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CASE REPORT

Mutation of *MET D1228N* as an Acquired Potential Mechanism of Crizotinib Resistance in NSCLC with *MET Y1003H* Mutation

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Abstract: Mesenchymal-epithelial transition (*MET*) gene has been identified as a promising target for treatments. However, different sites of the *MET* mutation show different effects to MET inhibition. Here, we reported a non-small cell lung cancer (NSCLC) patient harboring *MET Y1003H* mutation who achieved a durable partial response to crizotinib with a PFS of 22.4 months. Furthermore, we report for the first time the identification of *MET D1228N* as a possible mechanism of acquired resistance to crizotinib in a patient with *MET Y1003H* mutation during disease progression.

Keywords: *MET Y1003H*, *MET D1228N*, crizotinib, resistance, NSCLC

Introduction

Mesenchymal-to-epithelial transition factor (*MET*), a key regulator of cellular signaling and motility, has gained significant attention as a promising therapeutic target in cancer treatment. MET plays a pivotal role in cancer growth, invasion and metastasis, especially in non-small cell lung cancer (NSCLC).[1] Various MET alterations, including *MET* exon 14 (*METex14*) skipping alterations, *MET* kinase domain mutation, *MET* amplification and *MET* fusion, play an important role in the development of NSCLC and resistance to EGFR-TKI.[2,3] Among them, *METex14* skipping alterations and *MET* amplification are particularly notable for their ability to transform *MET* into a major oncogenic driver.[4]

The *MET Y1003* mutation, a specific point mutation in the *MET* kinase domain, is a rare but important alteration in NSCLC. The tyrosine residue *Y1003* in the juxtamembrane region of c-MET is the binding site of the E3 ubiquitin ligase casitas B lineage lymphoma (CBL), while exon 14 of the *MET* gene encodes a part that includes this binding site, which is responsible for regulating the ubiquitination and degradation of MET protein and is an important structure for the negative regulation of MET protein.[5] When the *MET* gene is altered, it disrupts important structures, such as the branch site, polypyrimidine tract, 3' splice site of intron 13, and 5' splice site of intron 14, it will lead to abnormal splicing of mRNA, resulting in *MET* ex14 skipping mutations, manifesting as the loss of exon 14 and the fusion of exons 13 and 15. This produces MET receptors that lack the Y1003 c-CBL E3 ubiquitin ligase binding site. After losing this binding site, MET protein ubiquitination decreases, and its downstream signaling pathway is continuously activated, ultimately leading to the occurrence and development of tumors.[5,6] In vitro, *Y1003* point mutation can lead to oncogenic transformation of lung cancer.[7] While it's precise functional impact on MET signaling remains to be fully elucidated, the presence of this mutation may confer specific biological and clinical phenotypes to NSCLC patients.[8–10] Therefore, understanding the response of *MET Y1003*-mutated NSCLC to targeted therapies, such as crizotinib, is of utmost importance.

Crizotinib, a tyrosine kinase inhibitor (TKI) targeting *MET* and *ALK*, has demonstrated significant clinical benefits in NSCLC patients harboring MET alterations.[11,12] However, acquired resistance to crizotinib is a major obstacle to long-term therapeutic efficacy. The mechanisms of crizotinib resistance are complex and heterogeneous, often involving

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multiple factors such as secondary mutations in the target kinase domain, increased drug efflux, and activation of alternative signaling pathways.[13–15]

In this study, we report on a patient with NSCLC carrying the *MET Y1003H* mutation who showed a persistent partial response to crizotinib treatment. In addition, during disease progression, we first identified *MET D1228N* as a potential mechanism for crizotinib resistance in this patient. This finding provides new insights into the complexity of crizotinib resistance and the prospects for the development of *MET* alterations in NSCLC.

