Letter to the Editor

SMARCA4-deficient non-small cell lung cancer: a case description and literature analysis

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Introduction

SMARCA4-deficient non-small cell lung cancer (*SMARCA4*-dNSCLC) is a rare subtype of epithelial cancer characterized by high malignancy. Compared to other types of NSCLC, *SMARCA4*-dNSCLC is highly aggressive, prone to early metastasis, and has a poor prognosis (1). There is limited information available regarding the imaging characteristics of *SMARCA4*-dNSCLC. Moreover, patients with *SMARCA4*-dNSCLC respond poorly to conventional therapeutic approaches, further complicating treatment (2,3). Here, we present a case of a 52-year-old male with *SMARCA4*-dNSCLC and a review of the relevant literature.

Case presentation

A man in his early 50s who had never smoked arrived at the Emergency Department of Zhejiang Hospital with a 6-day fever (temperature >39 ℃), cough, and fatigue. On examination of the patient's chest, a dull percussive sound was noted along with diminished breath sounds in the right lung. The patient underwent contrast-enhanced chest computed tomography (CT), which showed a 7.0×5.8 cm unevenly enhanced, irregular mass in the right lower lobe. The lesion showed burr and lobulation signs and was pulling the adjacent pleura. The right lower lobe bronchus showed obstruction, resulting in obstructive pneumonia and atelectasis in the distal bronchus. Smooth-edged nodules of uniform internal density and of various sizes were detected on both sides of the lung. Enlarged lymph nodes were observed in the right supraclavicular and upper mediastinal regions, with the largest measuring approximately 5.5×3.4 cm in size. Osteogenic lesions were observed in the sternal manubrium and several sternocostal joints (*Figure 1A-1C*). A ^{99m}technetium methylene diphosphonate bone scan suggested multiple bone metastases (*Figure 1D*). Bronchoscopic examination of the patient revealed the presence of numerous nodules in the lumens of the right middle and lower bronchi, accompanied by narrowing or obstruction of the luminal passages, thickening of the

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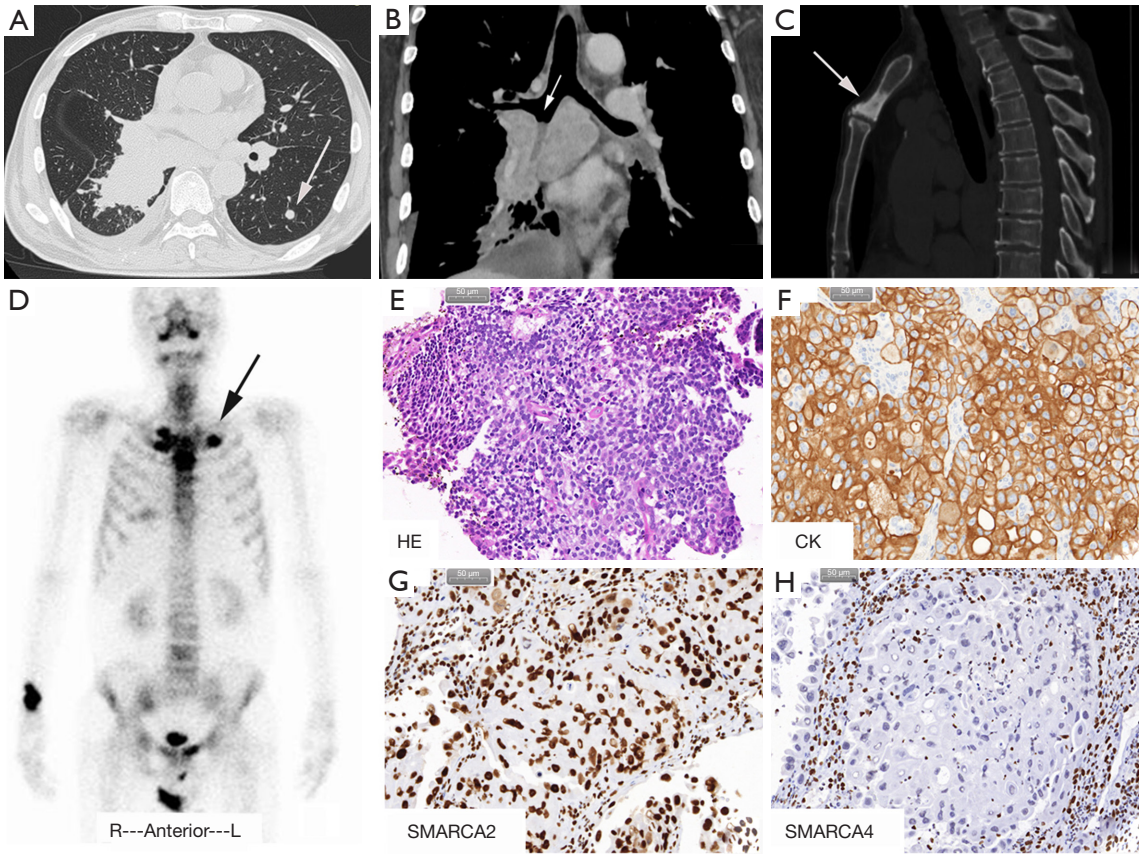

