CASE REPORT

Nagoya J. Med. Sci. **87**. 808–813, 2025
doi:10.18999/nagjms.87.4.808

Successful treatment with sintilimab plus anlotinib for SMARCA4-deficient non-small cell lung cancer with *MET exon 14 skipping*: a case report

Hongfei Zhao[1], Chi Zhang[1], Dongmei Chen[1], Wei Ye[2] and Qingming Shi[1]

[1]*Department of Oncology, Anhui Chest Hospital, Hefei, China*
[2]*Department of Pathology, Anhui Chest Hospital, Hefei, China*

ABSTRACT

SMARCA4-deficient non-small-cell lung cancer (SD-NSCLC) is a rare and highly aggressive epithelial tumor that originates in the lungs. SD-NSCLCs are more prevalent among male smokers, lacks mutations of the mesenchymal-epithelial transition g (MET) gene, and does not have an established treatment plan. Herein, we present a unique case of an SD-NSCLC, an adenocarcinoma with a MET14 skipping mutation, in the left upper lung lobe which was classified as cT4N3M1a stage IVa. Next-generation sequencing revealed a D1010H skip mutation in exon 14 of MET, and immunohistochemistry indicated a programmed death ligand 1 expression level of 90%. Owing to financial constraints and concerns regarding chemotherapy, the patient declined MET inhibitor-targeted therapy and chemotherapy. Instead, the patient received sintilimab and anlotinib. Following two treatment cycles, a notable reduction in the lesions in the left upper lobe and a significant decrease in lung metastases were observed, and the patient has attained a progression free survival of >2 years. This case represents the initial documentation of SD-NSCLC featuring MET14 skipping mutations and its effective management with programmed death protein 1 inhibitors, in conjunction with anti-angiogenic agents. We believe that the combination of sintilimab and anlotinib can be a viable therapeutic approach for the treatment of SD-NSCLCs.

Keywords: SMARCA4-deficient, non-small cell lung cancer, sintilimab, anlotinib, MET exon 14 skipping

Abbreviations:
NSCLC: non-small cell lung cancer
SD-NSCLC: SMARCA4-deficient NSCLC
MET: mesenchymal-epithelial transition (c-MET)
PD-1: programmed death protein 1
CT: computed tomography

INTRODUCTION

SMARCA4-deficient non-small-cell lung cancer (SD-NSCLC) is a rare pulmonary malignancy and a distinctive subtype of NSCLCs. Approximately 8% of NSCLC cases are linked to

Received: January 7, 2025; Accepted: March 27, 2025
Corresponding Author: Qingming Shi, MM
Department of Oncology, Anhui Chest Hospital, No. 397, Jixi Road, Hefei 230022, China
E-mail: QINGMINGshii@outlook.com

SMARCA4 mutations, which often correlate with compromised overall survival.[1] The efficacy of molecular targeted therapy is restricted in NSCLCs owing to the absence of driver gene mutations in *EGFR*, *ALK*, *ROS1*, *MET*, among others. Although previous investigations have underscored the advantages of immune checkpoint inhibitors (ICIs), their overall survival rates remain relatively limited. Currently, there is no universally accepted standard treatment for this condition.

Sintilimab, a humanized monoclonal antibody targeting programmed death protein 1 (PD-1), blocks the interaction between PD-1 and its ligands (PD-L1/PD-L2), thereby restoring T cell-mediated anti-tumor immunity. Anlotinib, a novel multi-target tyrosine kinase inhibitor, suppresses tumor angiogenesis by targeting VEGFR2/3, FGFR1-4, and PDGFR-α/β, while also inhibiting tumor proliferation via c-Kit and RET pathways. Preclinical studies suggest that anti-angiogenic agents may enhance the efficacy of PD-1 inhibitors by normalizing tumor vasculature, promoting T-cell infiltration, and reducing immunosuppressive factors, such as VEGF and Tregs. In NSCLC, the combination of PD-1 inhibitors with anti-angiogenic agents (eg, pembrolizumab + lenvatinib) has demonstrated synergistic anti-tumor activity in clinical trials.[2] We present a case of an SD-NSCLC, an adenocarcinoma harboring a mesenchymal-epithelial transition (MET) 14 skip mutation, that demonstrated swift remission following treatment with sintilimab combined with anlotinib. This case report suggests that the combination of PD-1 inhibitors with multi-target anti-angiogenic tyrosine kinase inhibitors could offer potential benefits for the treatment of SD-NSCLCs.

