


Treatment Response to Immunotherapy After Crizotinib Resistance in a Patient With Pulmonary Sarcomatoid Carcinoma Harboring MET Exon 14 Skipping Mutation: A Case Report

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Ling Gu¹, Xiaoying Wei¹, Zixiang Zhang² and Wei Heng¹ 

¹Department of Respiratory and Critical Care Medicine, The First Affiliated Hospital of Soochow University, Suzhou, China. ²Department of General Surgery, The First Affiliated Hospital of Soochow University, Suzhou, China.

ABSTRACT: Pulmonary sarcomatoid carcinoma (PSC) is a rare subtype of non-small cell lung cancer (NSCLC) with poor prognosis. The skipping mutation in exon 14 of *MET*, an oncogenic driver of NSCLC, occurs more frequently in PSC than other subtypes. Treatment options for patients with PSC include targeted therapies and immunotherapies, while the best treatment regimen has not been established due to limited number of patients. In this report, we presented a case with metastatic PSC harboring *MET* 14 exon skipping mutation. The patient received crizotinib but soon acquired drug resistance. Then, the patient turned to immunotherapy in combination with chemotherapy and has achieved a progression-free survival for 15 months as of the data cutoff date. The comprehensive genomic sequencing after crizotinib resistance revealed additional genetic alterations such as *CD274* (also known as programmed cell death ligand 1) amplification which might be associated with treatment response of the patient.

KEYWORDS: Non-small cell lung cancer, pulmonary sarcomatoid carcinoma, MET, exon skipping, crizotinib, nivolumab

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CORRESPONDING AUTHOR: Wei Heng, Department of Respiratory and Critical Care Medicine, The First Affiliated Hospital of Soochow University, 188 Shizi Street, Suzhou 215006, China. Email: hengwei1106@163.com

Introduction

Pulmonary sarcomatoid carcinoma (PSC) is a rare subtype of non-small cell lung cancer (NSCLC).¹ Although it only accounts for 0.1% to 0.4% among all lung cancer cases, the outcomes of PSC were significantly worse than other subtypes of NSCLC.¹ The mesenchymal-epithelial transition (*MET*) gene, located at chromosome 7q21-q31, plays an important role in oncogenic process of NSCLC.² Genomic profiling of lung adenocarcinoma identified 4% of patients harboring exon 14 skipping mutation in *MET*.³ In patient with PSC, the prevalence of *MET* exon 14 skipping mutation was 22%, which is far more frequent than other NSCLC subtypes.⁴ The *MET* exon 14 encodes the juxtamembrane domain.⁵ The skipping mutation results in the loss of *MET* exon 14 and would enhance the oncogenic potential of *MET* gene.⁵ Targeted therapies for patients with PSC harboring *MET* 14 exon skipping mutation include crizotinib and other *MET* inhibitors that are in clinical trials.⁶ In addition, immune checkpoint inhibitors (ICIs) blocking programmed cell death 1 (PD-1) or programmed cell death ligand 1 (PD-L1) have been used for patients with PSC as well but the treatment responses were varied among different cases.^{7,8}

Herein, we reported a patient with metastatic PSC harboring *MET* 14 exon skipping mutation. The patient received crizotinib but soon acquired drug resistance. Then, the patient received immunotherapy in combination with chemotherapy and had durable response with progression-free survival (PFS) approximately 7 months. Tissue sample of the patient before

and after crizotinib treatment was obtained and subjected to capture-based targeted sequencing using a panel consisting of 520 cancer-related genes. In addition to *MET* exon 14 skipping mutation, other genetic alterations emerged after crizotinib resistance such as *CD274* (also known as PD-L1) amplification might also be associated with treatment response of the patient.

Case Presentation

A 58-year-old male patient visited the First Affiliated Hospital of Soochow University on February 2020 due to cough with blood-tinged sputum for 1 week. The patient has hypertension for more than 10 years. He reported no smoking and drinking habits and no family history of tumor. The positron emission tomography-computed tomography indicated the right upper lung masses with multiple metastases of the pericardium and the left parietal lobe. Multiple lesions in descending colon and sigmoid colon were also observed. The abnormal increase of glucose metabolism indicated that the lesions of lung and colon might be malignant. The laboratory examination identified elevation of several tumor biomarkers, including CA125 (68.3U/mL), tumor-specific growth factor (76.9U/mL), and total prostate-specific antigen (5.849 ng/mL). The patient received laparoscopy and partial intestinal resection. The pathological evaluation of tissue sample obtained from surgery reported multifocal poorly differentiated adenocarcinoma with full-thickness infiltration which are the characteristics of sarcomatoid carcinoma (Figure 1A to D). The immunohistochemistry revealed



