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Effective response to crizotinib of concurrent *KIF5B-MET* and *MET-CDR2*-rearranged non-small cell lung cancer: A case report

Lian-Fang Liu, Jia-Ying Deng, Analyn Lizaso, Jing Lin, Si Sun

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Abstract

BACKGROUND

Due to the rarity of mesenchymal-epithelial transition factor (*MET*) fusions, the clinical efficacy of crizotinib has only been described in a few patients with *MET* fusions involving various fusion partners. Herein, we report the clinical response to crizotinib of a patient with advanced poorly differentiated non-small cell carcinoma (NSCLC) having concurrent *MET* fusions.

CASE SUMMARY

A 46-year-old woman was diagnosed with poorly differentiated NSCLC (T4N3M1). With no classic driver mutations, she was treated with two cycles of gemcitabine and cisplatin without clinical benefit. Targeted sequencing revealed the detection of two concurrent *MET* fusions, *KIF5B-MET* and novel *MET-CDR2*. Crizotinib was initiated at a dose of 250 mg twice daily. Within 4 wk of crizotinib therapy, repeat computed chromatography revealed a dramatic reduction in primary and metastatic lesions, assessed as partial response. She continued to benefit from crizotinib for 3 mo until disease progression and died within 1 mo despite receiving nivolumab therapy.

CONCLUSION

Crizotinib sensitivity was observed in an advanced poorly differentiated NSCLC patient with concurrent *MET* fusions *KIF5B-MET* and *MET-CDR2*. Crizotinib can serve as a therapeutic option for patients with *MET* fusions. In addition, our case also highlights the importance of comprehensive genomic profiling particularly in patients with no classic driver mutation for guiding alternative therapeutic decisions.

Key Words: Poorly differentiated; Non-small cell carcinoma; Mesenchymal-epithelial transition factor fusion; Crizotinib; Case report

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Core Tip: The most common mesenchymal-epithelial transition factor (*MET*) gene aberrations are gene amplifications and exon 14 splice variants found in approximately 2% to 10% of lung cancer patients. Chromosomal rearrangements resulting in gene fusions involving *MET* are generally rare but could account for *MET*-driven oncogenesis. The rarity and diversity of *MET* fusions in non-small cell lung cancer (NSCLC) limit the volume of evidence documenting the clinical efficacy of crizotinib in treating *MET*-rearranged NSCLC patients. Herein, we report the clinical response to crizotinib of a patient with advanced poorly differentiated NSCLC harboring concurrent *MET*-involving rearrangements, including a novel *MET-CDR2* gene fusion.

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INTRODUCTION

The mesenchymal-epithelial transition (*MET*) gene, located on chromosome 7q21-31, encodes a receptor tyrosine kinase and is activated by its ligand, hepatocyte growth factor[1,2]. The *MET* signaling pathway is often upregulated in various human malignancies, including non-small cell lung cancer (NSCLC)[2]. The most common *MET* gene aberrations are gene amplifications and exon 14 splice variants found *de novo* in approximately 2% to 10% of lung cancer patients[3]. Chromosomal rearrangements resulting in gene fusions involving *MET* are generally rare but could account for *MET*-driven oncogenesis[4]. Currently, a total of five *MET* fusion partner genes have been reported in NSCLC, including *KIF5B*[5,6], *STARD3NL*[5], *HLA-DRB1*[7,8], *UBE2H*[9], and *ATXN7L1*[10] (Table 1). Crizotinib, an FDA-approved tyrosine kinase inhibitor for *ALK*-rearranged and *ROS1*-rearranged NSCLC, has been originally designed to target *MET* amplifications and mutations[11]. Several cases and clinical studies have reported the efficacy of crizotinib and cabozantinib in targeting *MET* amplification [12,13], exon 14 skipping[14], and certain rearrangements[5-7,10] in NSCLC patients. A recent meta-analysis analyzed six clinical trials (cohort size range: 8-69) on *MET*-altered NSCLC revealed an objective response rate of 40.6% (95%CI: 28.3%–53.0%) and disease control rate of 78.9% (95%CI: 70.3%–87.4%) for crizotinib, with a median progression-free survival and overall survival of 5.2 and 12.7 mo, respectively[15]. Most of these studies enrolled few *MET* fusion-positive patients, because they are exceedingly rare. Current knowledge regarding *MET* fusions is mostly derived from two cohort studies in Chinese lung cancer patients, which identified one (0.04%, 1/2410) fusion[16] and fifteen (0.26%, 15/5695) fusions involving the *MET* kinase domain[17], respectively.