CASE PRESENTATION

A 53-year-old male patient presented to Anhui Chest Hospital in July 2022 with persistent dull pain in the left chest. He had a medical history of chronic non-atrophic gastritis, but no history of smoking or alcohol consumption, and no known familial predisposition for cancer. Upon admission, the patient underwent a chest computed tomography (CT) examination, revealing a sizable mass measuring about 6.2 cm × 5.4 cm within the upper lobe of the left lung (Fig. 1A). Both lungs displayed multiple nodules with well-defined margins, each reaching a maximum diameter of approximately 1.0 cm. Additionally, left pleural effusion was observed along with enlarged lymph nodes in the left hilum, supraclavicular area, and mediastinum. One day post-admission, closed drainage of the left thoracic cavity was performed, and cytological analysis of the pleural fluid revealed atypical cells. Subsequently, a left lung needle biopsy was performed two days later, with pathological confirmation of SMARCA4-deficient lung adenocarcinoma (Fig. 2A). The immunohistochemical profile revealed the following markers: CK (+), CK7 (+), TTF-1 (+), napsin A (partially +), Ki-67 (approximately 50%), Brg-1 (−) (Fig. 2B), P40 (−), and VIM (−). PD-L1 assessment revealed a tumor proportion score of 90%. Subsequent cranial magnetic resonance imaging, whole-body bone scans, and abdominal and pelvic CT scans revealed no signs of metastases. Molecular profiling of the lung biopsy tumor tissue using a comprehensive next-generation sequencing (NGS) panel conducted 5 days later revealed a D1010H mutation in exon 14 of MET, with a prevalence of 21.6%. Additionally, the analysis identified a frameshift mutation in *BRCA1*, a missense mutation in *MSH6*, and a non-frameshift mutation in *CDK12*. No tumor microsatellite instability or mutations in *ALK*, *ROS1*, *EGFR*, *KRAS*, *RET*, *STK11*, or *TP53* genes were detected. The conclusive diagnosis was an SD-NSCLC with a MET14 skipping mutation, at stage IVa, and with 90% PD-L1 expression.

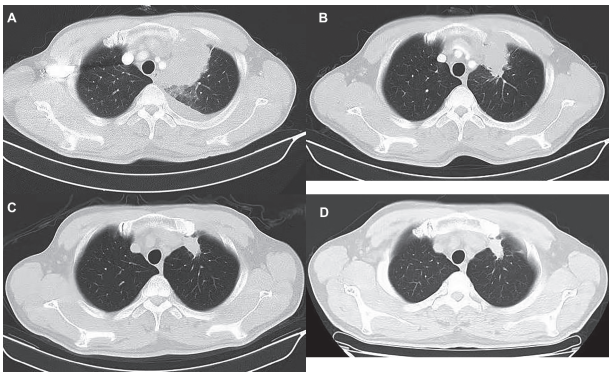

Fig. 1 Computed tomography findings
Fig. 1A: Primary lesion in the left upper lobe and pleural effusion at the initial presentation.
Fig. 1B: Partial response in the primary lesion and disappearance of left pleural effusion after 2 cycles of treatment.
Fig. 1C: After 22 cycles of treatment, the primary lesion reached the maximum depth of response.
Fig. 1D: After 32 cycles of treatment, continued control of the primary lesion was observed.