Figure 1 The imaging manifestations and pathological findings of a 52-year-old male with *SMARCA4*-dNSCLC. (A) Left lower lobe metastasis (arrow) and right lower lobe obstructive pneumonia with atelectasis (pulmonary window). (B) Obstruction of the right lower lobe bronchus (arrow) and mediastinal lymph node enlargement (coronal lung window in the venous phase). (C) Osteogenic bone metastases of the sternal styloid (sagittal bone window, arrow). (D) ^{99m}technetium methylene diphosphonate bone scan showing metastasis to the left first rib (arrow). (E) Microscopic appearance of the tumor in the right lower bronchial lumen, with HE staining showing diffuse sheets of small blue round tumor cells (×200). (F) Immunohistochemistry showing positivity for CK (×200). (G) Immunohistochemical staining showing positive expression of *SMARCA2* (×200). (H) Immunochemical staining of *SMARCA4* revealed the tumor cells were negative for *SMARCA4* expression (×200). HE, hematoxylin and eosin; CK, cytokeratin; *SMARCA4*-dNSCLC, *SMARCA4*-deficient non-small cell lung cancer.

bronchial walls, and coarse and bleeding mucosa. Biopsy results were highly suggestive of NSCLC. The results of the immunohistochemical staining were as follows: *SMARCA4* (–), Ki-67 (+50%), cytokeratin (pan) (+), thyroid transcription factor 1 (TTF-1) (–), napsin A (–), P40 (–), P63 (–), synuclein (SYN) (–), chromogranin A (CgA) (–), and CD56 (–). Meanwhile, the results for right supraclavicular lymph node aspiration biopsy pathological immunohistochemistry were as follows: *SMARCA4* (–), Ki-67 (+40%), cytokeratin 7 (+), CD34 (vascular +), SALL4 (–), P40 (–), TTF-1 (–), and *SMARCA2* (+) (*Figure 1E-1H*). The patient was finally diagnosed with *SMARCA4*-dNSCLC.

The patient's pretreatment assessment revealed moderate renal dysfunction (glomerular filtration rate below 50 mL/min), and his Eastern Cooperative Oncology Group performance status (ECOG PS) was 2 (4). The patient was considered to be at elevated risks of side effects if treated with more intensive chemotherapy. After consideration of the patient's specific situation and communication with the patient and his family, we adopted the following treatment plan.

The patient received the combination of anlotinib (8 mg, D1–D14, Q3W), nab-paclitaxel (260 mg/m^2, Q3W), and tislelizumab (200 mg, Q3W) beginning on July 19, 2022. The patient's treatment process timeline is shown in *Table 1*. This case report adheres to the CARE (Case Report)