Herein, we report the clinical efficacy of crizotinib in a patient with poorly differentiated NSCLC with *KIF5B-MET* and a concurrent novel *MET-CDR2* fusion.

CASE PRESENTATION

Chief complaints

In November 2018, a 46-year-old female never-smoker presented in our clinic with a complaint of persistent dry cough.

Table 1 Summary of case reports of crizotinib (250 mg/b.i.d. orally) in treating *MET*-rearranged non-small cell carcinoma

Ref.	Age	Sex	Smoker	Stage	Histology	<i>MET</i> fusion	Best overall response	PFS (mo)	Grade $\geq$ 3 AEs	Notes
[5]	33	F	Yes	IV	ADC	<i>KIF5B-MET</i>	PR	8	NR	
[5]	62	F	No	IV	ADC	<i>STARD3NL-MET</i>	PR	14	NR	
[6]	51	F	No	IV	ADC	<i>KIF5B-MET</i>	PR	10	NR	
[7]	74	F	No	Recurrent	ADC	<i>HLA-DRB1-MET</i>	Complete resolution of nodules while pleural effusion persisted	8	No	
[8]	59	F	No	Recurrent	ADC	<i>HLA-DRB1-MET</i>	Complete radiographic response	/	No	
[9]	43	F	No	IV	ADC	<i>MET-UBE2H</i>	PR	6.5	NR	<i>MET</i> fusion was acquired on <i>EGFR</i> -targeted therapy
[10]	56	F	No	IV	ADC	<i>MET-ATXN7L1</i>	PR	4	NR	

ADC: Adenocarcinoma; AE: Adverse event; NR: Not reported; PR: Partial response.

History of present illness

The cough had been lasted for over a week.

History of past illness

Past medical history was not remarkable for this patient.

Laboratory examinations

Histopathological analysis of tissue biopsy samples collected from the right lung revealed poorly differentiated NSCLC (Figure 1) with the immunohistochemistry results of AE1/AE3 (+), SMAC4 BRG1 (+), CK18 (+), INI-1 (+), CD56 (-), chromogranin A (-), synaptophysin (-), CK7 (-), ERG (-), GATA3 (-), CD34 (-), CDX2 (-), P40 (-), SALL4 (-), TTF-1 (-), Desmin (-), and S-100 (-). In addition, PD-L1 expression analysis revealed a tumor proportion score of 80%. Molecular analysis of the biopsies detected no driver alterations in *EGFR*, *ALK*, or *ROS1*.

Imaging examinations

Computed tomography (CT) and magnetic resonance imaging revealed a tumor in the lower lobe of the right lung, right hilar and mediastinal lymph node involvement, and multi-organ metastasis including the left pleura, liver, pericardium, and bone.

FINAL DIAGNOSIS

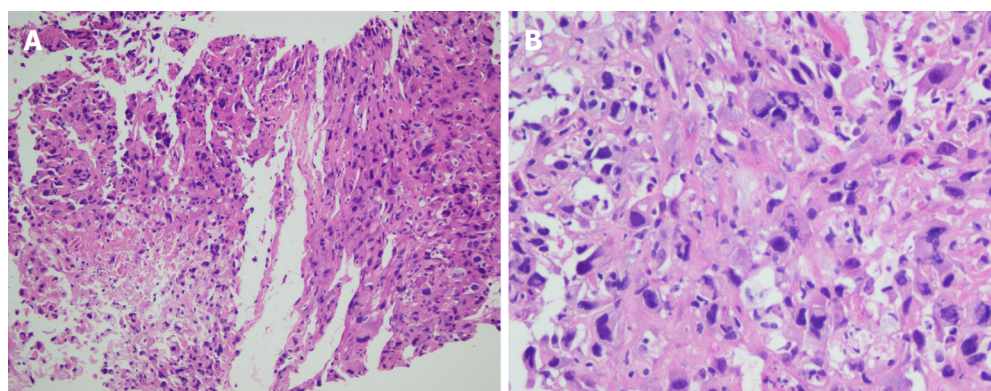
The final diagnosis of the patient was NSCLC stage IV (T4N3M1).

TREATMENT

Based on the findings presented above, the patient was then treated with two cycles of gemcitabine (1.0 g/m² on days 1 and 8) plus cisplatin (75 mg/m² on day 1) with no clinical benefit.