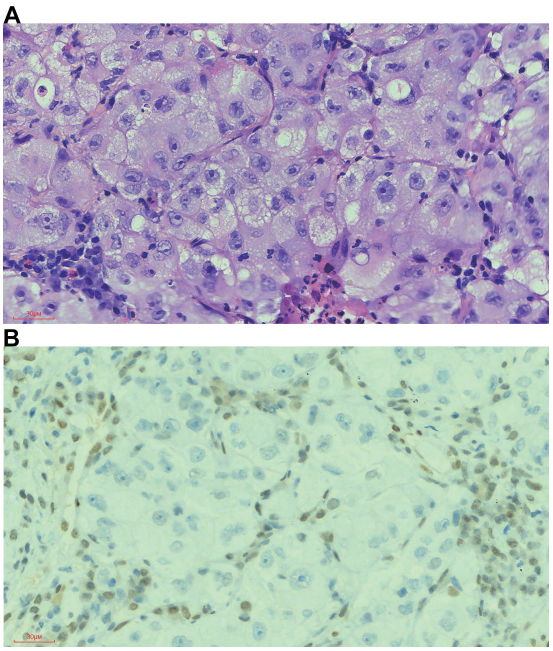

Fig. 2 Pathological and immunohistochemical features of SMARCA4-deficient left lung adenocarcinoma
Fig. 2A: Pathological examination of lung biopsy indicated adenocarcinoma.
Fig. 2B: Immunohistochemical staining showed loss of BRG1.

Owing to financial constraints and concerns regarding chemotherapy, the patient declined MET inhibitor-targeted therapy and chemotherapy. Instead, the patient received sintilimab (200 mg, day 1) and anlotinib (12 mg, day 1–14). Following two treatment cycles, a chest CT scan showed a notable reduction in the lesion in the left upper lung (Fig. 1B). During the 22nd treatment cycle, follow-up chest CT (Fig. 1C) demonstrated that the primary lesion had achieved its maximum depth of response. Subsequent monitoring of the 32nd treatment cycle via chest CT (Fig. 1D) indicated sustained control of the primary lesion. As of the current date, the patient has surpassed 2 years of progression-free survival. The patient exhibited favorable tolerance to combination therapy. During the first month, the patient presented with mild pruritus and a rash. After eight months, the patient developed hypertension, which was managed with irbesartan, and unstable angina pectoris for which coronary artery angioplasty was performed. After 16 months, the patient developed subclinical hypothyroidism, which was treated with levothyroxine.

Ethics approval and consent to participate

The study was conducted in accordance with the principles of the Declaration of Helsinki. This study was approved by Ethics Committee of Anhui Chest Hospital (KJ2024059). Written informed consent was obtained from the participant.

DISCUSSION

SMARCA4 is located on chromosome 19p13 and encodes BRG1, a transcription activator that serves as an essential ATP-dependent catalytic subunit of the chromatin-remodeling complex SWI/SNF.[3] Through its ATPase function, BRG1 facilitates the energy supply necessary for chromatin remodeling, thereby governing diverse cellular processes, such as DNA transcription, cell proliferation, differentiation, as well as the DAN damage repair.[4] Therefore, *SMARCA4* mutations have the potential to drive tumorigenesis and tumor progression. MET exon 14 skipping mutations result from splice site alterations (eg, point mutations or deletions), leading to the exclusion of the juxtamembrane domain containing the CBL E3 ubiquitin ligase binding site. This impairs MET protein degradation, causing constitutive activation of downstream oncogenic pathways (eg, RAS-MAPK and PI3K-AKT).[5]

