Case Report

A novel *HLA-DQB2::MET* gene fusion variant in lung adenocarcinoma with prolonged response to tepotinib: a case report

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Background: *MET* rearrangements are infrequently observed in non-small cell lung cancer (NSCLC). Advanced genomic detection techniques have unveiled such infrequent genomic variations, particularly *MET* fusions in approximately 0.5% of NSCLC patients. Tyrosine kinase inhibitors (TKIs) have revolutionized the standard of care in lung cancer and more recently a second generation MET TKI tepotinib received Food and Drug Administration (FDA) approval for MET exon 14 alterations in metastatic NSCLC. Despite this, the therapeutic landscape for *MET*-rearranged NSCLC patients remains significantly unexplored. The aim of our report is to detail a unique case of a patient with metastatic lung adenocarcinoma with a novel *HLA-DQB2::MET* fusion detected by next-generation sequencing (NGS) following previous treatment resistance.

Case Description: A 73-year-old female was initially started on carboplatin, pemetrexed and pembrolizumab with maintenance, but eventually had progression in the left upper lobe (LUL). Upon progression she was enrolled in a clinical trial of a monoclonal antibody with or without a PD-1 inhibitor, but brain metastasis progression was eventually detected by magnetic resonance imaging (MRI) requiring stereotactic radiosurgery (SRS) and a craniotomy. The trial drug was eventually discontinued due to progression and toxicity and NGS on bronchoscopy tissue revealed *HLA-DQB2::MET* fusion. The patient was initiated on tepotinib and continues with clinical and radiological stable disease for over 12 months. The patient's response to a MET inhibitor, tepotinib, underscores the potential efficacy of selective MET inhibitors for individuals with previously unexplored *MET* fusions.

Conclusions: The positive response to tepotinib of a patient with NSCLC harboring a novel *MET*-Fusion underscores the importance of the use of comprehensive next-generational sequencing-based panels and highlights the necessity for additional research and clinical exploration of selective MET inhibitors for managing NSCLC with *MET* rearrangements.

Keywords: Non-small cell lung cancer (NSCLC); *HLA-DQB2::MET* fusion; tepotinib; case report; targeted therapy

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Submitted Jan 11, 2024. Accepted for publication Mar 20, 2024. Published online May 29, 2024.
doi: 10.21037/tlcr-24-34
View this article at: https://dx.doi.org/10.21037/tlcr-24-34

Introduction

MET is a proto-oncogene that codifies a transmembrane tyrosine kinase receptor MET (1). Aberrant activation of MET in tumors of different histologies is related to the proliferation of cancer cells and angiogenesis (2). Adenosine triphosphate (ATP) competitive tyrosine kinase inhibitors (TKIs) have demonstrated antitumor effectiveness in patients with non-small cell lung cancer (NSCLC) presenting MET alterations, particularly *MET* exon 14 skipping mutations (3). However, the therapeutic relevance of MET TKIs in more complex structural rearrangements such as *MET* fusions is still largely unknown (4). We present a case of a 75-year-old patient heavily pre-treated harboring a novel *HLA-DQB2::MET* fusion who achieved a long-term response on selective MET-inhibitor tepotinib therapy. To the best of our knowledge, this is the first report of a patient with NSCLC harboring an *HLA-DQB2::MET* fusion responding to a MET inhibitor. We present this case in accordance with the CARE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-34/rc).

Highlight box

Key findings

- This is the first report of a patient with non-small cell lung cancer (NSCLC) harboring a novel *HLA-DQB2::MET* fusion responding to a MET inhibitor.

What is known and what is new?

- NSCLC infrequently exhibits *MET* fusions, a rare structural rearrangement. The emergence of advanced genomic detection techniques has revealed rare genomic variations, notably *MET* fusions.
- The therapeutic landscape for patients with MET-rearranged NSCLC remains substantially underexplored.

What is the implication, and what should change now?

