. However, the patient finally died after two rounds of radiation therapy in July 2020.

**Discussion and conclusions**

This case report describes the treatment courses of a lung adenocarcinoma patient with coexisting of MET exon14 skipping, MET amplification and EGFR exon20 insertion mutations. This patient, harboring MET alterations and EGFR exon 20ins was responded to Crizotinib for approximately 6 months but was resistant to immunotherapy despite the high level expression of PD-L1 and TMB-H status.

To our knowledge, this is the first report of lung adenocarcinoma carrying a double MET alterations (exon14 skipping and amplification) and EGFR exon 20 insertion mutations in an EGFR-TKIs-untreated patients, if similar cases are encountered in the future, our treatment strategy may have some implications for these patients and their clinicians.

MET and EGFR are established therapeutic targets in NSCLC. The incidence of MET exon 14 skipping mutations in NSCLC is 3–4%, and EGFR exon 20 insertion mutations account for about 4–12% of the total EGFR mutations [10, 11]. EGFR-TKIs have been the standard option for EGFR-sensitizing mutations, such as exon19 deletion, exon21 L858R and other common mutations, and Crizotinib has been recommended for high-level MET amplification or MET exon 14 skipping mutations [12, 13]. Among substantial EGFR exon 20 insertion types, the p.A763_Y76insFQEA mutation (5–6%) displays sensitivity to approved EGFR-TKIs, while the clinical efficacy of other types is extremely limited [14]. As previously studied, MET dysregulation is a mechanism of acquired resistance to EGFR-TKIs [15–18]. The coexistence of MET amplification with EGFR mutations (1.4%) was previously reported in 2012, indicating that the progression-free survival (PFS) of patients with coexisting mutations was significantly shorter than that for patients with EGFR mutations alone [19]. Another study included 207 patients with advanced NSCLC and acquired resistance to EGFR-TKIs and suggested that 6.8% (14/207) had coexisting MET over expression and EGFR T790M mutations with a medium post-progression survival time of 10.7 months when treated with EGFR-TKIs plus a MET-tyrosine kinase inhibitors (MET-TKIs) [20]. The most recent study reported a female lung adenocarcinoma patient with the EGFR L858R mutation at baseline. The patient progressed after adjuvant Erlotinib therapy for approximately 58 months, subsequent genetic testing at that time was positive for EGFR T790M, MET amplification and MET exon14 mutations (0.23%, 2/866), so the therapy was changed to Osimertinib with MET-TKI (Crizotinib) and achieved a durable clinical response to this combination [21].

Notably, an in-vitro study showed that the expression of MET exon14 up-regulated the phosphorylation of EGFR and the interaction of MET with EGFR could drive the activity of the EGFR gene, which resulted in a blunting of the inhibition of EGFR phosphorylation by EGFR-TKIs. However, MET inhibition restored the antagonistic effect of Osimertinib on EGFR signaling [21, 22]. This result suggested a complex interaction between MET and EGFR in NSCLC and provided evidence for potential management strategies that the combination of Osimertinib and Crizotinib may be applicable for EGFR/MET exon14 co-altered lung cancers. In our case, this patient harbored an EGFR exon 20ins mutation, and most of these uncommon mutations may predict resistance to EGFR-TKIs [23, 24]. Therefore, our patient received Crizotinib monotherapy rather than a combination regimen with EGFR-TKIs. The phase II METROS trial demonstrated that the PFS and overall survival (OS) with MET amplification or exon14 skipping mutations were 4.4 months (95% CI, 3.0–5.8) and 5.4 months (95% CI, 4.2–6.5) respectively [25]. Encouragingly, the current patient harboring MET exon14 skipping, MET amplification, and EGFR exon20ins achieved approximately 6 months of PR with Crizotinib treatment. Liquid biopsy of 1021 gene panel
plasma ctDNA sequencing was assessed at the time of resistance to Crizotinib. The results showed that MET exon14 skipping and EGFR exon20 still existed, but the MET amplification disappeared, which to some extent explained the mechanism of resistance to Crizotinib targeted therapy.

Immune checkpoints inhibitors (ICIs) are critical for maintaining autoimmune tolerance and regulating the duration and extent of immune responses in peripheral tissues. Although the patient showed high expression of PD-L1 and TMB status at baseline, he did not benefit from Camrelizumab and Bevacizumab. As previous reported, positive oncogenic mutations have a negative impact on immunotherapy [26–28], and EGFR exon 20ins mutations may be the reason why this patient did not receive benefit from the treatment.

This case report also has some limitations. First of all, the rarity of the case with a rare co-mutation that has never been reported, making it less persuasive. In addition, the patient with low compliance during the treatment course greatly discounted the treatment effect. In recent years, immunotherapy options have been employed for MET exon 14 skipping with highly variable results. Although the extent of benefit from immunotherapy is generally not promising for MET exon 14 skipping with a shorter survival benefit compared with MET-TKIs. A retrospective analysis from Wong et al. showed moderate efficacy offered by immunotherapy in subsets of patients with MET exon 14 skipping, with a disease control rate (DCR) of 70% [29]. However, the patient in our case progressed too fast after immunotherapy, leading the limited duration of immunotherapy effect to be further observed. In a word, the coexistence of MET alterations and EGFR exon20ins mutation is a very rare event with no standard therapy, and further in-depth research is needed to identify the appropriate treatment for these patients with coexisting driver gene mutations.

Abbreviations
BMI: Body mass index; CK5/6: Cytokeratin 5/6; CK7: Cytokeratin 7; CT: Computed tomography; CR: Completed remission; DCR: Disease control rate; EGFR-TKIs: Epidermal growth factor receptor tyrosine kinase inhibitors; IMRT: Intensity modulated radiation therapy; MET-TKIs: MET-tyrosine kinase inhibitors; MSI: Microsatellite instability; MRI: Magnetic resonance imaging; MSS: Microsatellite stable; Napsin: Aspartic proteinase A; NSCLC: Non-small cell lung cancer; ORR: Overall response rate; OS: Overall survival; PD: Progressive disease; PD-1: Programmed cell death-1; PD-L1: Programmed death ligand-1; PR: Partial response; PFS: Progression-free survival; ICLs: Immune checkpoints inhibitors; TMB: Tumor mutational burden; TTF-1: Thyroid transcription factor-1.

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Author contributions
JS and XY designed the investigation. YC and YH contributed to writing the paper. YC, CZ, CF and WZ performed investigation. DG, MZ, and MJ provided essential assistance and analyzed data. XY, JS and BJ revised the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Availability of data and materials
The raw data of sequencing of the patient in this study are not publicly available in order to protect participant confidentiality, but the datasets generated and analysed during the current study are available in the Genome Sequence Archive (GSA) repository (https://ngdc.cncb.ac.cn/gsa-human/s/9NNcOT1EN), accession number HRA002387.

Declarations

Ethics approval and consent to participate
The daughter of the patient signed a case report informed consent form which is available for review.

Consent for publication
Written informed consent was obtained from the daughter of the patients for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Competing interests
The authors declare that they have no competing interests.

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