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MET Y1003S point mutation shows sensitivity to crizotinib in a patient with lung adenocarcinoma

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ABSTRACT

Objectives: *MET* amplification or *MET* exon 14 skipping site mutation can be treated with crizotinib in non-small cell lung cancer patients. Y1003 is a binding site for E3 ubiquitin ligase, which is critical for MET degradation. Here we show an adenocarcinoma patient with Y1003S mutation and she got tumor remission after crizotinib treatment.

Materials and methods: A 61-year-old never-smoking female was admitted to our hospital due to increased carcino-embryonicantigen. Positron emission tomography (PET)-CT showed enlargement of bilateral cervical, left supraclavicular and multiple mediastinal lymph nodes. PET-CT also showed stripe in the left upper lobe. Adenocarcinoma cells were found from biopsy on her left supraclavicular lymph nodes. We detected cell-free circulating tumor DNA (ctDNA) from peripheral blood and identified a MET Y1003S mutation by next generation sequencing technology. Y1003 mutations predicted to be similar to *MET* exon 14 skipping in functionality based on the literature. After an extensive discussion of treatment options, the patient opted to treatment with crizotinib, a small-molecule dual inhibitor of the MET and ALK.

Results and conclusion: Dramatic response was observed within 1 months of treatment, which lasted more than 10 months. Chest CT scans revealed significant improvement of the lung focus and decrease in size of the lymph nodes lesions, meeting RECIST partial response criteria (−30%). Y1003 alterations may be diverse mutations and sensitive to MET inhibitors.

1. Introduction

The hepatocyte growth factor receptor (MET) is a potential therapeutic target for it can activate the downstream RAS/ERK/MAPK, PI3K/AKT, Wnt/b-catenin, and STAT signaling pathways and drive cell proliferation, survival, migration, motility, invasion, angiogenesis, and the epithelial-to-mesenchymal transition [1]. Aberrant activation MET/HGF signaling in lung cancer occurs through various mechanisms, including gene amplification, mutation, rearrangement, and protein overexpression [2]. High-level *MET* amplification or *MET* exon 14 alterationsin non–small cell lung cancer (NSCLC) patients have been reported the dramatic response to MET inhibitors and recommended to be treated with crizotinib by NCCN guidelines. The different sites of *MET* point mutations, however, display different effects (response or resistance) to different MET inhibition [3,4]. Y1003 residue is a product of exon14 and a binding site for the c-Cbl, which is an E3 ubiquitin ligase involved in the ubiquitination and degradation of MET. Y1003 point mutations can lead to oncogenic transformation in vitro [5] and have been reported in Lung cancer [6]. Dr.Drilon had reported a phase 1 trial of antitumor activity and safety of crizotinib in patients with advanced *MET* exon 14-altered non-small cell lung cancer in ASCO 2016 [7]. However, patients with Y1003S point mutation reacting to MET-targeted therapies have not yet been reported. Here we identified one such mutation using next generation sequencing technology in a lung adenocarcinoma patient and treated her with crizotinib.

2. Case report

A 61-year-old never-smoking female was admitted to our hospital in December 2016 due to increased carcino-embryonicantigen(CEA) in physical examination for half year, she had no respiratory symptoms or weight loss. The initial CEA was 67.6 ng/ml and computerized tomography (CT) of the chest revealed patches and nodules in both side of the upper pulmonary region and enlargement of mediastinal lymph nodes, the larger one of which was about 1.4*2.0 cm.Gastroscopy examination showed gastric fundus polyp and chronic gastritis. Colonoscopy showed colonic polyps. After polypectomy, the pathological changes were colonic hyperplastic polyps and gastric fundus