Patients with SD-NSCLC are predominantly male smokers with an average age of approximately 66. Most patients present with advanced-stage disease, characterized by large primary tumors that often exhibit vascular and pleural invasion. Furthermore, compared to NSCLC patients lacking SMARCA4 deficiency, those with SMARCA4 alterations demonstrated a higher frequency of PD-L1 positivity and an increased tumor mutation burden,[6] consistent with the findings in this case study. *SMARCA4* mutations frequently co-occur with *TP53*, *KEAP1*, *STK11*, and *KRAS* mutations, while exhibiting mutual exclusivity with key driver genes in NSCLC, such as *EGFR*, *ALK*, *MET*, *ROS1*, and *RET*.[1,7] However, these findings were mainly observed in non-Asian populations. A retrospective analysis of 127 cases of SD-NSCLC conducted by Li et al revealed that SMARCA4-deficient NSCLC was concomitant with *EGFR* mutations, *ALK* fusions, and *MET* amplification.[8] This disparity in findings can be attributed to the diverse ethnic backgrounds of the studies. ERFR mutations and ALK fusions are more prevalent in Asian populations than in Western populations. Notably, although EGFR mutations and ALK fusions are common in Asians, there have been no documented instances of SD-NSCLC with *MET14* skipping mutations.

Compared with wild-type NSCLC, SD-NSCLC exhibited reduced overall survival.[7] Research indicates that the median overall survival for advanced SD-NSCLC is only 15.6 months.[9] Although a successful case report detailing the fourth-line treatment of SMARCA4-deficient

lung adenocarcinoma with nivolumab has been documented,[10] some retrospective studies have not demonstrated the survival benefit of immunotherapy in SD-NSCLC.[7-9] Therefore, further studies are required to identify effective treatment strategies for SD-NSCLC.

Currently, investigations on the efficacy of ICIs in conjunction with anti-angiogenic agents for SD-NSCLC are in the nascent phase; however, early findings have shown promise. A literature review suggested a synergistic relationship between anti-angiogenic and ICI therapies. Anti-angiogenesis interventions contribute to modulating the balance between anti-tumor and pro-tumor immune cells while also diminishing the expression of multiple immune checkpoints to impede negative immune signaling pathways. In contrast, ICI treatment has the potential to facilitate vascular normalization.[11] Anlotinib, a novel small-molecule multi-target tyrosine kinase inhibitor, and sintilimab, a PD-1 inhibitor, constitute a dual therapeutic approach that not only restrains tumor growth via inhibition of tumor angiogenesis, but also exerts a synergistic anti-tumor effect by stimulating the immune system to target tumor cells. Tumor cells from NSCLC patients with MET exon 14 skipping may exhibit abnormal activation of the MET signaling pathway, leading to enhanced tumor cell proliferation, survival, and invasion. Simultaneously, this mutation may affect the tumor immune microenvironment by reducing the expression of antigen-presenting molecules on the surface of tumor cells, reducing the recognition and killing of tumor cells by immune cells, and enabling tumor cells to escape immune surveillance. PD-L1 is expressed at high levels in NSCLC patients with MET 14 exon skipping mutations. Preliminary confirmation of the efficacy and safety of sintilimab combined with anlotinib as first-line treatment for advanced NSCLC was demonstrated in a phase IB clinical study.[12] The rapid remission experienced by the patient with this combination regimen was attributed to the collaborative action of PD-1 inhibitors and anti-angiogenic agents.

CONCLUSION

This case report presents the first documented occurrence of a SD-NSCLC with a MET14 skipping mutation. Following the patient's decision to decline MET inhibitor-targeted therapy and chemotherapy, treatment with sintilimab in combination with anlotinib as initial therapy resulted in remarkable efficacy. Concurrent administration of sintilimab and anlotinib showed promise as a potential therapeutic strategy for managing SD-NSCLC. However, given the constraints of single-case reports, larger-scale clinical research is warranted to substantiate the safety and effectiveness of this regimen in the treatment of SD-NSCLC.

DECLARATIONS

Authors' contributions

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

Conceiving and designing the study: Hongfei Zhao, Qingming Shi.

Collecting the data: Hongfei Zhao, Chi Zhang, Dongmei Chen, Wei Ye.

Analyzing and interpreting the data: Hongfei Zhao, Chi Zhang, Dongmei Chen, Wei Ye.

Writing the manuscript: Hongfei Zhao.