Table 1 A detailed record of the treatment for the patient with SMARCA4-dNSCLC

Timepoint	Event description	Tumor size (cm)	Outcome criteria	ECOG performance status	Imaging evaluation
July 2, 2022: pretreatment (baseline)	Patients was diagnosed with stage IVB *SMARCA4*-dNSCLC	7.0 (*Figure 2A*)	RECIST 1.1	2	N/A
July–August 2022	Treatment was initiated with a combination regimen of anlotinib, nab-paclitaxel, and tislelizumab	N/A	RECIST 1.1	2	N/A
September 1, 2022 (2 cycles posttreatment)	Patients completed the second round of treatment, with assessment showing partial reduction in tumor size (*Figure 2A,2B*)	4.6 (*Figure 2B*)	RECIST 1.1	2	Partial response
September–November 2022	Treatment continued for three cycles	N/A	RECIST 1.1	2	N/A
November 20, 2022 (5 cycles posttreatment)	Assessment showed significant tumor shrinkage, with no significant side effects (*Figure 2C*)	2.8 (*Figure 2C*)	RECIST 1.1	2	Partial response
December 22, 2022	The patient complained of generalized bone pain, and assessment revealed tumor growth (*Figure 2D*)	6.2 (*Figure 2D*)	RECIST 1.1	3	Disease progression
January 2023	Following infection with COVID-19, the patient's condition deteriorated rapidly. He refused further treatment and unfortunately died	N/A	RECIST 1.1	5	N/A

Timepoints: specific times when assessments were conducted. Tumor size: the largest diameter of the tumor measured in centimeters. RECIST 1.1: the standard used to evaluate the tumor response (5). ECOG performance status: a scoring system used to assess the ability of cancer patients to perform activities of daily living. The score ranges from 0 to 5, with 0 indicating no activity limitations at all and 5 indicating death (6). Imaging evaluation: evaluation of the tumor response based on imaging data (computed tomography). *SMARCA4*-dNSCLC, SMARCA4-deficient non-small cell lung cancer; ECOG, Eastern Cooperative Oncology Group; RECIST, Response Evaluation Criteria in Solid Tumors; N/A, not applicable; COVID-19, coronavirus disease 2019.

guidelines, and patient details have been de-identified (7). All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this article and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

SMARCA4, also known as *BRG1*, is located on the short arm of chromosome 19 (8). It is an adenosine triphosphate (ATP)-dependent helicase that serves as a key element of the switch/sucrose nonfermentable (SWI/SNF) complex, using ATP hydrolysis to modulate the structure of chromatin (9). Mutations of *SMARCA4* have been strongly linked to cancer development and can be categorized into two types: class 1, including truncating mutations, fusions, and homozygous deletions; and class 2, including missense mutations (10,11). Loss of *SMARCA4* expression occurs in 4% of patients with NSCLC and is significantly associated with class 1 alterations.

SMARCA4 is a key gene in the development of cancer (9). The loss of *SMARCA4* causes the club cell secretory protein-positive (CCSP+) cells in the lung to become susceptible to cancerous changes and rapid tumor progression. This results in the development of highly aggressive, poorly differentiated tumors and an increased likelihood of metastasis (10). Recent research has shed light on the effect of *SMARCA4* mutations on different types of immune cells. It has been reported that *SMARCA4* deficiency impairs regulatory T-cell activation and increases background immune cell infiltration (12). Patients with *SMARCA4*-deficient lung cancer have a high infiltration of FOXP3+ cells and CD66b+ neutrophils, a feature of the immune milieu that may be associated with the aggressiveness and prognosis of lung cancer (13).

SMARCA4-dNSCLC was first described in the literature by Wong *et al.* in 2000 (14). Agaimy *et al.* later proposed that *SMARCA4*-dNSCLC is a distinct subtype of NSCLC with unique morphological, immunophenotypic, and