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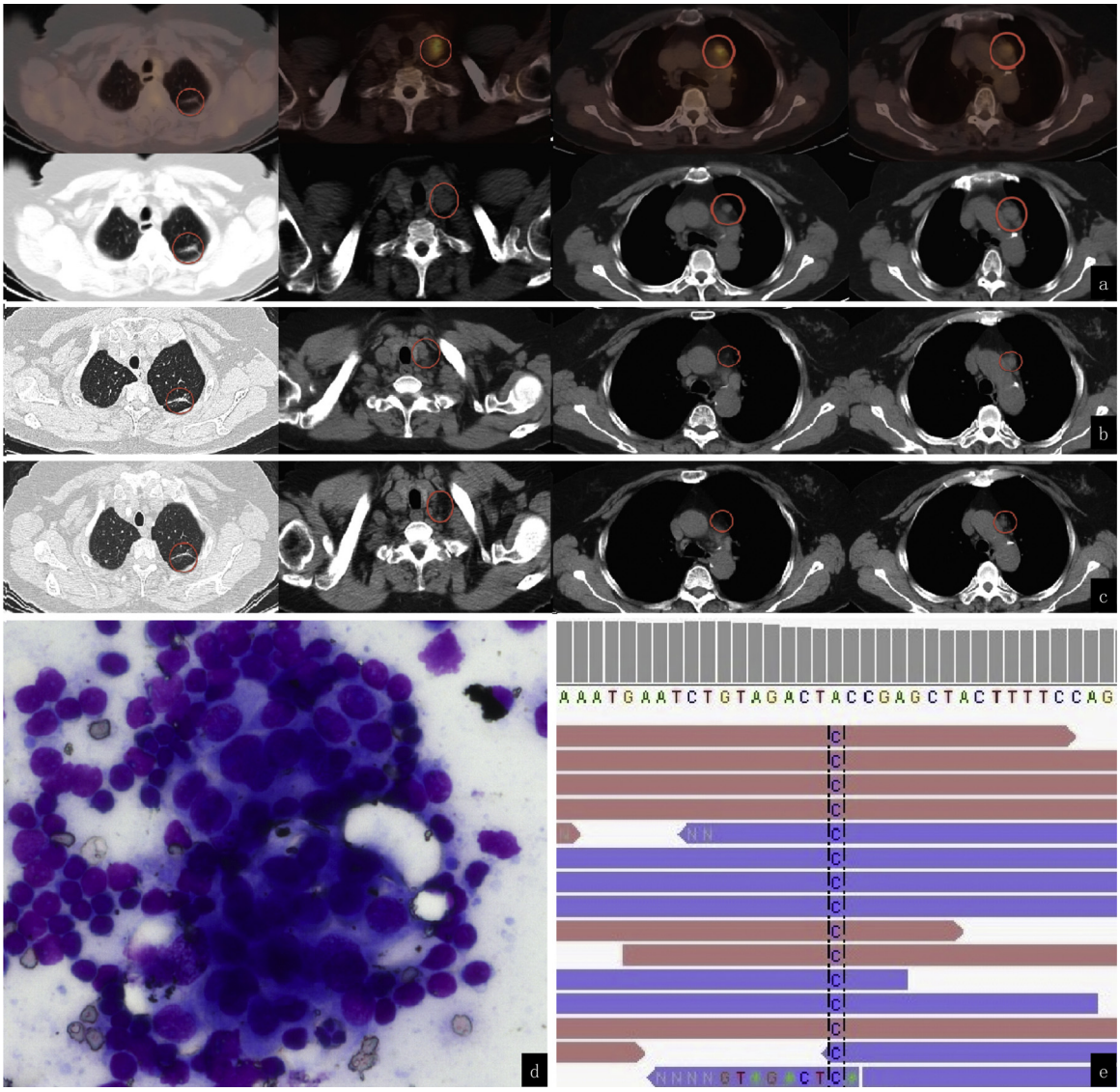

Fig. 1. Positron emission tomography (PET)-CT scan of primary lung focus and lymph nodes before crizotinib treatment (a).Chest CT scans revealing improvement of the lung focus and decrease in size of the lymph nodes after 1 months crizotinib treatment (b).Chest CT scans revealing improvement of the lung focus and decrease in size of the lymph nodes after 10 months crizotinib treatment (c).Histopathological findings of biopsy on the left supraclavicular lymph nodes: adenocarcinoma cells (d, Wright's staning, original magnification × 400).Genetic analysis showingY1003S point mutation(c.3008 A > C)of MET (e).

inflammatory polyp. After two months her CEA level was down to 40.51 ng/ml and a week before her admission it was 60.02 ng/ml. Positron emission tomography (PET)-CT showed enlargement of bilateral cervical, left supraclavicular and multiple mediastinal lymph nodes (Fig. 1a). All these lymph nodes displayed increased uptake of 18F-fluoro-2-deoxy-D-glucose (18 F-FDG). PET-CT also showed stripe in the left upper lobe (Fig. 1a). Furthermore, adenocarcinoma cells were found from biopsy on her left supraclavicular lymph nodes (Fig. 1d). All together, she was diagnosed with adenocarcinoma of the left lung and the TNM stage was IIIB (T1N3M0).