- Patients with novel *MET* fusions may respond to selective MET inhibitors such as tepotinib.
- The patient's positive response to the MET inhibitor, tepotinib, indicates the potential efficacy of selective MET inhibitors for individuals with previously unexplored *MET* fusions.

Case presentation

A 73-year-old female, a never-smoker, no family history of cancer, with a past medical history of localized breast cancer that was treated 20 years ago with no signal of recurrence. Initially presented with a persistent cough, no alterations on physical exams and her workup included a computed tomography (CT) of the chest which demonstrated a 5-cm left upper lobe (LUL) mass and a left pleural effusion with nodular left pleural thickening (*Figure 1*). Staging with a positron emission tomography (PET)-CT showed additionally to the lung mass and pleural effusion, fluorodeoxyglucose (FDG) avid medial supraclavicular lymph node, and left precarinal lymph node. Magnetic resonance imaging (MRI) of the brain was performed and showed no initial metastatic disease to the central nervous system. This patient underwent an endobronchial ultrasound (EBUS) guided endobrochial biopsy of the left lung mass. Pathology results from the lung mass biopsy confirmed lung adenocarcinoma with immunohistochemistry (IHC) stains reporting thyroid transcription factor-1 (TTF-1) positive, cytokeratin 7 (CK7) positive, napsin A positive; GATA-3, estrogen receptor (ER), calretinin, p63—all negative. Pleural fluid cytology analysis was consistent with lung primary metastatic adenocarcinoma. EBUS-fine needle aspiration procedures revealed the absence of malignant cells in suspect mediastinal and supraclavicular lymph nodes found on PET-CT. The patient was clinically staged as IVA (cT2, cN0, pM1a) based on AJCC 8th edition criteria.

Molecular profiling of left lung mass (CARIS) revealed PD-L1 (22C3) expression at 2%, with no actionable mutations, low tumor mutational burden (TMB), and stable microsatellite instability (MSI) status. Molecular profiling of the left pleural fluid with next-generation sequencing (NGS) (HopeSeq) revealed negative results for actionable mutations and PD-L1 (22C3) expression at 0%. Guardant 360 assessment detected no tumor-associated somatic alterations in circulating cell-free DNA. First-line systemic therapy was started with carboplatin (AUC 5), pemetrexed (500 mg/m^2), and pembrolizumab (200 mg) every 3 weeks and continued with stable disease. After six cycles, maintenance therapy