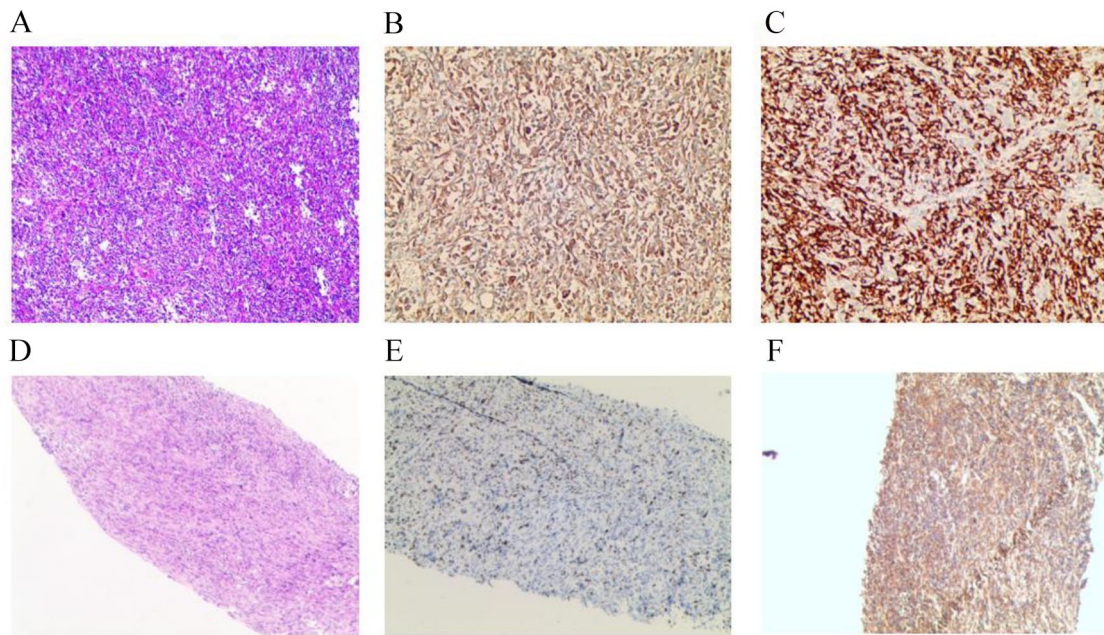


Figure 1. Pathological evaluation on tissue samples obtained from laparoscopic intestinal resection (A-C) and right forearm biopsy (D-F).

positive CK, CK7, Vimentin, TTF-1, Ki-67 (>80%), and PD-L1 (tumor proportion score [TPS] >90%) and negative CD34, LCA, SATB2, CK20, Napsin A, Villin, CDX2, and CEA. Therefore, the patient was diagnosed with metastatic PSC. The tissue sample was also subjected to high-throughput sequencing of 520 cancer-related genes. The *MET* exon 14 skipping mutation c.3028 + 3A > G and somatic mutations in *ATR* and *TP53* were identified (Table 1). Meanwhile, no mutations were identified in plasma of the patient.

One week after the surgery, the patient had dizziness and impaired movement of the right limb due to metastatic tumor of the left parietal lobe. The symptoms were improved after reducing intracranial pressure and cranial radiotherapy. In addition, tumor progression was observed in the right upper lung from 39.3*28.75 to 48*45 mm. The patient received targeted therapy with crizotinib since March 31, 2020 (Figure 2). The follow-up on April 28, 2020, through chest CT showed that tumor in the right upper lung was decreased and the patient achieved partial response (PR) (Figure 2). However, the next follow-up on May 8, 2020, observed tumor increase of the right upper lung (Figure 2) as well as new tumor lesions in the left ilium and the right clavicle, thigh, ulna which were indicative of progressive disease. Then, anlotinib was administered to the patient instead of crizotinib but was suspended due to skin rash on leg. Meanwhile, the patient received the second pathological evaluation on right forearm biopsy which reported invasive, poorly differentiated metastatic adenocarcinoma consisting of mainly sarcomatoid component (Figure 1D to F). The immunohistochemistry revealed positive CK, CK7, CK18, Vimentin, and Ki-67 (>40%) and negative SMA, CD34, S100, CD68, State 6, Desmin, ALK, TTF-1, and Napsin-A. In addition, the right forearm biopsy sample of the patient obtained after crizotinib resistance was

Table 1. Genomic sequencing results of the patient.

