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CASE REPORT

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Concurrent SMARCA4-deficient and poorly differentiated adenocarcinomas in separate lung lobes: a case report and literature review

Lu Wang[1†], Yeqin Wu[1†], Liqian Hu[1] and Gangping Wang[1*]

Abstract

Background SMARCA4 and *SMARCA2*, mutually exclusive catalytic ATPase subunits of human mammalian Switch/Sucrose-Nonfermentable chromatin remodeling enzymes, function as tumor suppressor genes. SMARCA4-deficient adenocarcinoma (SMARCA4-dADC) is a relatively rare subtype of TTF1/P40-negative non-small cell lung cancer. The concurrent presentation of SMARCA4-dADC and poorly differentiated adenocarcinoma with SMARCA2 (also known as BRM) loss in separate lobes of the same patient is even less common. This report describes such a case involving the simultaneous occurrence of these two tumor types in distinct locations within the lungs.

Case presentation A 68-year-old male presented with a three-week history of vague pain in the right side of the chest, with no obvious trigger. Imaging revealed solid masses in the upper and lower lobes of the right lung with bilateral enlarged cervical lymph nodes. So, both of these masses underwent wedge resection. Histopathological examination confirmed that the lower lobe tumor was SMARCA4-dADC, while the upper lobe tumor was diagnosed as poorly differentiated adenocarcinoma. Although histologically similar, both exhibiting predominantly solid sheets and complex glandular structures, the two tumors displayed distinct immunohistochemical and molecular profiles. The lower lobe mass showed complete loss of BRG1 protein expression and partial loss of BRM. Immunohistochemical analysis revealed negative expression of TTF1, Napsin A, SALL4, CD34, and SOX2, and positive expression of CK7, pan-Cytokeratin (CK-pan), and HepPar-1. Molecular analysis identified mutations in *SMARCA4*, *KRAS*, and *STK11*. Conversely, the upper lobe mass retained BRG1 expression but showed complete loss of BRM protein expression, and negative expression of SALL4, CD34, and HepPar-1, positive expression of CK7, CK-pan, TTF1, Napsin A, and SOX2. A *KRAS* mutation was also detected in this tumor.

Conclusion The simultaneous occurrence of SMARCA4-dADC and conventional adenocarcinoma in different locations within the same patient is exceedingly rare. However, the distinct immunophenotypic and molecular characteristics of SMARCA4-dADC differentiate it as a unique entity from conventional adenocarcinoma. We recommend including SMARCA4 in the marker panel used to evaluate TTF1-negative adenocarcinomas of potential or uncertain pulmonary origin. This report underscores the diagnostic challenge of concurrent SMARCA4-dADC

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and poorly differentiated adenocarcinoma, proposing a standardized immunohistochemical workflow to guide therapeutic decisions.

Keywords Non-small cell lung cancers, SMARCA4, Brahma-related gene 1 (BRG1) protein, SMARCA2

Background

SMARCA4 (also known as BRG1), one of two core catalytic ATPase subunits of the human mammalian Switch/Sucrose-Nonfermentable (mSWI/SNF) chromatin-remodeling enzymes, is altered in approximately 5–7% of all human malignancies [1]. SMARCA4-deficient tumors have been described in various aggressive carcinomas and sarcomas, often exhibiting rapid progression and a poor prognosis [2–5]. Within the thoracic and pulmonary regions, SMARCA4 is implicated in the pathogenesis of two distinct tumor subtypes: SMARCA4-deficient undifferentiated tumors (SMARCA4-UT) with a phenotype resembling malignant rhabdoid tumors and bona fide carcinomas (SMARCA4-deficient non-small cell lung cancers [NSCLCs]) [6]. The 2021 World Health Organization (WHO) Classification of SMARCA4-UT as a distinct entity of rare malignancies characterized by an undifferentiated or rhabdomyolysis-like phenotype and SMARCA4 deficiency, often exhibiting an aggressive clinical course [4]. SMARCA4-deficient NSCLC (SMARCA4-dNSCLC), a relatively uncommon subtype representing approximately 10% of NSCLCs, is associated with a worse prognosis compared to SMARCA4-intact NSCLC [7]. SMARCA4-dNSCLC can be distinguished from thoracic SMARCA4-UT by features such as cellular cohesion, glandular architecture, and positive expression of epithelial markers, including epithelial membrane antigen (EMA) and pan-cytokeratin (CK-pan) [4]. SMARCA2 (also known as BRM) is the other core catalytic ATPase subunit of the human SWI/SNF chromatin remodeling enzymes. Loss of BRM protein is also associated with a poor prognosis [8, 9]. This report describes a case of the simultaneous occurrence of these two tumor types in different locations within the lungs and examines their clinicopathological characteristics and genetic-molecular alterations.