OUTCOME AND FOLLOW-UP

In January 2019, an abdominal CT scan revealed the enlargement of the lung primary and liver metastases. To explore potentially actionable mutations, tumor biopsy samples were submitted for capture-based targeted sequencing using a panel with 520 cancer-related genes (OncoScreen Plus, Burning Rock, China). As shown in Figure 2, the analysis revealed the detection of two concurrent *MET* fusions with respective partner genes *KIF5B* (K24:M15) and *CDR2* (M15:C3). No other classic lung cancer driver mutations were detected apart from *TP53* C277X. Due to economic and insurance conditions and out of concern over evidence suggesting reduced efficacy of immunotherapy in non-



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Figure 1 Hematoxylin and eosin staining photomicrographs of a right lung tumor tissue biopsy. A: Original magnification (×20); B: Original magnification (×40).

small cell lung cancer patients carrying oncogenic driver alterations[18], crizotinib (250 mg, p.o. bid) was started as the second line treatment in February 2019. After 4 wk of therapy, review of chest CT revealed a dramatic reduction of the lesions in the left and right lobes of the lungs with no new lesions, which was evaluated as partial response with Response Evaluation Criteria in Solid Tumors v.1.1 (RECIST 1.1) (Figure 3A and B). At approximately 3 mo from the start of targeted therapy, the patient continued to benefit from crizotinib without side effects. However, the disease progressed afterwards in May, 2019 as per RECIST 1.1. Specifically, compared with the previous evaluation (Figure 3B), new lesions emerged mostly in the right lung, accompanied by growth of the previously reduced tumor (Figure 3C and D).

After crizotinib failure, we chose nivolumab (a human IgG4 PD-1 antibody) as a salvage therapy because of the high PD-L1 expression. However, the patient did not benefit from nivolumab and her condition was declining significantly. She was hospitalized for worsening respiratory function and died shortly thereafter with an overall survival (OS) of 7 mo from diagnosis.

DISCUSSION

Gene alterations in *MET* are emerging as clinically relevant biomarker for predicting the response to *MET* inhibitors[2]. However, due to the rarity of *MET* fusions, treatment responses have only been clinically evaluated for *MET* amplification and exon 14 skipping[12-14] and only a few case reports have reported the efficacy of crizotinib in patients with *MET* fusions with various partners[5-7]. In our report, we describe the detection of *KIF5B-MET* co-occurring with a novel gene fusion involving *MET* and *CDR2* and provided the clinical evidence of the efficacy of crizotinib in a *KIF5B-MET* and *MET-CDR2*-rearranged poorly differentiated NSCLC patient. *KIF5B-MET* K24:M15 has been reported in 0.5% (1/206) of adenocarcinoma and 4% (2/28) of sarcomatoid lung cancer patients in a recent study in Taiwanese patients[19]. *In vitro* and *in vivo* studies consistently demonstrated the oncogenic potential of *KIF5B-MET* fusion and sensitivity to crizotinib[19]. Consistently, several case reports have observed clinical efficacy of crizotinib in K24:M14[6] and K24:M15[5] *KIF5B-MET*-rearranged NSCLC[5,6]. The dramatic response to crizotinib observed in our patient highly suggests that the fusions acting either solely or in synergy served as oncogenic driver/s in the patient's tumor which confers sensitivity to crizotinib. The oncogenic potential and sensitivity to crizotinib or other *MET* inhibitors of the novel gene fusion *MET-CDR2* as well as the presence of two concurrent *MET* fusions require further investigations.

The negative results for histopathologic markers TTF-1, CK7, P40, and CDX2 and classic driver mutations in *EGFR*, *ALK*, and *ROS1* provided neither clear indication of the cell differentiation nor any therapeutic targets. With a poor response to the first-line chemotherapy regimen, our patient had a very poor prognosis. Comprehensive genomic profiling allowed us to understand the mutation landscape of the tumor and explore alternative therapeutic targets that provided benefit to our patient. The detection of the potentially targetable *MET* fusions in our patient with poorly differentiated NSCLC highlights the importance of comprehensive genomic profiling regardless of tumor histology, particularly in patients with no known driver mutations to guide therapeutic decisions.

After the failure of crizotinib, we chose an immune checkpoint inhibitor (ICI) as a salvage therapy. Although with high PD-L1 expression, the patient did not benefit from the ICI. This is similar with the finding of previous studies that ICIs are less effective in NSCLC with *EGFR* mutation or *EML4-ALK* fusion[18,20].