Case Presentation

A 67-year-old man smoking presented to our hospital with paroxysmal cough without obvious inducement, accompanied by right chest swelling and discomfort for one month. A chest X-ray at a local hospital revealed a right lower lung infection and a right pleural effusion. CT of the upper abdomen in our hospital showed consolidation of the lower lobe of the right lung (65*34 mm, Figure 1A) and right pleural effusion. Anti-infective treatment was given on June 25, 2020. Pleural effusion pathology suggested lung adenocarcinoma. Laboratory examinations revealed elevations in the levels of carcinoembryonic antigen (CEA: 17.68 ng/mL), carbohydrate antigen 125 (CA125: 98.63U/mL), and neuron-specific enolase (NSE: 23.50 ng/mL), whereas no abnormalities were observed in CA19-9, CA153, alpha-fetoprotein (AFP). Furthermore, in order to explore potential therapeutic strategies, we conducted DNA-based next-generation sequencing (NGS) on circulating tumor DNA (ctDNA) samples using a commercial panel encompassing 733 genes. The NGS testing was carried out on an Illumina HiSeq sequencer (Illumina, San Diego, CA) at a College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA) certified laboratory (3D Medicine Inc. Shanghai, China). The results showed the *MET Y1003H* [Variant allele frequency (VAF): 0.24%; Figure 1B], *PIK3CA P539R* (VAF: 0.02%), *PMS2 cc.2006+2T>G* (VAF: 0.08%), *TP53 R248W* (VAF: 0.53%) and *Y205** (VAF: 0.06%) pathogenic mutations. Informed consent was obtained from the patient. The patient was initiated with crizotinib from July 14, 2020. After eight cycle's treatment, the tumor lesion in the right lung significantly decreased (from 65*34 mm to 8*6 mm, Figure 1C), so that the efficacy was assessed as partial response (PR) according to iRECIST criteria. At this moment, CEA (15.08 ng/mL) and CA125 (54.44 U/mL) were both reduced, but still above normal levels. No grade ≥3 adverse events were reported, and the dose was not reduced during treatment.

Until May 17, 2022, the patient felt unwell, manifested as cough suppression and wheezing, and after re-examination, the NSE was elevated (67.13 ng/mL). At the same time, chest CT showed irregular masses in the right lower lung (50*47 mm) with pleural effusion, diffuse nodular shadows in both lungs, with different sizes, solid and random distribution, and hilar lymph node enlargement (Figure 2A). In addition, pathological results of pleural effusion revealed metastatic adenocarcinoma, with immunoreactivity to AE1/AE3, Ki-67 (about 10% positive), WT-1, D2-40, TTP-1 (+), Napsin A (+), CK7 (+), and calretinin, and negative for P40, CK20, and CDX2. The pleural effusion tissue was subjected to DNA-based NGS analysis, and no abnormalities were not found *in EGFR, ALK, ROS1* and other driver gene. But pathogenic *MET D1228N* (VAF: 1.46%), *MET Y1003H* (VAF: 5.03%), *TP53 R248W* (VAF: 0.73%), and *Y205** (VAF: 2.54%) mutations were detected (Figure 2B). The progression free survival was 22.4 months. Ten days later, he died of respiratory failure. The overall survival was 23.4 months.

Discussion

The present study highlights the significance of *MET D1228N* mutation as a potential mechanism of acquired resistance to crizotinib in a NSCLC patient harboring the *MET Y1003H* mutation. Our findings add to the understanding of the complex mechanisms underlying resistance to MET inhibitors, particularly in the context of NSCLC.

MET, a transmembrane receptor tyrosine kinase, plays a crucial role in cancer progression, metastasis, and drug resistance. The *MET Y1003H* mutation, located in the kinase domain of *MET*, has been shown to confer oncogenic properties and contribute to tumor growth and invasiveness.[10] However, the precise mechanisms underlying MET inhibitor resistance in patients with *MET* mutations remain poorly understood.[13–15]

Our investigation reveals that despite an initial favorable, sustained partial response to crizotinib therapy, the emergence of the *MET D1228N* mutation during disease progression points to a novel, acquired resistance mechanism. Specifically, *MET D1228N* is a mutation residing within the juxtamembrane domain of *MET*, a pivotal region for