Case presentation

Clinical features

A 68-year-old man presented with right-sided chest pain of insidious onset three weeks prior (September 22, 2023). The patient reported a 40-year history of tobacco use, consuming approximately 20–40 cigarettes daily. Computed tomography (CT) imaging revealed two solid nodules in the upper and lower lobes of the right lung. A clustered high-density shadow measuring 16 × 13 mm, exhibiting the adjacent bronchial stump sign, was identified in the dorsal segment of the right lower lobe (Fig. 1a, b). A second solid nodule, measuring 31 × 26 mm and characterized by peripheral spiculation (burrs) and adjacent pleural thickening, was observed in the posterior segment of the right upper lobe (Fig. 1c, d). The patient subsequently underwent segmental resection of the right upper and lower lobes via video-assisted thoracoscopic surgery (VATS) on October 12, 2023.

Pathological features

Macroscopically, the gross appearance of the masses in both the lower and upper lobes of the right lung was similar. The tumors exhibited a white-gray coloration, soft consistency, and extensive necrosis. Located in the peripheral lung parenchyma without visceral pleural involvement, they displayed indistinct margins and infiltrative growth. Microscopically, both tumors demonstrated a comparable histological pattern characteristic of a high-grade malignant neoplasm with poorly defined tumor borders and infiltrative growth. Both the lower and upper lobe tumors were predominantly composed of solid adenocarcinoma (60% and 50% of the tumors, respectively), complex acinar carcinoma (30% and 40% of the tumors, respectively), and a minor component of micropapillary carcinoma (10% and 10% of the tumors, respectively) (Fig. 2a, d). The predominant features included extensive necrosis and diffuse sheets of variably discohesive, large, round to epithelioid cells with vesicular chromatin and prominent nucleoli (Fig. 2b, e). The nuclei were relatively monotonous, with occasional cells displaying mild to moderate pleomorphism. Rhabdoid cells were present in focal areas. Numerous mitoses were observed (Fig. 2c, f).

Immunohistochemical staining was performed using a Leica Bond III autostainer, with signal visualization achieved using diaminobenzidine (DAB) substrate, resulting in yellow staining of the target protein. Antibody details are provided in Supplementary Table S1 and the key differences of immunohistochemistry (IHC) findings shown in Table 1. The SMARCA4-dADC in the right lower lobe exhibited complete loss of BRG1 protein expression and partial loss of BRM, along with negative expression of TTF1, Napsin A, SALL4, CD34, and SOX2. Conversely, it showed positive expression of CK7 and CK-pan, and focal but strong positive expression of HepPar-1 (Fig. 3). The conventional high-grade adenocarcinoma in the right upper lobe demonstrated retained BRG1 expression, complete loss of BRM protein expression, and negative expression of SALL4, CD34, and HepPar-1. It also showed positive expression of CK7, CK-pan, TTF1, Napsin A, and SOX2 (Fig. 3). Both tumors