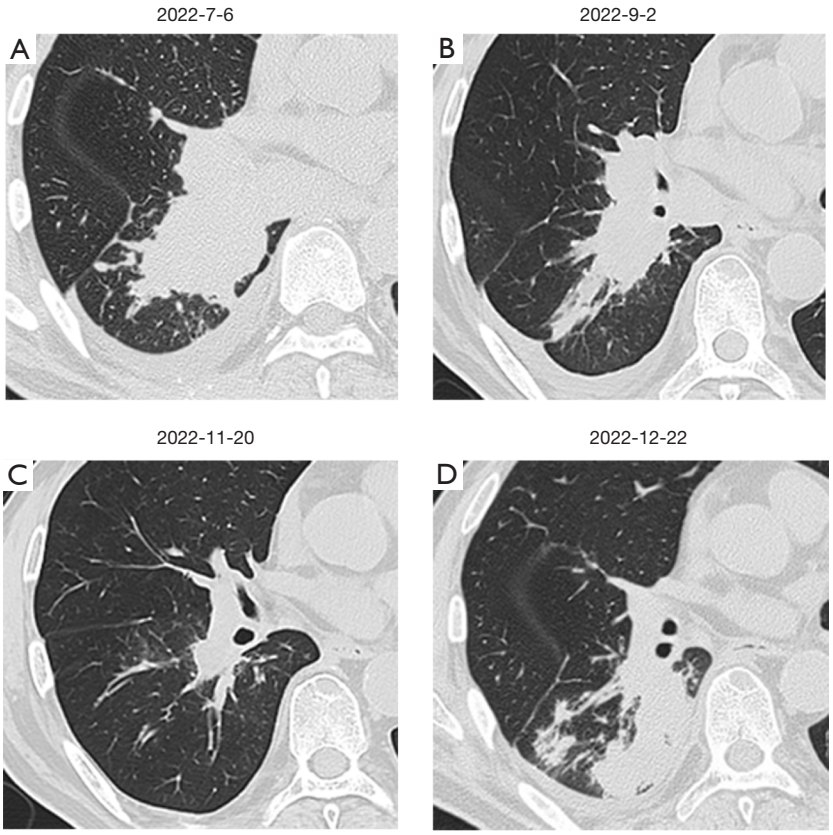

Figure 2 Chest computed tomography images. (A) Computed tomography images at baseline before treatment, (B) after two cycles of therapy, (C) after five cycles of therapy showing partial response, and (D) 1 month after showing progressive disease.

molecular genetic characteristics (15). The 2021 WHO Classification of Thoracic Tumors (fifth edition) lists *SMARCA4*-dNSCLC as an entity independent of thoracic tumors (16).

Several case reports and studies have reported the clinicopathologic features of *SMARCA4*-dNSCLC (1,3,14). *SMARCA4*-dNSCLC is a heterogenous group in terms of cytomorphology, ranging from a relatively well-differentiated adenocarcinoma pattern or squamous differentiation to an undifferentiated morphology (1,3,15).

There have been few reports describing the imaging features of *SMARCA4*-dNSCLC. After a comprehensive search of the PubMed, Web of Science, and Science Direct databases, we only retrieved two related case reports. Wumener and colleagues reported a case of a 45-year-old man diagnosed with *SMARCA4*-dNSCLC. Imaging with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)/CT revealed a highly FDG-absorbent lesion in the upper left lobe of the lung with a notably elevated maximum standardized uptake value (SUVmax) of 22.4 (17). Koizumi *et al.* reported two cases of *SMARCA4*-dNSCLC, with one showing a nodule in the lower lobe of the right lung and the other showing a large mass in the upper lobe of the left lung (18). All three patients had a history of smoking. In two of these cases, the tumors were located in the upper lobe of the left lung, while in the other case, the tumor grew near the hilum in the lower lobe of the right lung. However, our case never smoked. He had a right lower paraspinal mass with right lower obstructive pneumonia and multiple metastases. The peritumor tissue invasion and early multiple metastases in our case were similar to the features reported in the literature, which strengthens the view that *SMARCA4*-dNSCLC is aggressive and has a poor prognosis.

SMARCA4-dNSCLCs typically manifests in the fourth or fifth decade of life, with a higher prevalence among males and a notable correlation with a history of smoking. The majority of patients with *SMARCA4*-dNSCLC have stage

IV disease, with aggressive tumors, rapid tumor growth, elevated levels of proliferation markers such as Ki-67, and a high incidence of adrenal and lymph node metastases (1,19).