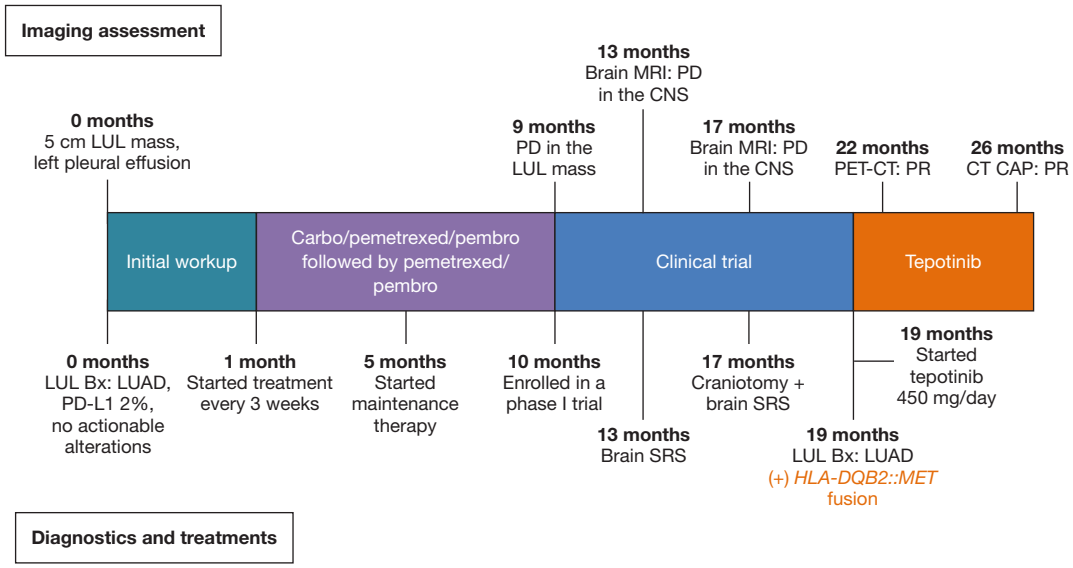

Figure 1 Patient's cancer history timeline. LUL, left upper lobe; Bx, biopsy; LUAD, lung adenocarcinoma; carbo, carboplatin; pembro, pembrolizumab; PD, progressive disease; MRI, magnetic resonance imaging; CNS, central nervous system; SRS, stereotactic radiosurgery; PET, positron emission tomography; CT, computed tomography; PR, partial response; CAP, chest, abdomen and pelvis.

was initiated and continued for 4 months until a CT of the chest, abdomen, and pelvis (CAP) showed progression in the LUL mass increasing to 6.6 cm × 5.2 cm from 5.5 cm × 4.7 cm. Subsequently, the patient was enrolled in a phase I clinical trial of a monoclonal antibody with or without a PD-1 inhibitor. After 2 months of treatment, a CT CAP and PET-CT were performed and demonstrated enlarged FDG avid upper lobe and right middle lobe small nodules—and additionally, a new liver lesion was detected 2.2 cm × 1.4 cm. Therapy was halted for further evaluation. A bronchoscopy and liver biopsies were performed and revealed necrosis and IHC stains consistent with pseudo-progression. Around the same time, a brain MRI was also performed and found new hemorrhagic brain metastases in the left anterior of the frontal lobe, right high frontal lobe, and right parietal lobe.

The patient underwent stereotactic radiosurgery (SRS) to the brain with a total dose of 27 Gray delivered in 3 fractions. Following central nervous system disease control and symptom resolution, the patient was allowed to continue treatment within the clinical trial. Three months later, a new MRI showed brain disease progression, prompting a neurosurgery referral. The patient underwent a left frontal craniotomy followed by SRS 17 months after diagnosis without complications. The brain tumor excision pathology revealed extensive hemorrhagic necrosis with no evidence of viable carcinoma shown, thus no NGS was performed. Post-surgery, systemic treatment with the experimental drug was briefly resumed but discontinued due to toxicity.

An NGS panel of 523 Genes was performed on the bronchoscopy of LUL main mass tissue, detecting single-nucleotide variants (SNVs), insertions/deletions (Indels), copy number variants (CNVs), from the extracted DNA, and selected gene rearrangements from the extracted RNA in the following genes. This panel identified the following pathogenic variants: *HLA-DQB2::MET* fusion, *CCNE1* amplification, *DNMT3A* (c.2259G>A;p.W735*), *FRS2* amplification, *H3F3C* amplification, *KMT2C* (c.3274C>T;p.R1092*), *MDM2* amplification nonsense alteration. TMB: low and MSI: stable. In addition, variants of uncertain significance (VUS) were identified (*Table 1*). The breakpoints for the *MET* fusion detected by NGS were chr6:32725550, chr7:116414935 with the sequence as follows: GCAAGATGCTGAGTGGCATTGGAGGCTTCGTGCTGGGGCTGATCTTCCTCGGGCTGGGCCTTATCATCCATCACAGGAGTCAGAAAGATCAGTTTCCTAATTCATCTCAGAACGGTTCATG (Figure S1).