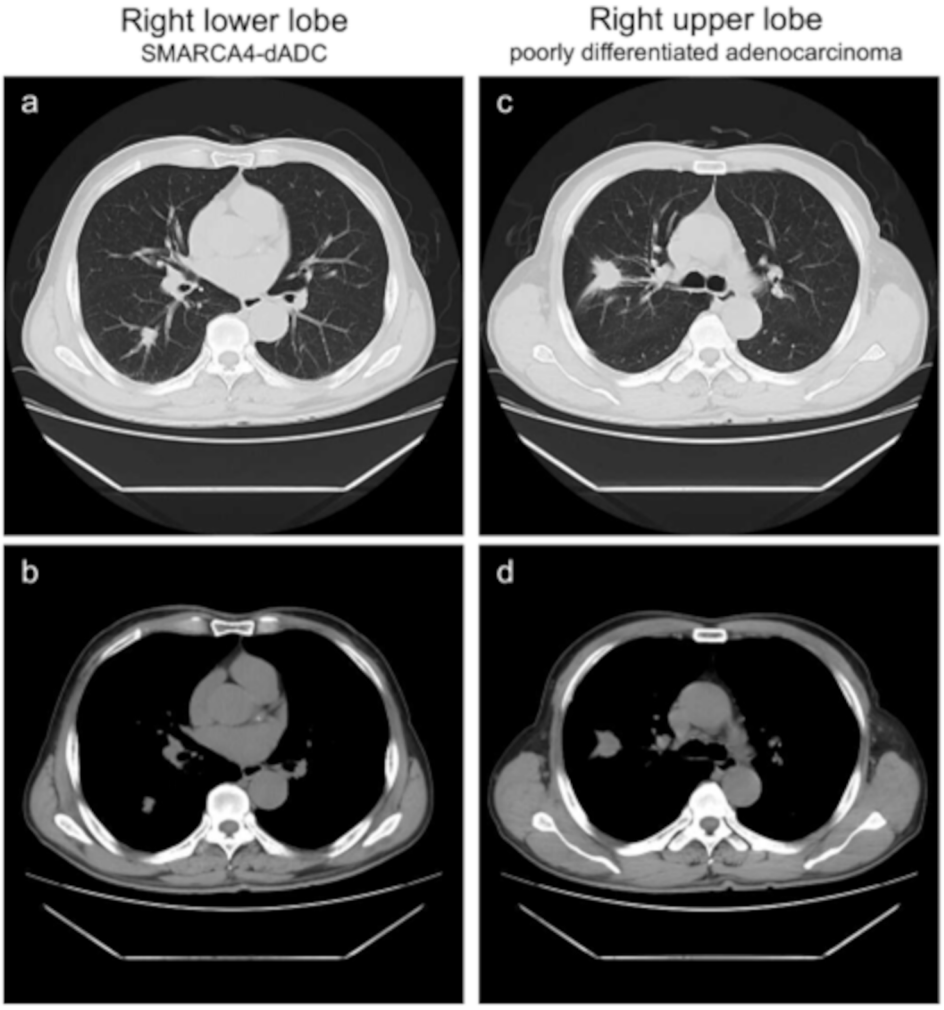

Fig. 1 Chest CT images of the patient. (**a**) CT images of the lung window with a lung mass in the right lower lobe. (**b**) CT images of the mediastinum window with a lung mass in the right lower lobe. (**c**) CT images of the lung window with a lung mass in the right upper lobe. (**d**) CT images of the mediastinum window with a lung mass in the right upper lobe

retained SMARCB1 (INI1) expression, and neither tumor expressed P40 (Fig. S1). The Ki-67 proliferation index was approximately 60% in both the SMARCA4-dADC in the lower lobe and the poorly differentiated adenocarcinoma in the upper lobe (Fig. S1).

PD-L1 expression was evaluated on the Leica Bond-Max platform using the E1L3N clone antibody. The tumor proportion score, defined as the percentage of tumor cells exhibiting membranous PD-L1 staining at any intensity, was assessed. A PD-L1-positive result was defined as a tumor proportion score of 1% or greater. Both tumors in the right lung were PD-L1 negative (Fig. S1).

Molecular analysis was performed using multiplex Polymerase Chain Reaction (PCR)-based analysis and next-generation sequencing (NGS). Multiplex PCR-based analysis was conducted using the AmoyDx Pan Lung Cancer PCR Panel (AmoyDx Biology, Shanghai, China). NGS was performed by AmoyDx Medical Laboratory (AmoyDx Biology, Shanghai, China) using high-throughput sequencing technology based on the Illumina platform (Illumina NovaSeq 6000/NextSeq CN500 instruments) and a hybrid capture method. The key differences of molecular findings shown in Table 1. The lower lobe tumor of the right lung exhibited a *KRAS* G12D mutation by PCR (Fig. 4a). NGS identified six gene mutations, three of which were of clinical significance (associated with targeted therapy): *KRAS* G12D, *STK11*, and a nonsense mutation in *SMARCA4* (Fig. 4c). The remaining three mutations were of unknown clinical significance: *BRCA1*, *POLE*, and *STK11* (Fig. 4c). The upper lobe tumor of the right lung exhibited a *KRAS* G12C mutation by PCR (Fig. 4b). NGS detected four gene mutations in this tumor, one of which was clinically significant (related to targeted therapy): *KRAS* G12C (Fig. 4d). The remaining three mutations of unknown