At present, there is no recommended therapy for treating *SMARCA4*-dNSCLC, as this subtype lacks targetable alterations such as *EGFR*, *ALK*, and *ROS1*. In the preclinical models of *SMARCA4*-deficient tumors, inhibitors of *SMARCA2*, *topoisomerase II*, *EZH2*, *ATR*, *CDK4/6*, and *SMARCA2* have shown antitumor activity (9). *SMARCA2* has been recognized as a crucial target for synthetic lethality in tumors lacking *SMARCA4* (20). The investigational drug PRT3789 is currently in a phase I clinical trial for the treatment of advanced or metastatic solid tumors harboring the *SMARCA4* mutation. In addition, chemotherapy or immunotherapy is often used in patients with *SMARCA4*-dNSCLC (9,19). Bell *et al.* reported that the combination of cisplatin and vinorelbine may be an effective treatment approach for resectable *SMARCA4*-dNSCLC in stages IB to II (21). However, a small-sample retrospective study showed that *SMARCA4*-dNSCLC responds poorly to platinum doublet chemotherapy or chemotherapy plus immunotherapy (22).

The therapeutic potential of immune checkpoint inhibitors (ICIs) in *SMARCA4*-deficient thoracic tumors has been supported by numerous studies (23). Naito *et al.* reported a male patient with *SMARCA4*-dNSCLC who achieved a partial response after receiving nivolumab as a fourth-line treatment. The patient's disease remained stable for over 14 months (24). In an immunotherapy trial by Shinno *et al.*, the response rate of immunotherapy for *SMARCA4*-deficient thoracic tumors was 42%, and the progression-free survival time for those treated with ICIs was longer with the first-line treatment than with the second-line or later treatment (23).

In addition to immune monotherapy, the combination of ICIs with agents that inhibit angiogenesis has shown some success. ICIs and antiangiogenic agents can inhibit tumor development and progression by modulating the interaction between angiogenesis and the programmed cell death protein 1/programmed death-ligand 1 (PD-1/PD-L1) pathway in the tumor microenvironment (25). Carboplatin-paclitaxel in combination with bevacizumab plus atezolizumab is considered the standard first-line treatment for patients with metastatic nonsquamous NSCLC (26). Kawachi *et al.* reported that the concurrent use of atezolizumab in an initial regimen of bevacizumab, paclitaxel, and carboplatin (ABCP) resulted in sustained efficacy in patients with thoracic sarcoma who lacked *SMARCA4* (27).

Our patient's renal insufficiency and high EOCG score suggested that administration of platinum-based drugs would involve a high degree of risk. Accordingly, we treated the patient with nab-paclitaxel combined with tislelizumab plus anlotinib (28,29). Anlotinib has been demonstrated to enhance the tumor immune microenvironment by decreasing PD-L1 expression on vascular endothelial cells, which impedes tumor proliferation. This antitumor effect could also be enhanced with the help of ICIs (30). Nab-paclitaxel was found to be both tolerable and beneficial for patients with advanced NSCLC who also had mild-to-moderate renal dysfunction (31,32). Chemotherapy combined with antiangiogenic and anti-PD-L1 therapy was reported to improve patient outcomes by increasing $CD8^+$ T-cell infiltration and activation, altering the tumor microenvironment, promoting sustained vascular normalization, and establishing a more immune-supportive tumor microenvironment (33). To our knowledge, our patient is the first known case of *SMARCA4*-dNSCLC to be treated with this combined therapy. Five cycles of treatment was found to yield significant short-term efficacy. However, our patient showed progressive disease at the reassessment 1 month later.

SMARCA4-dNSCLC is a relatively newly discovered entity associated with rapid proliferation, high malignancy, strong invasive ability, and short overall survival. Most *SMARCA4*-dNSCLCs manifest as primary lung masses with nonspecific radiological features. To the best of our knowledge, our case is the third to be reported with specific imaging features of *SMARCA4*-dNSCLC, and our patient is the first known case of *SMARCA4*-dNSCLC to be treated with anlotinib, nab-paclitaxel, and tislelizumab. This regimen may be a promising treatment option for patients with *SMARCA4*-dNSCLC and renal impairment. However, as this is a single case, further research is needed. There may be significant differences in efficacy and survival impact between patients due to factors such as age, gender, genetic background, tumor stage, and treatment history. More high-quality randomized controlled trials are required to strengthen the evidence for the efficacy and safety of this therapy. Additional prospective multicenter studies with large sample sizes are warranted to better characterize the imaging features of *SMARCA4*-dNSCLC. Accurately identifying *SMARCA4*-dNSCLC and providing more precise and effective treatments to enhance patients' quality of life and survival rate remains an urgent challenge in clinical practice.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1813/coif). The 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 this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this article and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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