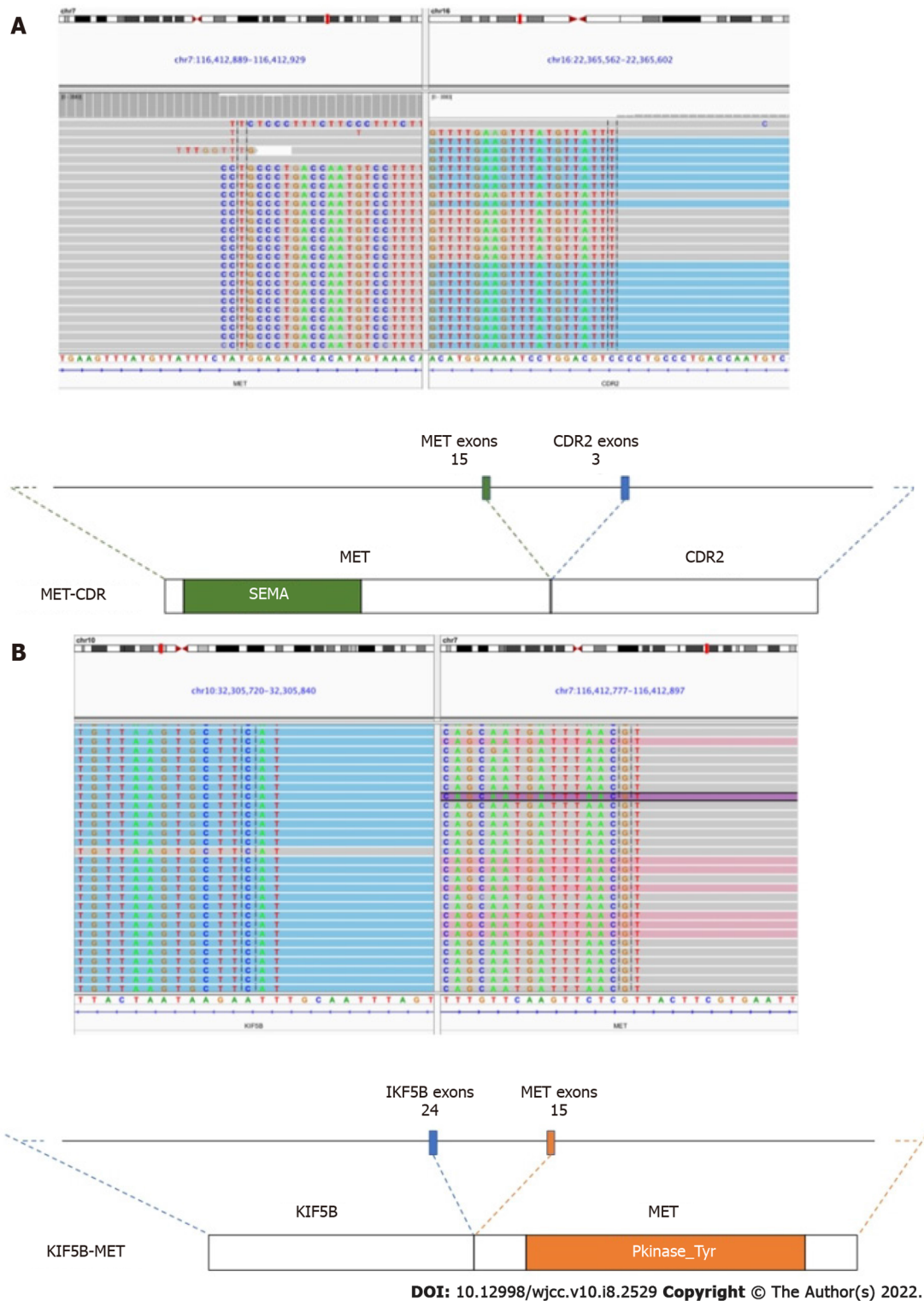
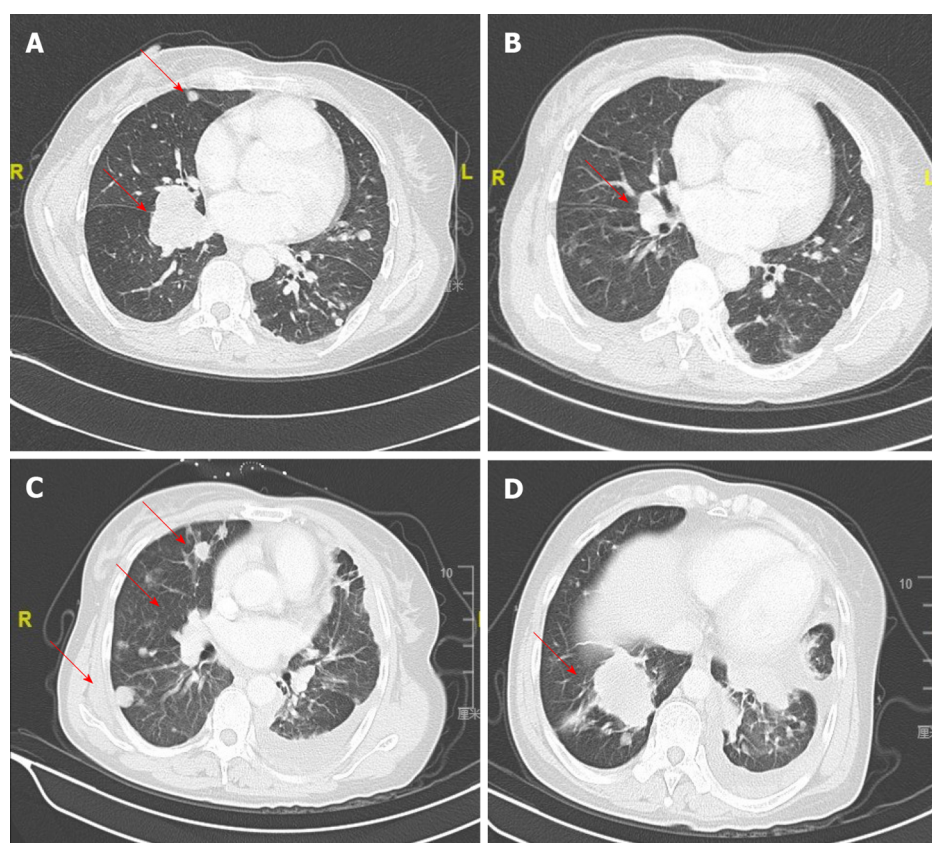


