



Non-small cell lung cancer with MET exon 14 skipping alteration responding to immunotherapy: a case report

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Abstract: Immunotherapy has been proved to be a promising candidate for advanced non-small cell lung cancer (NSCLC). Despite MET mutations are regarded as an independent factor of programmed death ligand 1 (PD-L1) high expression, the efficacy of immune checkpoint inhibitors (ICIs) across NSCLC harboring Mesenchymal-epithelial transition factor exon 14 skipping alteration (METex14) is still unclear. Moreover, when the resistance of PD-1 antibody occurs, the questions of how to interpret the resistance and how to overcome the resistance are worth exploring. We report a case of NSCLC with METex14 developed a right femoral metastasis after responding well to neoadjuvant immunotherapy, a successful lobectomy, and adjuvant immunotherapy. The subsequent attempts of MET targeted inhibitor, concurrent chemoradiotherapy, and notably programmed cell death protein 1 (PD-1) antibody plus vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGFR-TKI) failed to prevent disease progression. However, a regimen of anti-PD-1 plus anti-cytotoxic t-lymphocyte associated protein 4 (CTLA-4) reversed the progression to a complete response. This case shows that METex14 had a significant response to immunotherapy, which would be especially beneficial for those who developed targeted therapy resistance. Importantly, this is the first case reporting that salvage CTLA-4 antibody and PD-1 antibody could reverse the progression in NSCLC harboring METex14 when the anti-PD-1 resistance occurred.

Keywords: Non-small cell lung cancer (NSCLC); MET exon 14 skipping alteration; immunotherapy; programmed cell death protein 1; cytotoxic t-lymphocyte associated protein 4 (CTLA-4)

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Introduction

Abnormal activation of the Mesenchymal epithelial transition factor (MET) pathway is associated with the occurrence and development of multiple cancer types, including three main types: MET exon 14 skipping alteration (METex14), MET amplification, and MET overexpression. Among them, METex14 has been identified as an oncogenic driver in multiple cancer types and occurs in 3–4% of non-small cell lung cancer

(NSCLC), which causes continuous activation of the MET pathway (1). Previous clinical studies have shown that METex14 significantly responded to MET-targeted kinase inhibitors. The results of overall response rate (ORR) in METex14 treated by crizotinib, capmatinib, tepotinib, savolitinib were 32%, 40.6%, 46.5%, 49.2% respectively (2-5). Despite the initial effectiveness of MET-TKI in patients with METex14 NSCLC, therapeutic resistant genes (e.g., D1228N/E/G/H, Y1230C/D/S/H/N) will ultimately appear (6-8).

Among anti-tumor therapy innovations, immunotherapy has attracted tremendous attention and brought survival benefits to countless patients with cancers. Prospective clinical trials revealed that anti-PD-1 could remarkably improve the outcomes of the patients with NSCLC, regardless of their histologic types or expression levels of PD-L1 (9-11). Despite immune checkpoint inhibitors (ICIs) are widely used to treat patients with advanced NSCLC, the efficacy of ICI across NSCLC harboring METex14 is poorly characterized. Recent studies showed that MET is significantly associated with negative checkpoint regulators of the immunoresponse and promotes PD-L1-expression in a cell-autonomous manner (12). Therefore, immunotherapy might be a potential treatment option for NSCLC with METex14. Here, we report a case of NSCLC with METex14 responding remarkably to anti-PD-1 and salvaged by adding CTLA-4 antibody upon resistance. We present the following article in accordance with the CARE reporting checklist (available at <http://dx.doi.org/10.21037/atm-20-6829>).