Because there was insufficient biopsy material for IHC and multiple genomic alterations tests cited in NCCN guideline, we detected cell-free circulating tumor DNA (ctDNA) from peripheral blood and identified a MET Y1003S mutation by next generation sequencing technology (Fig. 1e). We detected rare mutations in ctDNA using the Illumina NextSeq CN 500 sequencing system (Geneplus Technology, Beijing). There were no *EGFR* mutations, *MET* amplification, or *ALK/ROS1* fusion events detected (Table 1). Y1003 mutations predicted to be similar to *MET* exon 14 skipping in functionality based on the literature [5]. After an extensive discussion of treatment options, the patient opted to treatment with crizotinib, a small-molecule dual inhibitor of the MET and ALK. Dramatic response was observed within 1 months of

Table 1
Genomic alterations detected by next generation sequencing for the patient.

Gene	Mutation
MET 14exon	c.3008 A > C
MET amplification	(-)
EGFR18/19/20/21 exon	(-)
ALK rearrangements	(-)
ROS1 rearrangements	(-)
KRAS12/13/61/146 codon	(-)
RET rearrangements	(-)
BRAF 600 codon	(-)
NRAS 12/13/61 codon	(-)
HER2 amplification	(-)
HER2 20 exon	(-)
KIT 9/11/13/17 exon	(-)
PDGFRA 12/18 exon	(-)

treatment, which lasted more than 10 months. Chest CT scans revealed significant improvement of the lung focus and decrease in size of the lymph nodes lesions, meeting RECIST partial response criteria (−30%) (Fig. 1b and c).Till now she regular reexamines in our department, and she is in stable condition. Her survival period is far more than the average progression-free survival time of treatment of crizotinib.

3. Discussion

Our case demonstrates that MET inhibitor crizotinib shows antitumor response to a lung adenocarcinoma patient with Y1003S mutation for the first time, although Y1003 point mutations have been reported in lung cancer samples by several researchers [5,6].

The receptor tyrosine kinase MET is an important regulator of cell growth, regeneration and development. Lots of alterations in MET have been reported in various human cancers including small and non–small cell lung cancers [1]. *MET* exon 14 encodes a juxtamembrane domain containing the Y1003 residue. Codon Y1003 in juxtamembrane domain, as a regulator of MET signaling, is critical for the recruitment of the c-Cbl for ubiquitination of MET. Exon 14 skipping is thought to lead to decreased MET ubiquitination and degradation, which results in oncogenic transformation. Several researchers had described that genomic alterations that affect the Y1003 residue such as MET Y1003 F or MET exon 14 deletion can result in a similar biology without affecting splicing [8,9]. PMET (phosphorylation of MET)Y1003 preferential expressed in tumor cells in the invasive front of the NSCLC tumor tissues observed by Patrick C. Ma et al [10]. High expression of nuclear pMET Y1003 represented poor prognostic in lung cancer patients [11]. So Y1003 may relate to aggressiveness of the tumor. Alexa B. Schrock et al reported 6 cases of Y1003X mutation in their research of lung cancer [6]. Y1003C amino acid substitution was detected in a NSCLC patient and this mutation might be the main reason for MET overexpression [12]. In addition, Y1003 F substitution mutation had been shown to converting the receptor into a transforming protein in the absence of ligand [5]. All these show that Y1003 mutations may lead to oncogenic transformation, and would be an actionable site for TKIs. Our case proved that Y1003S point mutation in lung cancer patients could have a response to crizotinib.

Precision medicine for NSCLC patients with *EGFR*, *ALK* and *ROS1* mutations has been the major progress so far, and whose responserates are 60%–80%. The NCCN guidelines recommend using next generation sequencing technologyto detect more gene alterations before treatment. In this setting, a rare mutation, sometimes of uncertain significance, may be found. Basing on the previous researches, we search an available inhibitor directed against that mutation, which may provide a novel treatment opportunity. In this case, we detected the potential driver mutation through the next generation sequencing. After treatment with crizotinib, the tumor volume lessened obviously and the patient got sustained remission till now. Thus it is the first report to show antitumor response to crizotinib with MET Y1003S mutation in lung adenocarcinoma.

As previously reported, Y1003 point mutations could have several variations: Y1003F [5], Y1003X [6], and Y1003C [12]. Here we only proved that the Y1003S point mutation was response to crizotinib. Further studies are needed to validate the hypothesis that Y1003 alterations may be diverse mutations and confer sensitivity to MET inhibitors.

In conclusion, Our case demonstrates that MET inhibitor crizotinib shows antitumor response to a lung adenocarcinoma patient with Y1003S mutation for the first time, which may be a new targetable site for MET inhibitor therapy.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form,the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understand that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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