Successful tepotinib treatment of adenocarcinoma with MET exon 14 skipping and discordant results between Oncomine Dx target test and ArcherMET: A case report

YOKO ONODERA, AKIMASA SEKINE, ERI HAGIWARA, SHO YAMADA, SATOSHI IKEDA, ERINA TABATA, HIDEYA KITAMURA, TOMOHISA BABA, SHIGERU KOMATSU, KOJI OKUDELA and TAKASHI OGURA

Department of Respiratory Medicine, Kanagawa Cardiovascular and Respiratory Center, Yokohama, Kanagawa 236-0051, Japan

Received December 6, 2022; Accepted March 31, 2023

DOI: 10.3892/mco.2023.2645

Abstract. Patients with non-small cell lung cancer (NSCLC) are often positive for oncogenic driver mutations, such as EGFR, ALK, BRAF, RET and MET exon 14 skipping mutations (METex14 skipping). Recently, METex14 skipping has become a functional biomarker for NSCLC with the approval of MET kinase inhibitors. Tepotinib is an oral MET kinase inhibitor. Its overall response rate is 46%, and the median duration of the response is 11.1 months. In Japan, companion diagnostics for tepotinib are limited with the ArcherMET and AmoyDx test, but not with Oncomine Dx target test. The present study reports the case of a 60-year-old male patient with lung adenocarcinoma harboring METex14 skipping, which was positive on Oncomine DxTT, but not on ArcherMET. In his sample used for Oncomine DxTT, the read count of MET(13)-MET(15) products was only 46. He was treated with various chemotherapeutic agents, but developed cardiac tamponade due to the progression of the disease of mediastinal lymph node metastases. Tepotinib was administered following pericardial drainage, resulting in an immediate response in all lesions. The majority of the discordant samples between Oncomine DxTT and ArcherMET had read counts <800, and the patient described herein had only 46. Therefore, the results of the present study indicate that the use of tepotinib should be considered even in patients whose METex14 skipping results were negative with ArcherMET, yet positive on Oncomine DxTT, particularly relatively with low lead counts.

Correspondence to: Dr Akimasa Sekine, Department of Respiratory Medicine, Kanagawa Cardiovascular and Respiratory Center, 6-16-1 Tomioka-higashi, Kanazawa-ku, Yokohama, Kanagawa 236-0051, Japan
E-mail: akimasa.sekine@gmail.com

Key words: MET exon14 skipping, Oncomine Dx target test, Archer MET, tepotinib, lung cancer

Introduction

A mesenchymal-epithelial transition (MET) gene encodes a receptor tyrosine kinase and its activation promotes the tumor cell proliferation. MET exon 14 (METex14) is crucial for the ubiquitination and degradation of MET proteins, and its skipping produces incomplete MET proteins, which grow abnormally and become cancerous (1).

In non-small cell lung cancer (NSCLC), METex14 skipping mutation is observed in 3-4% of cases and typically occurs in the absence of other driver mutations (2). The incidence of METex14 skipping is 2% in adenocarcinoma, 6% in adenosquamous cell carcinoma and 13% in pulmonary sarcomatoid carcinoma (2,3). METex14 skipping is more closely associated with old age, the female gender and never-smoking histories compared with patients without METex14 skipping (3). Some oral MET kinase inhibitors, such as crizotinib (4), tepotinib (1), capmatinib (5) and savolitinib (ClinicalTrials.gov Identifier: NCT02897479) have been found to be effective based on clinical trials. Of these oral MET kinase inhibitors, tepotinib and capmatinib have been approved for use in Japan (3). The VISION trial, which investigated the effectiveness of tepotinib in patients with MET ex14 skipping, demonstrated an overall response rate of 46% and a median duration of response of 11.1 months (1).

ArcherMET, AmoyDx test and Oncomine Dx target test (DxTT, Thermo Fisher Scientific, Inc.) are next-generation sequencing platforms used for the detection of oncogenic driver mutations and can detect METex14 skipping. However, for the use of MET kinase inhibitors in Japan, positive results are required on ArcherMET or AmoyDx test, but not on Oncomine DxTT, as companion diagnostics (CDx) (6). The present study reports the case of a patient with NSCLC with METex14 skipping who was successfully treated with tepotinib, although METex14 skipping was positive on Oncomine DxTT, but not on ArcherMET.