Case presentation

A 48-year-old, smoking male with a history of stage IIIB (T3N2M0) lung adenosquamous carcinoma (based on the Eighth Edition of the TNM Classification for Lung Cancer) had the imaging showing a nodule sized 57 mm × 52 mm, pleural infiltration, and mediastinal lymphadenopathy, therefore surgery would not be beneficial. He had a fine needle biopsy of the lung lesion and was pathologically diagnosed as poorly differentiated squamous carcinoma in February 2019. Additionally, next-generation sequencing (NGS) showed positive METex14, positive MET D1228N, negative EGFR, and negative ALK. Consequently, a combination of nivolumab (200 mg, Q2W) with gemcitabine (1,600 mg, Q2W) and carboplatin (400 mg, Q2W) (GC) was prescribed. After two cycles, he had a good partial response with dramatic shrinkage of the tumor (39 mm × 28 mm) and mediastinal lymph nodes, staging IB (T2aN0M0) (*Figure 1*). Unfortunately, after the third cycle, the patient presented with persistent high fever, hyponatremia, hypokalemia, bone marrow suppression, coagulation dysfunction, liver damage, and other 3rd-grade adverse effects, which led to the discontinued of immunochemotherapy. Also, this situation represented a dramatic response in his immune system. After the use of steroids, the patient gradually recovered from these conditions.

A month later, the patient underwent video-assisted thoracic lobectomy and mediastinal lymph node dissections, followed by a resumption of nivolumab (200 mg, Q2W) plus gemcitabine (1,600 mg, Q2W) and carboplatin (400 mg, Q2W). However, metastasis appeared in his right femur after four additional cycles and failed several lines of therapy afterward, including crizotinib (250 mg BID) alone and gemcitabine (1,200 mg, Q2W) plus carboplatin (400 mg, Q2W) with local radiotherapy (DT: 60 Gy/20 F) (*Figure 1*). A femur biopsy was conducted and confirmed metastatic adenocarcinoma with METex14 and MET D1228N and a PD-L1 TPS of 10% in September 2019 (*Figure 1*). Although another PD-1 antibody and VEGFR-TKI (pembrolizumab 200 mg Q3W plus cabozantinib 140 mg Q3W) were ordered, the pain reduced initially but turned worse again two months later.

Under this situation, we changed the regimen to PD-1 antibody (pembrolizumab 200 mg Q3W) plus CTLA-4 antibody (ipilimumab 50 mg Q9W) and observed a relief of femoral pain and reduced serum tumor marker. Moreover, the PET/CT reexamination reported no metabolic increase in the whole body, including the right femur lesion, which represents that the tumor activity was suppressed (*Figure 1*). To solve the mobility problem, we performed femoral mass resection and hip replacement in April 2020. Pathologically, necrosis, fibrous tissue hyperplasia, and calcification were observed, but no cancer cells were found without pathological findings of cancer cells (*Figure 1*). The function of the right thigh recovered well, and he is in a state of complete response till now. All procedures performed in studies involving human participant were in accordance with the ethical standards of the institutional and national research committees, and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this study and any accompanying images.

Discussion

The therapeutic efficacy of immune checkpoint inhibitor (ICI) relies on the activation of cytotoxic CD8 T cells, the expansion of intra-tumoral CD4 Th1 lineage cells, and the generation of long-term memory T cells (13-15). In recent years, immunotherapies, whether as neoadjuvant, first-line, or second-line therapy, have been considered as promising approaches for treating NSCLC (9-11). In particular, anti-PD-1 has been promoted as a first-line treatment for NSCLC (6). Nevertheless, various efficacies