BEFORE CRIZOTINIB TREATMENT*		
GENE	ALTERATIONS	ALLELIC FREQUENCY
ATR	c.5739-2A>C	12.77%
MET	c.3028 + 3A > G	38.92%
TP53	p.R282W	28.84%
AFTER CRIZOTINIB RESISTANCE*		
GENE	ALTERATIONS	ALLELIC FREQUENCY
MET	c.3028 + 3A > G	87.76%
MET	Copy number amplification	CN: 3.8
NRAS	p.Q61R	58.24%
CD274	Copy number amplification	CN: 4.8
CDKN2A	Copy number loss	CN: 0.6
CDKN2B	Copy number loss	CN: 0.7

*Samples were obtained from laparoscopic intestinal resection (before crizotinib treatment) and right forearm biopsy (after crizotinib resistance), respectively.

subjected to targeted sequencing of 520 cancer-related genes as well. As shown in Table 1, the sequencing additionally identified copy number variations in several genes, including *MET* and *CD274* (PD-L1) as well as a point mutation of *NRAS* (p.Q61R). As the patient acquired resistance to crizotinib and was intolerable to anlotinib, chemotherapy plus immunotherapy became the subsequent treatment option considering high expression of PD-L1 was observed in the intestine tissue.

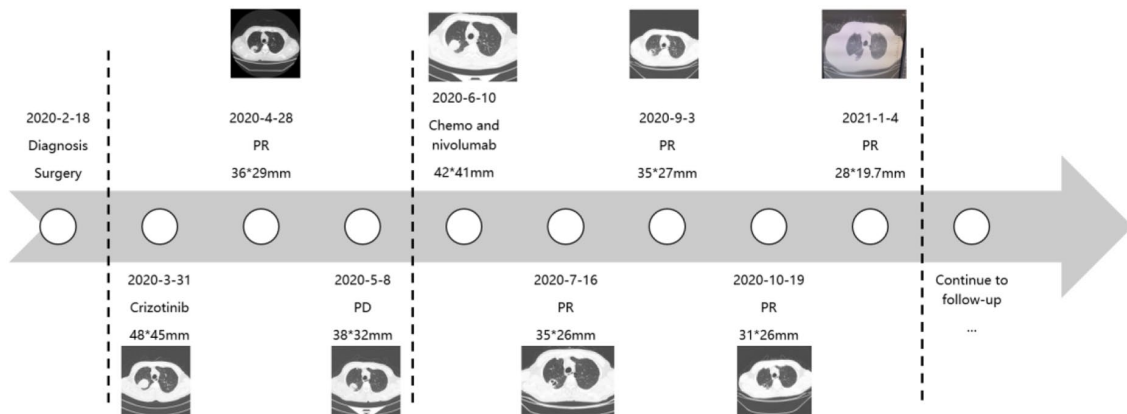


Figure 2. Treatment summary of the patient from diagnosis to the latest follow-up.

The patient received the first treatment cycle consisting of nanoparticle albumin-bound paclitaxel (nab-paclitaxel, 200 mg d1, 100 mg d7 and d15), carboplatin (0.4g d1), and nivolumab (200 mg d1 and d15) since June 10, 2020. The follow-up on July 16, 2020, observed tumor reduction in the right upper lung from 42*41 to 35*26 mm (Figure 2). Tumor lesions in the right clavicle, thigh, and ulna were almost disappeared, while tumor lesion in the left ilium was significantly decreased. Treatment response evaluation indicated that the patient achieved PR. The second treatment cycle consisting of nab-paclitaxel (200 mg d1), carboplatin (0.4g d1), and nivolumab (200 mg d1) was administered to the patient on July 17, 2020, and the follow-up on September 3, 2020, indicated PR. Adverse effects observed during chemotherapy and immunotherapy included fever, feet edema, renal function impairment, and low albumin level which might be associated with the use of chemotherapy drugs. Therefore, only nab-paclitaxel (200 mg d1) and nivolumab (200 mg d1) was administered to the patient in the third treatment cycle. After 3 treatment cycles, the patient started nivolumab (200 mg d1) monotherapy as maintenance treatment. The follow-up on January 4, 2021, indicated that the patient remained PR. The treatment process of the patient was summarized in Figure 2. Until September 7, 2021, the patient remained PR with the PFS of 15 months since immunotherapy.

Discussion

In this study, we reported a case with PSC showing marked responses to immunotherapy after crizotinib resistance. The patient harbored a skipping mutation in exon 14 of *MET* which has been recognized as an oncogenic driver of NSCLC. Although PSC is a rare subtype of NSCLC, the *MET* exon 14 skipping mutation is more frequently presented in PSC than other subtypes.⁴ Crizotinib is a multikinase inhibitor which targets several driver genes of NSCLC including *ALK*, *ROS1*, and *MET*. The in vitro investigation found that inhibition of *MET* with crizotinib could decrease downstream signaling and inhibit tumor cell growth and proliferation in *MET* exon 14 skipped cell lines.⁴ Treatment responses of crizotinib were observed in sporadic cases with PSC.^{4,9} The patient in our