Figure 2 Next-generation sequencing revealed two concurrent *MET* fusions with different fusion partners, *MET-CDR2* and *KIF5B-MET*. A: Images from the Integrative Genomics Viewer demonstrating the chromosomal rearrangement involving *MET* (chromosome 7, sequencing reads with gray background) and *CDR2* (chromosome 16, sequencing reads with blue background); B: *KIF5B* (chromosome 10, sequencing reads with blue background). Illustrations below demonstrate the protein structure resulting from the gene fusions indicating the breakpoints of the nearby exons.

Attention should be paid to managing toxicities associated with crizotinib monotherapy. In a study of 2028 Japanese *ALK*-rearranged patients receiving crizotinib, adverse drug reactions occurred in 91.6% of patients, the most common (incidence $\geq 15\%$) of which were nausea (32.2%), diarrhea (24.3%), photopsia (18.9%), vomiting (17.5%), and dysgeusia (16.8%). A considerable proportion of patients (623, 30.7%) discontinued treatment within 12 wk after therapy initiation due to adverse events. Only 68.2% of patients remained on crizotinib after 3 mo, 55.2% after 6 mo, and 36.1% after 12 mo, with a median duration of 7.9 mo[10]. Therefore, it is advised to monitor patients for these adverse reactions during the



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Figure 3 Clinical efficacy of crizotinib treatment in a patient with *KIF5B-MET* and *MET-CDR2*-rearranged, poorly differentiated lung cancer. A: Thoracic computed tomographic image at baseline; B: 1 mo after initiating crizotinib therapy; C and D: After disease progression and another 2 mo later in May, 2019.

clinical use of crizotinib.

CONCLUSION

The efficacy of crizotinib in an advanced poorly differentiated NSCLC patient with concurrent *KIF5B-MET* and *MET-CDR2* gene fusions suggests that crizotinib can serve as a therapeutic option in patients with *MET* fusions. Further clinical studies are required to confirm the clinical value of crizotinib or other *MET* inhibitors in patients with *MET* fusion.

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FOOTNOTES

Author contributions: Liu LF and Deng JY contributed to the study concept and design and performed the statistical analysis; Liu LF, Deng JY, and Lin J contributed to the acquisition, analysis, and interpretation of the data; Liu L, Deng J, and Lizaso A contributed to the drafting of the manuscript; Sun S contributed to the critical revision of the manuscript for important intellectual content.

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