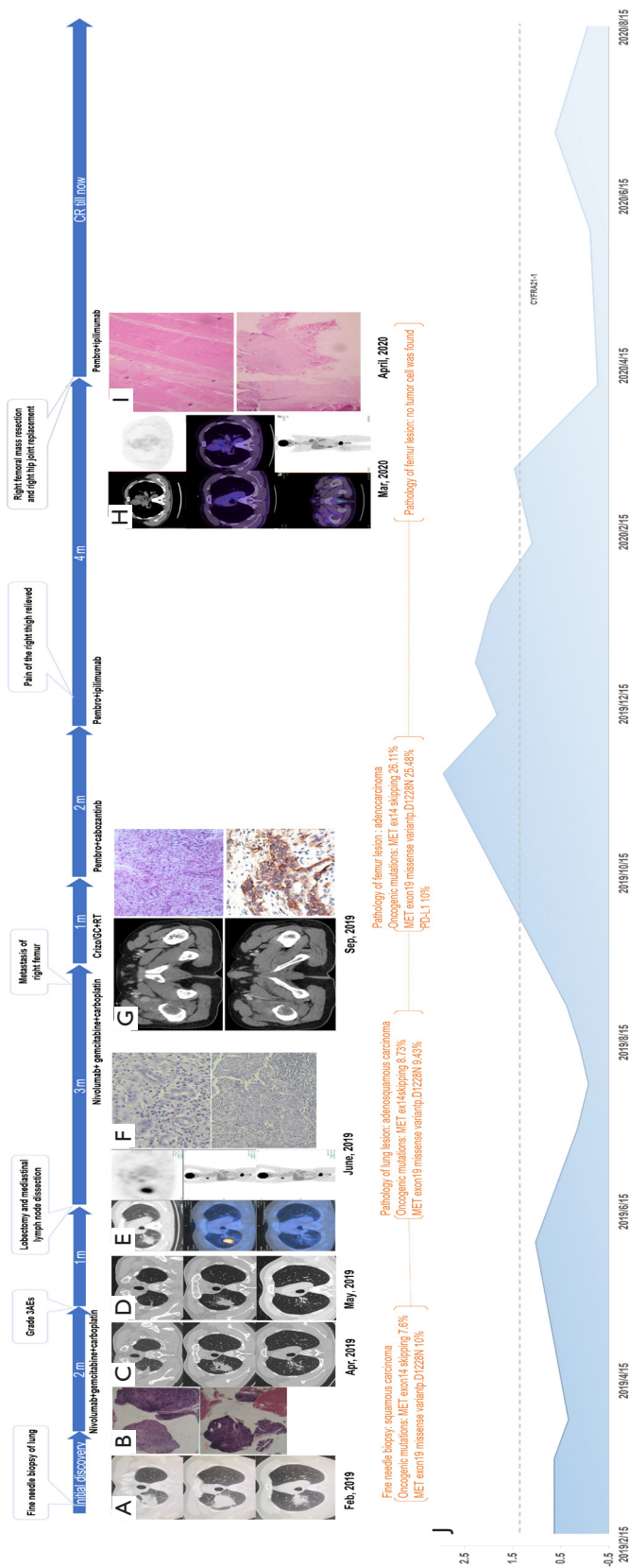


Figure 1 The process of using PD-1 to treat NSCLC MET exon14 skipping. (A) Three different layers of the first CT scan at baseline of the right upper lung lesion. (B) The Hematoxylin and eosin (HE) of lung biopsy by fine-needle aspiration was Lung squamous carcinoma (Magnification, 40x) with METex14 and D1228N. (C) The second CT images show a shrinkage of the primary tumor. (D) The third CT images of the on-going shrinkage of the primary lung lesion. (E) No metastatic increases were observed in the mediastinal lymph nodes via whole-body PET/CT before surgery. (F) The result of the resected primary lung lesion biopsy was adenocarcinoma (Top, HE, 200x; Bottom, HE, 100x) with METex14 and D1228N. No cancer cells were found among the 27 resected lymph nodes. (G) The metastasis of the right femur was found by CT scan. The femoral lesion biopsy confirmed metastatic adenocarcinoma (HE, 100x) and PD-L1 expression was 10% (Immunohistochemical staining, 200x). (H) Reexamination of whole-body PET/CT showed that no recurrent lesions or metabolic increases were found. (I) No cancer cells were found in the resected femoral lesion (HE, 40x). (J) The dynamic curve of serum tumor markers during the therapy and the value is converted logarithmically.