Case report

A 60-year-old male with a 38-pack-year history of smoking was referred to the authors' hospital, Kanagawa

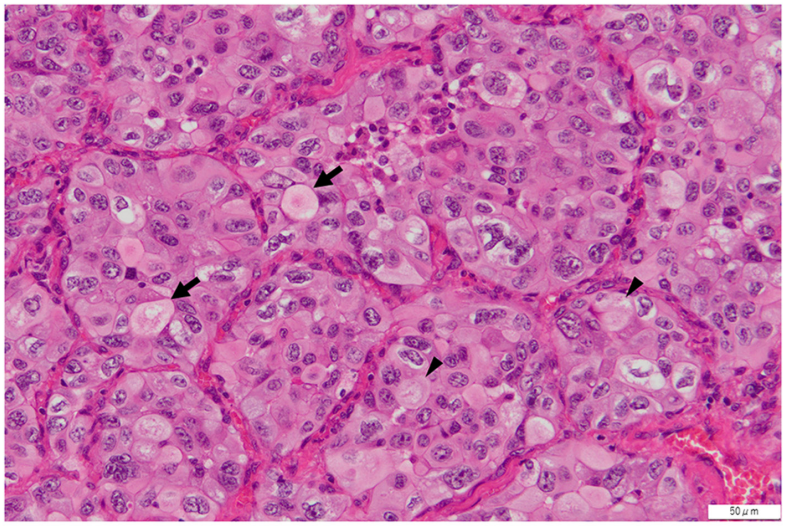

Figure 1. An operatively micrograph of the primary lung tumor illustrating the neoplastic cells arranged in fulfilled acinar units (hematoxylin and eosin staining; magnification, x200). Mucin is observed in the lumen of the nest (arrows) and in the cytoplasm of the tumor cells (arrowheads). The staining was performed by department of pathology of Yokohama City University.

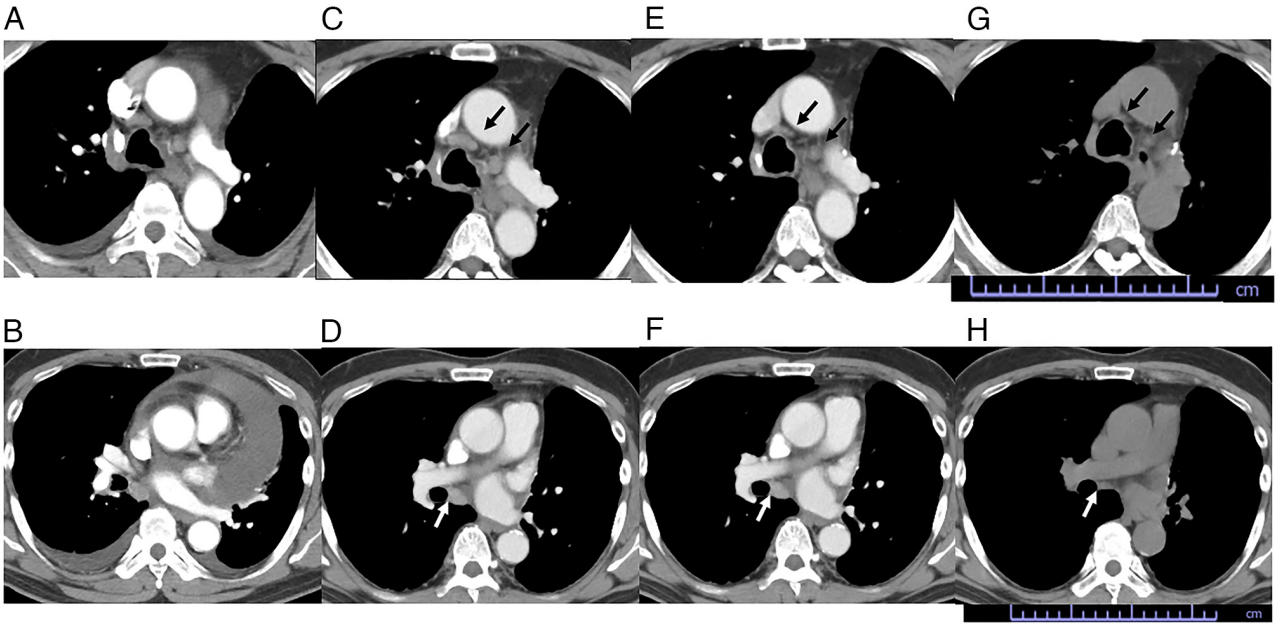

Figure 2. Chest CT images before and after initiating tepotinib treatment. (A and B) Following fourth-line chemotherapy, the tumor grew rapidly, and caused cardiac tamponade and thus required immediate drainage. (C and D) A CT scan immediately prior to tepotinib treatment revealed enlarged mediastinal lymph nodes (arrows). At 4 weeks following the initiation of tepotinib treatment, (E and F) the mediastinal lymph nodes shrank rapidly (arrows) and (G and H) the response was maintained for 2 months (arrows indicate shrunken lymph nodes).