study showed PR to crizotinib, but the disease was then progressed in a short time. In a previous study of 20 NSCLC patients harboring *MET* exon 14 skipping mutation and resistant to *MET*-TKIs, secondary mutations of *MET* and activation of bypass signaling pathways were identified in 15 patients (75%).¹⁰ Acquired mutations in kinase domain of *MET* including D1228 and Y1230 were reported in 6 patients receiving type I *MET* inhibitors such as crizotinib, while acquired *MET* amplification was only identified in 1 patient.¹⁰ Other off-target genetic alterations involving *EGFR* (Epidermal Growth Factor Receptor) family and *MAPK* (Mitogen-Activated Protein Kinase) pathway may also contribute to crizotinib resistance.¹⁰ In our study, the second NGS (Next-generation sequencing) test after crizotinib resistance indicated that the patient acquired *MET* amplification, while mutations in *NRAS*, *CDKN2A* and *CDKN2B* were also identified. The underlying mechanism of crizotinib resistance in our case remains to be further investigated.

Recent years, ICIs have also been used in patients with NSCLC harboring driver mutations.¹¹ The humanized monoclonal antibodies against PD-1, such as pembrolizumab and nivolumab, significantly improved treatment outcomes for advanced NSCLC patients with high expression of PD-L1.^{12,13} A study indicated that high expression of PD-L1 seems more common in lung cancer patients with *MET* exon 14 mutations of which 41% patients had TPS more than 50%.¹⁴ In PSC, 63.6% patients showed high expression of PD-L1 with the median TPS of 70%.¹⁴ In our study, the patient showed very high PD-L1 expression with TPS more than 90%, therefore was considered for immunotherapy after crizotinib resistance. The patient achieved PR with PFS lasting approximately 15 months after chemotherapy in combination with nivolumab. Other studies also reported the use of immunotherapy in lung cancer patients with *MET* exon 14 skipping mutation but the therapeutic effects were varied.^{7,8,15} A number of adenocarcinoma and PSC cases harboring *MET* exon 14 skipping mutation received ICIs and 6 of the 13 patients had durable response with PFS over 18 months.⁷ A patient with stage IV PSC received paclitaxel-carboplatin chemotherapy and nivolumab

and achieved complete response.⁷ Meanwhile, no clinical benefit of immunotherapy was also reported in a PSC patient with both MET exon 14 skipping mutation and high PD-L1 expression.⁸ A more recent case reported a PSC patient with high PD-L1 expression and KRAS mutation.¹⁵ Nivolumab combined with anlotinib was used in combination and the patient archived PR.¹⁵ It was reported that immunotherapies are only effective in a subset of patients, while a number of predictive biomarkers, including PD-L1 expression, microsatellite instability, and tumor mutational burden, have been used for immunotherapies.¹⁶ To further analyze the treatment effects of immunotherapy in our case, we performed genetic sequencing on biopsy sample obtained after crizotinib resistance. In particular, we identified amplification of *CD274* (PD-L1), which was emerged as a novel biomarker of immunotherapy.¹⁶ Although expression of PD-L1 has been approved as a predictive biomarker for ICI treatments, some patients with higher PD-L1 TPS may not benefit from ICIs. It remains to be an unmet clinical need to precisely identify candidate patients for ICIs. Previous studies reported that *CD274* amplification was associated with higher PD-L1 expression.^{17,18} Patients with *CD274* amplification and high expression of PD-L1 seem more likely to benefit from ICIs.^{17,18} Given relatively low prevalence of *CD274* amplification, there lack of convincing clinical studies and evidence to support if *CD274* amplification are better than PD-L1 expression. Currently, *CD274* amplification may be used in combination with other biomarkers such as PD-L1 expression in patient stratification. A retrospective study reported that 66.7% of patients with *CD274* (PD-L1) amplification showed objective response to immunotherapy.¹⁶ In our case, the treatment effect of nivolumab observed might also be associated with the presence of *CD274* (PD-L1) amplification.

In conclusion, this study reported a patient with metastatic PSC harboring *MET* exon 14 skipping mutation. The patient benefited from immunotherapy in combination with chemotherapy after acquired resistance to crizotinib. The comprehensive genomic sequencing could contribute to explain varied therapeutic effects of immunotherapy observed in different cases. Further clinical studies are warranted to explore appropriate treatment options for patients with PSC.

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Author Contributions

Ling Gu and Xiaoying Wei drafted the article and contributed to editing and revision. Zixiang Zhang and Wei Heng

contributed to editing and revision of the article. All authors approved submission of the manuscript.

Informed Consent

Written informed consent was obtained from the participants for publication of this article and any accompanying tables/images. A copy of the written consent is available for review by the Editor of this journal.

ORCID iD

Wei Heng  <https://orcid.org/0000-0001-9771-1228>

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