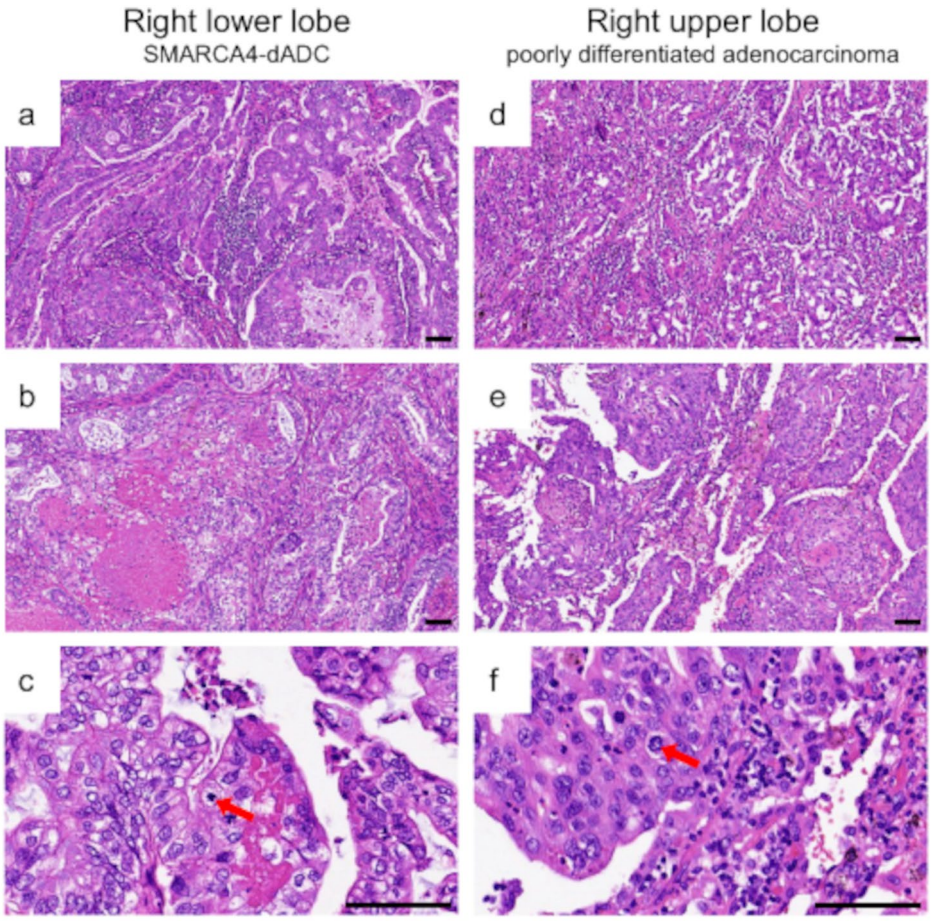

Fig. 2 Histological analysis. (**a-c**) H&E staining of the right lower lung lobe mass. (**d-f**) H&E staining of the right upper lung lobe mass. (**a**, **d**) Solid and complex glandular regions. Scale bar:50 μm. (**b**, **e**) Necrosis regions. Scale bar:50 μm. (**c**, **f**) Red arrows: nuclear mitotic image. Scale bar:200 μm

Table 1 The differences of IHC and molecular findings

	Right lower lobe (SMARCA4-dADC)	**Right upper lobe (poorly differentiated adenocarcinoma)**
IHC findings		
BRG1(SMARCA4)	Completely loss	Expression, no loss
BRM(SMARCA2)	Partial loss	Completely loss
TTF1/Napsin A	Neg / Neg	Pos/ Pos
SALL4/ CD34/ SOX2	Neg / Neg / Neg	Neg / Neg / Pos
HepPar-1	Pos	Neg
CK7/CK-pan	Pos / Pos	Pos / Pos
Molecular findings		
SMARCA4 mutation	Pos, nonsense mutation	Neg
KRAS mutation	Pos, c.35G > A, p.G12D, 16.28%	Pos, c.34G > T, p.G12C, 13.33%
STK11 mutation	Pos	Neg
Mutations with unknown clinical significance	BRCA、POLE、STK11	BRCA1、PIK3R1、STK11

IHC: Immunohistochemistry. Pos: positive. Neg: negative

clinical significance were *BRCA1*, *PIK3R1*, and *STK11* (Fig. 4d).

Based on atypical histopathology, immunohistochemistry (IHC), PCR, and NGS genomic analysis, the mass in the lower lobe of the right lung was diagnosed as SMARCA4-dADC, and the mass in the upper lobe of the right lung was diagnosed as poorly differentiated adenocarcinoma. The patient was followed up for 28 months. An ECT scan performed 7 months postoperatively