Cardiovascular and Respiratory Center (Yokohama, Japan) due to cough and abnormal chest shadows. He underwent left upper lobectomy for the resection of lung adenocarcinoma stage IIB (pT1bN1M0). The largest diameter of the tumor was 15 mm, and its histological subtype was solid, as illustrated in Fig. 1. The left lobar lymph node (#12) was pathologically positive, whereas the other lymph nodes were free of cancer cells. He received two cycles of adjuvant chemotherapy consisting of cisplatin and vinorelbine. At 6 months after surgery, the mediastinal lymph node (#4) was enlarged. Post-operative recurrence was confirmed using endobronchial ultrasound-guided transbronchial needle aspiration. Whereas other oncogenic driver mutations such as epidermal growth factor receptor gene (EGFR) mutation was negative, METex14 skipping was positive on Oncomine DxTT. However, it was negative on ArcherMET, although the same residual RNA sample was used. In this sample used for Oncomine DxTT, the read count of MET(13)-MET(15) products were only 46. The patient then received four lines of anticancer drug therapy serially for 2 years: first, cisplatin pemetrexed and pembrolizumab; second, TS-1; third, pembrolizumab; fourth, pemetrexed. However, the tumor grew along with pericardial effusion, causing cardiac tamponade, which required immediate drainage. Under the circumstances of limited treatment

options, he was admitted to the authors' hospital in June 2022 and tepotinib was administered at a dose of 500 mg once daily under careful observation. After 4 weeks, a chest computed tomography scan confirmed a partial response by shrinking of the enlarged lymph nodes (Fig. 2) according to RECIST (7). After 2 months, the patient developed grade 2 peripheral edema as a treatment-related adverse effect, and the dose was reduced to 250 mg and administration was continued. The response still continued 7 months following the initiation of tepotinib treatment.

Discussion

In the present case MET kinase inhibitor was not used initially, as METex14 skipping was positive with Oncomine DxTT, but negative with ArcherMET. However, cancer progression caused cardiac tamponade after several rounds of chemotherapy, and therefore the treatment options are limited. Tepotinib was administered with careful observation and all lesions were successfully treated. This clinical course strongly indicates a false negative result with ArcherMET.

To date, Oncomine DxTT is used worldwide for lung cancer diagnosis to detect several oncogenic drivers as CDx. This panel test can also detect METex14 skipping through RNA-based amplicon sequencing using Ion PGM Dx. However, in Japan, CDx for MET kinase inhibitors are limited to ArcherMET, FoundationOne or AmoyDx test, but not Oncomine DxTT (6), although no specific molecular assays have been assigned for MET kinase inhibitors in the United States and Europe. Among several studies reporting high rates of false negatives for METex14 skipping (8-12), there were two studies referring to the discordance between Oncomine DxTT and ArcherMET. A previous study demonstrated a case of successful treatment with the MET kinase inhibitor although METex14 skipping was positive with ArcherMET and negative with Oncomine DxTT (13). In another study, 26 samples were positive in Oncomine DxTT results, but eight samples (30.8%) did not reveal METex14 skipping with ArcherMET (12). The majority of the discordant samples had read counts <800 of MET(13)-MET(15) products. This discordance was concluded to be a false positive for Oncomine DxTT in samples with relatively low read counts, although the effectiveness of MET inhibitor was not documented (12). In the present case, the sample obtained had only 46 read counts, which supports this study. However, all tumor lesions exhibited rapid shrinkage after initiating tepotinib treatment, and the clinical course in the case described herein strongly indicates a false negative for ArcherMET due to relatively low read counts.

