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CASE REPORT

Successful treatment with nivolumab for SMARCA4-deficient non-small cell lung carcinoma with a high tumor mutation burden: A case report

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Abstract

SMARCA4 is a subunit of the switch/sucrose non-fermentable (SWI/SNF) chromatin-remodeling complex. An effective treatment for SMARCA4-deficient non-small cell lung carcinoma (NSCLC) has not yet been established. Correlations between a response to immune checkpoint inhibitors and the SWI/SNF complex have been suggested, but little is known about the efficacy of immune checkpoint inhibitors against SMARCA4-deficient NSCLC. A 43-year-old man underwent left upper lobe lung resection and was diagnosed with SMARCA4-deficient lung adenocarcinoma. Two months after surgery, multiple lung metastases appeared. Immunohistochemical analysis showed no PD-L1 expression. Whole-exon sequencing revealed a relatively high tumor mutation burden at 396. After the failure of three standard chemotherapy regimens, the patient was treated with nivolumab as fourth-line treatment. An obvious reduction in the lung metastases was obtained for more than 14 months. We report the first case of SMARCA4-deficient NSCLC with a high tumor mutation burden successfully treated with nivolumab. Anti-PD-1 antibodies might be a promising treatment strategy for patients with SMARCA4-deficient NSCLC.

Introduction

SMARCA4 is a subunit of the switch/sucrose non-fermentable (SWI/SNF) complex that plays important roles in the process of chromatin remodeling and thus in the regulation of vital cellular processes and functions such as gene expression, proliferation, and differentiation.[1] SMARCA4-inactivation is critical for cancer development and progression.[2]

The loss of SMARCA4 immunoreactivity occurs in up to 10% of non-small cell lung carcinoma (NSCLC) cases.[3] SMARCA4-deficient NSCLC is both aggressive and refractory.[4] Although the development of therapies for SMARCA4-deficient NSCLC is a topic of ongoing investigation, an effective treatment for SMARCA4-deficient NSCLC has not yet been established.[5–8]

Nivolumab is a PD-1 antibody approved for the treatment of NSCLC. Some reports have demonstrated that PD-L1 expression, DNA mismatch-repair (MMR) deficiency, and tumor mutational burden (TMB) are predictive biomarkers of a response to PD-1 antibodies.[9–11] Although correlations between a response to immune checkpoint inhibitors and the loss of the SWI/SNF complex have been reported, little is known about the efficacy of immune checkpoint inhibitors for SMARCA4-deficient NSCLC.[12–14] Herein, we report the first case of SMARCA4-deficient NSCLC with a high TMB successfully treated with nivolumab.

Case report

A 43-year-old man was introduced to our hospital because of persistent left chest pain. He had a history of smoking

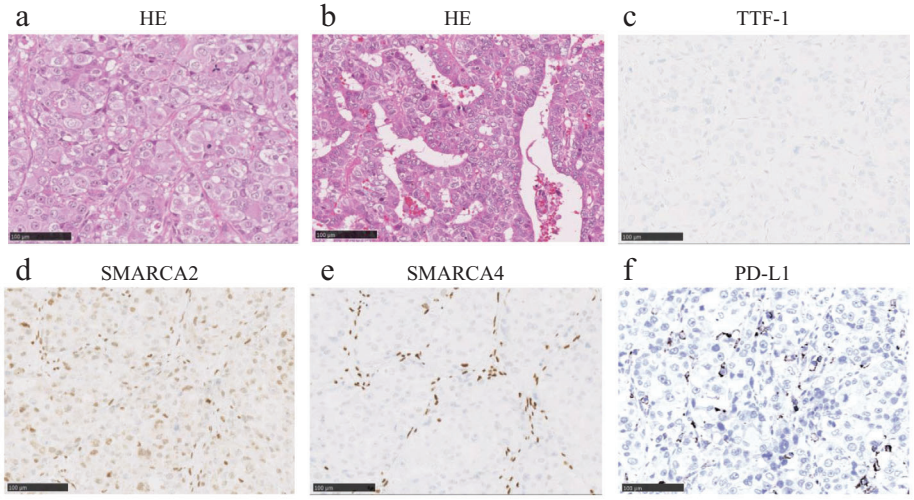

Figure 1 (**a–f**) Histopathological and immunohistochemical findings of the primary lung tumor (x40). (**a,b**) Hematoxylin and eosin (H&E) staining shows a poorly differentiated carcinoma and a partly glandular structure. (**c**) TTF-1 (SP141), (**d**) SMARCA2 (HPA029981), (**e**) SMARCA4 (EPNCIR111A), and (**f**) PD-L1 (28-8).

(Brinkman index: 460) but did not have a family history of cancer. A chest computed tomography (CT) scan revealed a mass in the left upper lobe. The patient subsequently underwent left upper lobe lung resection.

The resected tumor was mainly composed of a poorly differentiated carcinoma and partly composed of a glandular structure (Fig 1). The immunohistochemical staining results were as follows: TTF-1 (SP141), negative; SMARCA2 (HPA029981), partial loss; SMARCA4 (EPNCIR111A), loss; and PD-L1 (28-8), 0%. He was finally diagnosed with SMARCA4-deficient poorly differentiated lung adenocarcinoma. The pathological stage was T4N0M0 stage IIIA. Next-generation sequencing using the Oncomine Cancer Research Panel revealed the absence of driver alterations for lung cancer (Table S1). Whole-exon sequencing showed a relatively high TMB at 396 mutations.