Providing critical revisions that are important for the intellectual content: Qingming Shi.

Approving the final version of the manuscript: All authors.

Conflicts of interest

All authors declare that they have no conflicts of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Acknowledgements

The patient and his family are to be thanked by all authors for granting permission for this case study to be published.

REFERENCES

1 Schoenfeld AJ, Bandlamudi C, Lavery JA, et al. The Genomic Landscape of SMARCA4 Alterations and Associations with Outcomes in Patients with Lung Cancer. *Clin Cancer Res*. 2020;26(21):5701–5708. doi:10.1158/1078-0432.Ccr-20-1825

2 Makker V, Aghajanian C, Cohn AL, et al. A Phase Ib/II Study of Lenvatinib and Pembrolizumab in Advanced Endometrial Carcinoma (Study 111/KEYNOTE-146): Long-Term Efficacy and Safety Update. *J Clin Oncol*. 2023;41(5):974–979. doi:10.1200/JCO.22.01021

3 Rodriguez-Nieto S, Sanchez-Cespedes M. BRG1 and LKB1: tales of two tumor suppressor genes on chromosome 19p and lung cancer. *Carcinogenesis*. 2009;30(4):547–554. doi:10.1093/carcin/bgp035

4 Mittal P, Roberts CWM. The SWI/SNF complex in cancer – biology, biomarkers and therapy. *Nat Rev Clin Oncol*. 2020;17(7):435–448. doi:10.1038/s41571-020-0357-3

5 Yu Y, Dong W, Shi Y, et al. A pooled analysis of clinical outcome in driver-gene negative non-small cell lung cancer patients with MET overexpression treated with gumarontinib. *Ther Adv Med Oncol*. 2024;16:17588359241264730. doi:10.1177/17588359241264730

6 Naito T, Udagawa H, Umemura S, et al. Non-small cell lung cancer with loss of expression of the SWI/SNF complex is associated with aggressive clinicopathological features, PD-L1-positive status, and high tumor mutation burden. *Lung Cancer*. 2019;138:35–42. doi:10.1016/j.lungcan.2019.10.009

7 Fernando TM, Piskol R, Bainer R, et al. Functional characterization of SMARCA4 variants identified by targeted exome-sequencing of 131,668 cancer patients. *Nat Commun*. 2020;11(1):5551. doi:10.1038/s41467-020-19402-8

8 Li SL, Wu CY, Zhang LP, et al. Clinicopathological features and prognosis of SMARCA4-deficient non-small cell lung carcinoma: an analysis of 127 cases. Article in Chinese. *Zhonghua Bing Li Xue Za Zhi*. 2023;52(7):665–670. doi:10.3760/cma.j.cn112151-20221107-00923

9 Alessi JV, Ricciuti B, Spurr LF, et al. SMARCA4 and Other SWItch/Sucrose NonFermentable Family Genomic Alterations in NSCLC: Clinicopathologic Characteristics and Outcomes to Immune Checkpoint Inhibition. *J Thorac Oncol*. 2021;16(7):1176–1187. doi:10.1016/j.jtho.2021.03.024

10 Naito T, Umemura S, Nakamura H, et al. Successful treatment with nivolumab for SMARCA4-deficient non-small cell lung carcinoma with a high tumor mutation burden: A case report. *Thorac Cancer*. 2019;10(5):1285–1288. doi:10.1111/1759-7714.13070

11 Yi M, Jiao D, Qin S, Chu Q, Wu K, Li A. Synergistic effect of immune checkpoint blockade and anti-angiogenesis in cancer treatment. *Mol Cancer*. 2019;18(1):60. doi:10.1186/s12943-019-0974-6

12 Chu T, Zhong R, Zhong H, et al. Phase 1b Study of Sintilimab Plus Anlotinib as First-line Therapy in Patients With Advanced NSCLC. *J Thorac Oncol*. 2021;16(4):643–652. doi:10.1016/j.jtho.2020.11.026