In conclusion, the present study reports a case of successful treatment with tepotinib, although METex14 skipping was only positive with Oncomine DxTT and not with ArcherMET. It may thus be necessary to consider the use of MET kinase inhibitors in patients with METex14 skipping proven only with Oncomine DxTT, particularly when the sample has relatively low read counts.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YO and AS analyzed and interpreted the data and wrote the manuscript. YO, AS, EH, SY, SI, ET, HK, TB, SK and TO evaluated the patient and participated in the therapy. KO was involved in the pathological diagnosis. EH and SY confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The patient provided his written informed consent for participation in the present study.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of this case report and any associated images.

Competing interests

TB has received consultation fees from Merck Pharma Japan (the supplier of tepotinib distributed in Japan). All remaining authors declare that they have no competing interests.

References

1. Paik PK, Felip E, Veillon R, Sakai H, Cortot AB, Garassino MC, Mazieres J, Viteri S, Senellart H, Van Meerbeeck J, *et al*: Tepotinib in non-small-cell lung cancer with MET Exon 14 skipping mutations. N Engl J Med 383: 931-943, 2020.
2. Heist RS, Shim HS, Gingipally S, Mino-Kenudson M, Le L, Gainor JF, Zheng Z, Aryee M, Xia J, Jia P, *et al*: MET Exon 14 skipping in non-small cell lung cancer. Oncologist 21: 481-486, 2016.
3. Socinski MA, Pennell NA and Davies KD: MET Exon 14 skipping mutations in non-small-cell lung cancer: An overview of biology, clinical outcomes, and testing considerations. JCO Precis Oncol 5: PO.20.00516, 2021.
4. Drilon A, Clark JW, Weiss J, Ou SI, Camidge DR, Solomon BJ, Otterson GA, Villaruz LC, Riely GJ, Heist RS, *et al*: Antitumor activity of crizotinib in lung cancers harboring a MET exon 14 alteration Nat Med 26: 47-51, 2020.
5. Wolf J, Seto T, Han JY, Reguart N, Garon EB, Groen HJM, Tan DSW, Hida T, de Jonge M, Orlov SV, *et al*: Capmatinib in MET exon 14-mutated or MET-amplified non-small-cell lung cancer N Engl J Med 383: 944-957, 2020.
6. Pharmaceuticals and Medical Devices Agency: Information on in vitro diagnostic products or medical devices approved for the purpose of determining the indication of a drug. Accesed Dec 23, 2022. https://www.pmda.go.jp/files/000239775.pdf.
7. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, *et al*: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45: 228-247, 2009.
8. Schrock AB, Frampton GM, Suh J, Chalmers ZR, Rosenzweig M, Erlich RL, Halmos B, Goldman J, Forde P, Leuenberger K, *et al*: Characterization of 298 Patients with Lung Cancer Harboring MET Exon 14 Skipping Alterations. J Thorac Oncol 11: 1493-1502, 2016.

9. Poirot B, Doucet L, Benhenda S, Champ J, Meignin V and Lehmann-Che J: MET Exon 14 Alterations and new resistance mutations to tyrosine kinase inhibitors: Risk of inadequate detection with current amplicon-based NGS panels. J Thorac Oncol 12: 1582-1587, 2017.
10. Davies KD, Lomboy A, Lawrence CA, Yourshaw M, Bocsi GT, Camidge DR and Aisner DL: DNA-Based versus RNA-Based Detection of MET Exon 14 skipping events in lung cancer. J Thorac Oncol 14: 737-741, 2019.
11. Champagnac A, Bringuier PP, Barritault M, Isaac S, Watkin E, Forest F, Maury JM, Girard N and Brevet M: Frequency of MET exon 14 skipping mutations in non-small cell lung cancer according to technical approach in routine diagnosis: Results from a real-life cohort of 2,369 patients. J Thorac Dis 12: 2172-2178, 2020.
12. Teishikata T, Shiraishi K, Shinno Y, Kobayashi Y, Kashima J, Ishiyama T, Yoshida T, Mori T and Yatabe Y: An alert to possible false positives with a commercial assay for MET Exon 14 skipping. J Thorac Oncol 16: 2133-2138, 2021.
13. Takamori S, Seto T, Yamaguchi M, Kinoshita F, Fujishita T, Ito K, Toyozawa R, Shoji F and Okamoto T: Case report: Success of tepotinib therapy in overcoming resistance to osimertinib in a patient with EGFR-mutant lung adenocarcinoma with a potential acquired MET exon 14 skipping mutation. Front Oncol 12: 965741, 2022.