Two months after surgery, multiple lung metastases rapidly developed, and the patient was diagnosed with recurrence. He was treated with four cycles of carboplatin (AUC 5–6, day 1), paclitaxel (180-200 mg/m^2, day 1), and bevacizumab (15 mg/kg, day 1; best overall response: stable disease), followed by four cycles of docetaxel (50-60 mg/m^2, day 1) and ramucirumab (10 mg/kg, day 1; best overall response: stable disease). After two cycles of pemetrexed (500 mg/m^2, day 1; best overall response: progressive disease), nivolumab (3 mg/kg, day 1, every 2 weeks) was administered as a fourth-line treatment.

After four does of nivolumab, obvious reduction in the lung metastases was observed (Fig 2). Chest CT images obtained after 22 doses of nivolumab showed continuous lesion shrinkage (best overall response: partial response). Disease control has been maintained for more than 14 months since the start of nivolumab treatment.

The patient provided informed consent for the publication of all clinical details and images.

Discussion

This is the first report of a case of successful treatment of a SMARCA4-deficient NSCLC using nivolumab.

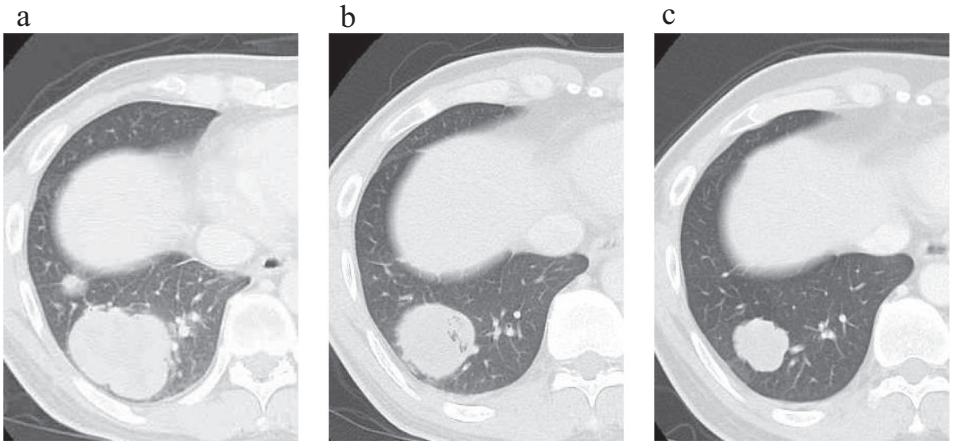

Figure 2 Chest computed tomography images: (**a**) Baseline before nivolumab treatment; (**b**) partial response after four doses of nivolumab; and (**c**) after 22 doses of nivolumab.

SMARCA4-deficient NSCLC is now considered a distinct subtype with a heterogeneous spectrum because of its morphological diversity, lack of a lepidic growth pattern, and TTF-1-negative phenotype.[15] In addition, *SMARCA4* mutations have attracted interest as candidate driver genes because of their mutual exclusivity with other driver alterations.[16] However, treatment strategies targeting SMARCA4-deficient NSCLC have not yet been developed.

Patients with SMARCA4-deficient NSCLC have a statistically significantly poor survival outcome.[17] Thus, this report is important, demonstrating that an anti-PD-1 antibody could potentially be effective against SMARCA-4 deficient NSCLC.

Metastatic renal cell carcinoma harboring inactivating mutations in *PBRM1*, which encodes a subunit of the SWI/SNF complex, is reportedly likely to respond to nivolumab treatment.[12] A study demonstrated that melanoma tumor cells in which a specific SWI/SNF complex had been experimentally inactivated were sensitive to T cell-mediated killing. The tumor cells were responsive to interferon-γ, leading to the increased secretion of cytokines that promote antitumor immunity.[14] Furthermore, whole-exon sequencing analysis of multiple cancer types indicated an association between a response to immunotherapy and epigenetic regulators in the SWI/SNF complex.[13]

In the CheckMate-026 study, a phase III trial that compared the efficacy of nivolumab to platinum-based chemotherapy in patients with stage IV or recurrent NSCLC, exploratory analysis showed the effects of the TMB on the treatment efficacy of nivolumab.[9] Among patients with a high TMB (≥ 243 mutations), the response rate and progression-free survival were superior in the nivolumab group than in the chemotherapy group. SMARCA4 is reportedly required for MMR.[18] In addition, MMR deficiency is associated with a high TMB.[19] In the present case, we believe that SMARCA4 deficiency caused a decrease in MMR function, which in turn induced a high TMB. Although a high TMB is associated with a good response to nivolumab, the SMARCA4 deficiency might have been a key component in the high TMB in this case.

We report the first case of SMARCA4-deficient NSCLC with a high TMB successfully treated with nivolumab. Anti-PD-1 antibodies might be promising treatment for patients with SMARCA4-deficient NSCLC. Given the limitations of single case reports, however, further validation of the efficacy of anti-PD-1 antibodies in a larger patient cohort with SMARCA4-deficient NSCLC is required.

Disclosure

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Supporting Information

Additional Supporting Informationmay be found in the online version of this article at the publisher's website:

Supplemental Table 1. The result of next-generation sequencing using the Oncomine Cancer Research Panel.