were reported in NSCLC when taking different oncogenic drivers into account (7,8). A prior trial showed that MET activation promotes the expression of several negative checkpoint regulators of the immunoresponse (e.g., PD-L1, PDCD1LG2, and SOCS1R) and it is an independent factor to the regulation of PD-L1 expression in lung cancer (12). Subsequently, the association between MET mutations and high expression of PD-L1 was further proved by several clinical studies (16,17). Moreover, some retrospective researches of a small sample size demonstrated that the efficacy of ICI in METex14 NSCLC seemed similar to or slightly better than that in unselected NSCLC (16,17).

In addition to anti-PD-1, other ICIs play different roles in activating the immune response, including the anti-tumor response. For instance, CTLA-4 regulates T cell proliferation in the early stage of lymph node immune response, while PD-1 inhibits T cell immune response in peripheral tissues (18). Therefore, blocking both pathways leads to a synergistic effect leading to a long-lasting anti-tumor immune response (19). Salvage ipilimumab and nivolumab has been demonstrated to be safe and effective in ICI refractory melanoma and clear cell renal cell carcinoma patients (20-22). The application of ipilimumab with nivolumab as salvage therapy has been reported in patients with melanoma, with approximately 50% of patients demonstrating disease control (20). Another retrospective study evaluated the use of ipilimumab and nivolumab as salvage therapy in patients with immunotherapy-refractory mRCC and a 40% partial response rate was showed (22).

Given the dynamic and complex nature of anti-cancer immunity and the differences of the immune microenvironment in different tissue, different treatment strategies will have apparent efficacy variations (23).

Our case provides direct evidence that NSCLC with METex14 had a significant response to anti-PD-1. Even though targeted therapy has become the mainstay regimen of NSCLC with METex14, therapeutic resistant genes will ultimately appear. Our case suggests that immunotherapy may be a promising candidate for treating advanced NSCLC patients with METex14 alterations, especially those harboring MET-TKI resistant mutations (e.g., D1228N/E/G/H, Y1230C/D/S/H/N). Thus, it is worthy of further verification through prospective clinical trials. Moreover, the interpretation of immunotherapy resistance could be tricky in some circumstances. Previous studies revealed that the organ-specific niche, e.g., bone and liver, might be resistant to the development of T_h1 effector CD4 T cells or CD8 cytotoxic T cells, which might be why PD-1 antibody

plus VEGFR-TKI fail to control bone metastases. In this case, however, the patient presented with systemic adverse responses, including high fever, electrolyte disturbances, and bone marrow suppression after an initial partial response to immunotherapy, which represented a well-functioning immune system of the patient. This raised the thinking that if the immunotherapy should be abandoned given the well-functioning immune system. Furthermore, the subsequent complete response to immunotherapy implied that immune resistance to PD-1 inhibitors should be evaluated in each lesion independently because of inter-lesion heterogeneity in tumor per se and immune microenvironment. The resistance of a particular lesion, e.g., bone/liver metastasis, which represents an immunosuppressive niche, should not be perceived prematurely as systemic immune resistance to anti-PD-1. Last but not least, our case firstly reports that salvage CTLA-4 antibody and PD-1 antibody can be effective in resistant anti-PD-1 patients with NSCLC. Therefore, we proposed a strategy in overcoming the resistance to anti-PD-1 therapy is to consider combination with other immunomodulators or immune agonists, such as CTLA-4 antibody, rather than discontinue its use.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at <http://dx.doi.org/10.21037/atm-20-6829>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/atm-20-6829>). JH serves as an editor in chief of *Annals of Translational Medicine* from Jun 2019 to May 2024. The other 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 studies involving human participant were in accordance with the ethical standards of the institutional and national research committees, and with the Helsinki Declaration (as revised in 2013). Written informed consent

was obtained from the patient for publication of this study and any accompanying images.

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