According to the NGS test that revealed an *HLA-DQB2::MET* fusion, the patient initiated tepotinib (450 mg once daily), a kinase inhibitor, 19 months after diagnosis. A PET-CT scan was performed 3 months after initiating

Table 1 Pathogenic variant table

Genomic alteration detected	Allele frequency	Predicted effect
HLA-DQB2::MET fusion	N/A	Pathogenic
CCNE1 amplification	N/A	Pathogenic
DNMT3A (c.2259G>A;p.W735*)	1%	Pathogenic
FRS2 amplification	N/A	Pathogenic
H3F3C amplification	N/A	Pathogenic
KMT2C (c.3274C>T;p.R1092*)	2%	Pathogenic
MDM2 amplification	N/A	Pathogenic
ARID1A (c.4724C>A p.P1575Q)	48%	VUS
ARID2 (c.2246C>T p.T7491)	38%	VUS
ASXL2 (c.2026G>A p.A676T)	8%	VUS
ATM (c.6373C>T p.H2125Y)	54%	VUS
ATRX (c.3065G>A p.R1022Q)	50%	VUS
LRP1B (c.11440G>T p.D3814Y)	15%	VUS
LRP1B (c.4247C>T p.T14161)	51%	VUS
LRP1B (c.2281A>G p.1761V)	54%	VUS
RANBP2 (c. 1937A>G p.Y646C)	13%	VUS
RECQL4 (c.795C>G p.N265K)	67%	VUS
SPTA1 (c.1216G>A p.E406K)	8%	VUS
TAF1 (c.3267G>T p.Q1089H)	9%	VUS
TFE3 (c.1633C>T p.R545W)	8%	VUS
TRAF2 (c.1063A>C p.1355L)	42%	VUS

N/A, not applicable; VUS, variants of unknown significance.

treatment and showed a substantial decrease in the left suprahilar mass measuring 4.5 cm × 2.5 cm with a maximum standardized uptake value (SUV) of 6.6, previously the tumor was measured 6.7 cm × 5.5 cm with a maximum SUV of 20.1 (*Figure 2*). The treating oncologist determined this was a partial response (PR). A brain MRI 1 month later also showed intracranial response with the largest lesion in the left parietal lobe measuring 12 mm × 11 mm as compared to at the start of tepotinib therapy measuring 32 mm × 25 mm. At the latest follow-up, the patient has been receiving tepotinib therapy for 12 months, with clinically and radiologically stable disease and no treatment-related adverse events. All procedures performed in this study were in accordance with the ethical standards of the City of Hope Institutional Review Board and the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Exon 14 skipping mutation, originally identified by our team, is the most common actionable MET alteration in NSCLC found in approximately 2% of patients (5-7). The frequency of *MET* amplifications is similar or higher than that of *MET* exon 14 skipping depending on the patient populations (8-10). However, other *MET* rearrangements including the fusion detected in our patient are identified in only 0.5% of patients with NSCLC (4). In the present study a fusion of the *HLA-DQB2* (exon 4) to *MET* (exon 15) gene was detected. These fusions often include the kinase domain on exon 15 as demonstrated in this report and many upstream partners provide dimerization domains, resulting in ligand-independent constitutive MET activation. *MET*-fused genes were identified on various chromosomes of the human genome, but primarily on chromosome 7, which contains the *MET* gene (11). Type I MET-directed targeted treatments have been recommended for *MET* exon 14 mutations and Type II are currently under investigation in advanced NSCLC (3). Nevertheless, the therapeutic implications of *MET* fusions are inadequately comprehended requiring further scientific research (12). Responses to treatment with MET inhibitors were documented in patients with glioma, and in one patient included in the MET 14 cohort of PROFILE 1001. This patient was diagnosed with NSCLC harboring a *MET* fusion resulting in exon 14 skipping (13). The efficacy and safety described in the use of MET inhibitor tepotinib in this study is in line with a series of case reports revealing novel detectable *MET* fusions with the following partners: *KIF5B*, *CAV1*, *CDR2*, *ARL1*, *CUX-1*, *HLA-DRB1*. These rearrangements had their pathologic signaling pathways suppressed by MET inhibitors, mostly crizotinib (14-19).