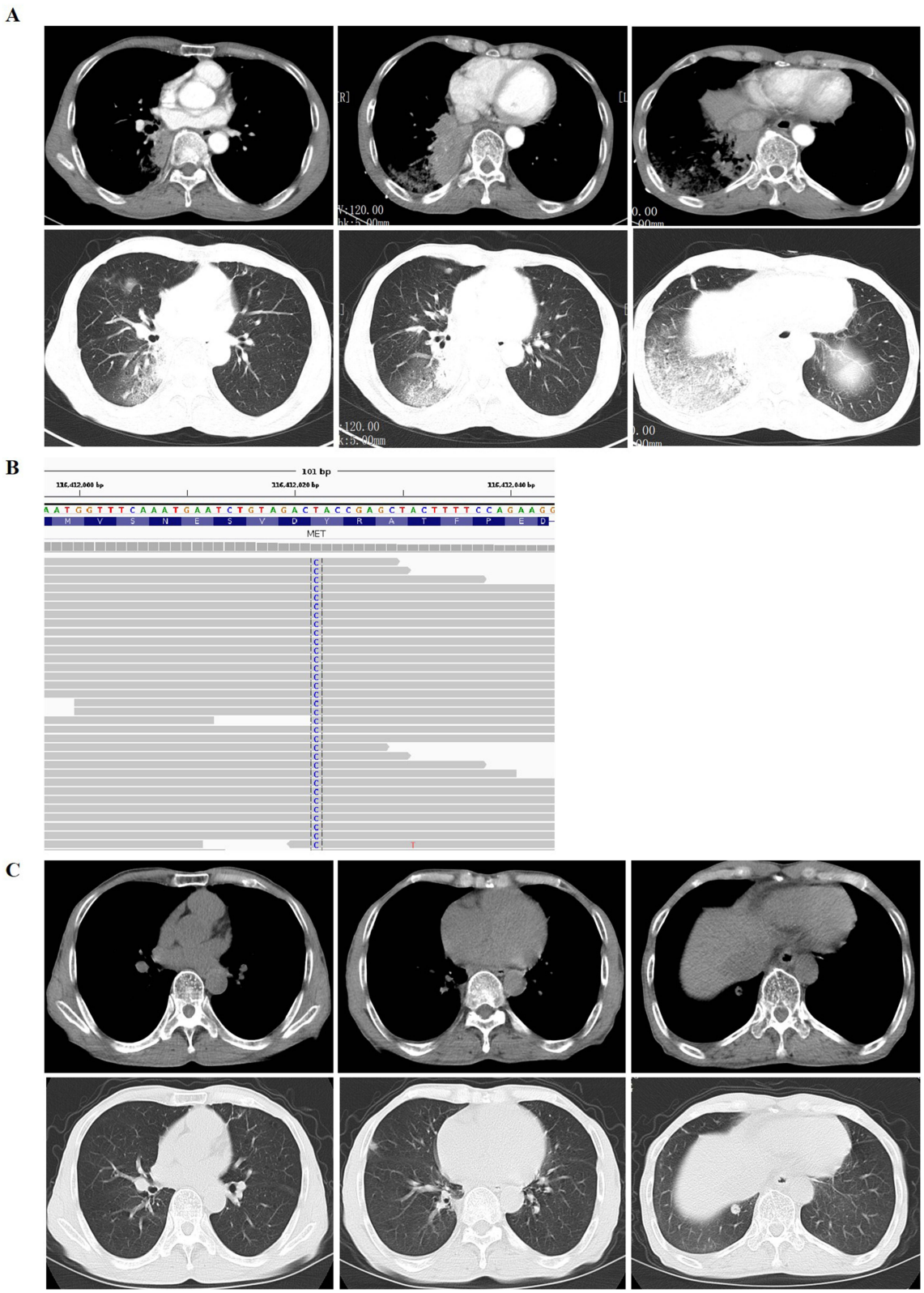

Figure 1 The patient's initial diagnosis and lesion changes after treatment. **(A)** CT result of initial diagnosis. (**B**) *MET Y1003H* mutation was found. (**C**) Lesions assessment after treatment.

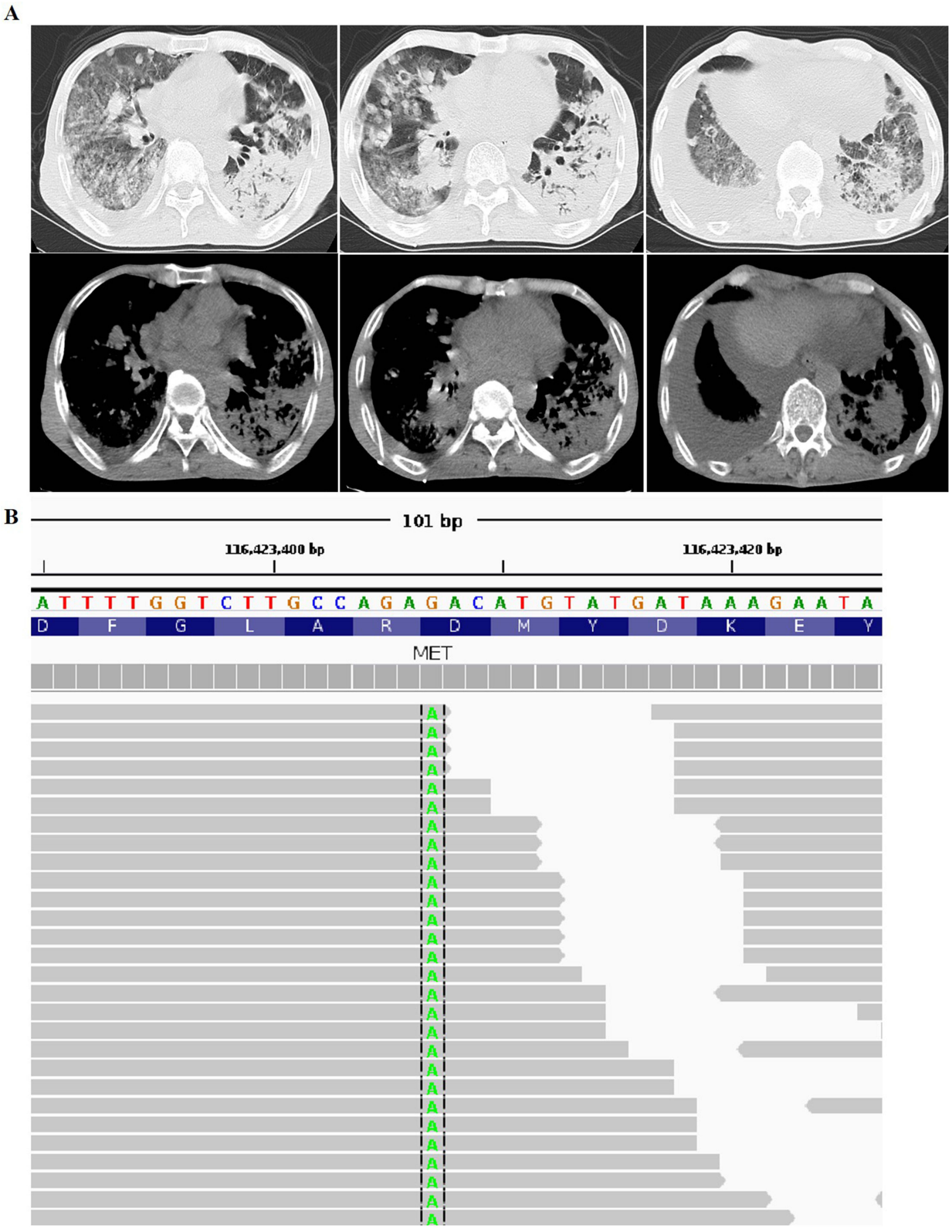

Figure 2 The mechanism of crizotinib resistance. **(A)** The lesion change after crizotinib resistance. **(B)** Genetic analysis showing *D1228N* point mutation.

regulating MET kinase activity. Prior research underscores that mutations in this domain can unravel MET's autoinhibitory mechanisms, thereby triggering constitutive kinase activation and facilitating tumor progression.[16–18] Notably, *MET D1228N* has been identified as a resistance mutation to crizotinib in various contexts, including NSCLC patients

with *MET* exon 14 skipping,[14] those harboring de novo *MET* fusions,[19] and in MET-amplified triple-negative breast cancer.[20] Consequently, *MET D1228N* is recognized as a resistance mutation against type I MET inhibitors, like crizotinib and capmatinib. However, its sensitivity to type II inhibitors remains uncertain in clinical practice.[16,20,21]

A retrospective analysis underscores the significance of *MET D1228N/H* mutations, with a notably higher frequency observed in *MET*ex14-altered or MET-amplified NSCLC patients compared to baseline and EGFR-TKI-treated cohorts. This study further corroborates the association of *D1228N* with acquired resistance to MET-TKIs in NSCLC.[22] Our results align with these findings, indicating that the *MET D1228N* mutation potentially imparts resistance to crizotinib by activating MET kinase independently of kinase domain mutations, thereby underscoring its role in evading therapeutic intervention.

The identification of *MET D1228N* as a mechanism of resistance is particularly important given the limited therapeutic options for NSCLC patients with MET mutations. While MET inhibitors such as crizotinib have shown promising results in these patients, the development of resistance remains a significant challenge. Targeting both the kinase domain and the juxtamembrane domain of *MET* may be necessary to overcome resistance and achieve durable responses.

Furthermore, our study highlights the need for continued monitoring of *MET* mutations during the course of treatment. The emergence of secondary mutations, such as *MET D1228N*, may indicate the development of resistance and necessitate a change in treatment strategy. Future studies are needed to elucidate the precise mechanisms underlying MET inhibitor resistance and to develop novel therapeutic approaches that can overcome these resistance mechanisms.

Conclusions

In this report, we present a case of a NSCLC patient with a *MET Y1003H* mutation who exhibited a sustained partial response to crizotinib, resulting in a PFS of 22.4 months. Additionally, we are the first to document *MET D1228N* as a potential mechanism of acquired resistance to crizotinib in this patient upon disease progression. These findings provide new insights into the mechanisms of resistance to MET inhibitors in NSCLC patients with MET mutations. The identification of *MET D1228N* as a potential mechanism of acquired resistance to crizotinib suggests that targeting both the kinase domain and the juxtamembrane domain of MET may be necessary to achieve durable responses in these patients. Future studies are warranted to further elucidate these mechanisms and develop novel therapeutic approaches.

Ethics Approval and Consent to Participate

The authors declare that written informed consent was obtained from the patient's and institutional approval for the publication of data and images.

Consent for Publication

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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