Our patient achieved a durable response with tepotinib, a selective and potent type 1b MET inhibitor, referred to as ATP-competitive TKIs, operated by interacting with the MET activation loop. The inhibition of the abnormal MET/hepatocyte growth factor pathway prevents the growth, survival, and invasive characteristics of cancer cells. This drug effectively penetrates the blood-brain barrier and actively controls brain metastasis in tumors with *MET* alterations (19,20). This report demonstrated the potential effectiveness in targeting MET, irrespective of the fusion

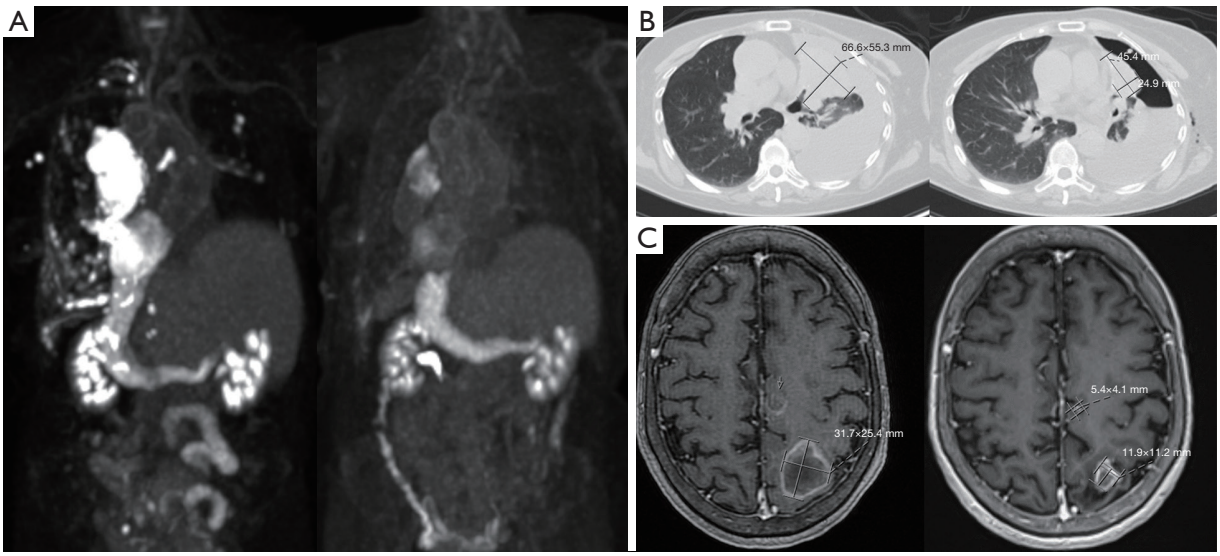

Figure 2 Before and after imaging on tepotinib. (A) PET-CT whole body. (B) CT of the chest. (C) Brain MRI. PET, positron emission tomography; CT, computed tomography; MRI, magnetic resonance imaging.

partner demonstrating the importance of the use of NGS-based large-panel tests and NGS-based RNA fusion scans enabling the identification of rare genomic alterations and offering targeted treatment for a wider range of patients.

Conclusions

In conclusion, we identified the first case of a novel *MET* fusion. Therefore, this case contributes to expanding our understanding of the genomic landscape in NSCLC, emphasizing the importance of identifying and exploring rare molecular alterations such as *HLA-DQB2::MET* fusions. The successful response to tepotinib highlights the need for further investigation and clinical exploration of selective MET inhibitors in the management of *MET*-rearranged NSCLC.

Acknowledgments

We would like to thank City of Hope nurses and clinical staff for their dedication to taking care of patients.
Funding: The work was in part supported by the National Cancer Institute of the National Institutes of Health under award number P30CA033572.

Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-34/rc

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-34/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-34/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the City of Hope Institutional Review Board and the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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Cite this article as: Dias e Silva D, Mambetsariev I, Fricke J, Babikian R, Dingal ST, Mazdisnian F, Badie B, Arvanitis L, Afkhami M, Villalona-Calero M, Salgia R. A novel *HLA-DQB2::MET* gene fusion variant in lung adenocarcinoma with prolonged response to tepotinib: a case report. Transl Lung Cancer Res 2024;13(5):1163-1168. doi: 10.21037/tlcr-24-34