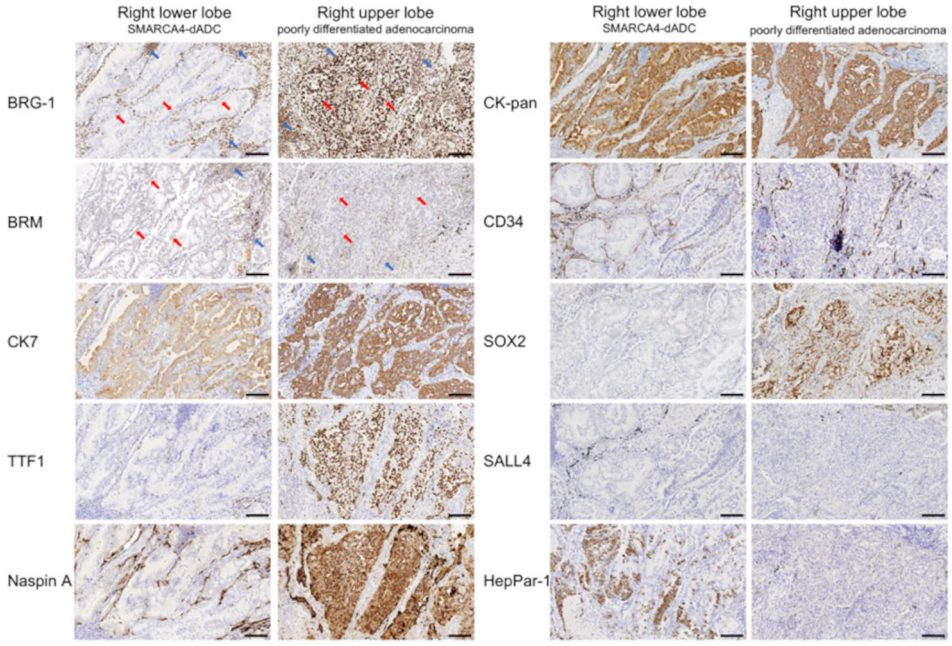

Fig. 3 Immunohistochemical staining for BRG-1, BRM, CK7, TTF1, Naspin A, CK-pan, CD34, SOX2, SALL4 and HepPar-1 in the right lung lower and upper lobe masses. Red arrows: tumor cell. Blue arrows: mesenchymal cell (internal positive control). Scale bar:100 μm

revealed metastasis to the fourth lumbar vertebral body and sacrum (Fig. S2).

Discussion

SMARCA4-deficient adenocarcinoma, typically characterized by complete or significant loss of BRG1 expression, is relatively uncommon. The concurrent presentation of SMARCA4-dADC and poorly differentiated adenocarcinoma (with concurrent SMARCA2 loss) in separate lobes of the same patient is exceedingly rare. This report describes the case of an elderly male with two distinct tumors located in the upper and lower lobes of the right lung. Histologically, both tumors shared certain features, including a predominance of solid sheets and complex glandular structures, with a minor component of micropapillary adenocarcinoma and extensive necrosis—features suggestive of poorly differentiated lung adenocarcinoma. However, they also exhibited diffuse sheets of variably discohesive, large, round to epithelioid cells with vesicular chromatin, prominent nucleoli, relatively monotonous nuclei, moderate pleomorphism, and rhabdoid features. These histological characteristics are consistent with undifferentiated lung tumors (Fig. 2) [10]. Nonetheless, distinct differences were observed in their immunohistochemical and molecular profiles. The upper lobe mass demonstrated positive expression of CK7, EMA, TTF1, Napsin A, and SOX2, and negative expression of SALL4, CD34, and HepPar-1. BRG1 expression was retained, while BRM protein expression was completely lost (Table 1; Fig. 3). Molecular analysis revealed a *KRAS* G12C mutation (Table 1; Fig. 4). Based on these atypical histopathological and immunohistochemical findings, the upper lobe mass was diagnosed as poorly differentiated adenocarcinoma. Conversely, the lower lobe mass exhibited complete loss of BRG1 protein expression and partial loss of BRM protein. It showed negative expression of TTF1, Napsin A, SALL4, CD34, and SOX2, but positive expression of CK7, EMA, and HepPar-1 (Table 1; Fig. 3). Molecular analysis identified *SMARCA4*, *KRAS* G12D, and *STK11* mutations (Table 1; Fig. 4). Consequently, the combination of atypical histopathological findings, immunohistochemistry, PCR, and NGS genomic analyses led to a definitive diagnosis of SMARCA4-dADC.

The mSWI/SNF complex utilizes energy derived from ATP hydrolysis to remodel nucleosomes and modulate transcriptional activity. This mSWI/SNF-mediated chromatin remodeling is crucial for regulating gene expression in diverse cellular processes, including differentiation, proliferation, and stemness [11, 12]. A clinically and histologically indistinguishable rhabdoid tumor predisposition syndrome is also caused by germline *SMARCA4* mutations, in which malignant rhabdoid tumors exhibit loss of BRG1 rather than INI1 [13, 14]. This disease was previously termed "SMARCA4-deficient thoracic sarcoma" [15–17]. However, recent molecular findings demonstrating a strong genomic association with smoking-related NSCLC [2], have led to a reinterpretation of most cases as dedifferentiated or undifferentiated lung carcinoma. Consequently, the WHO, in the

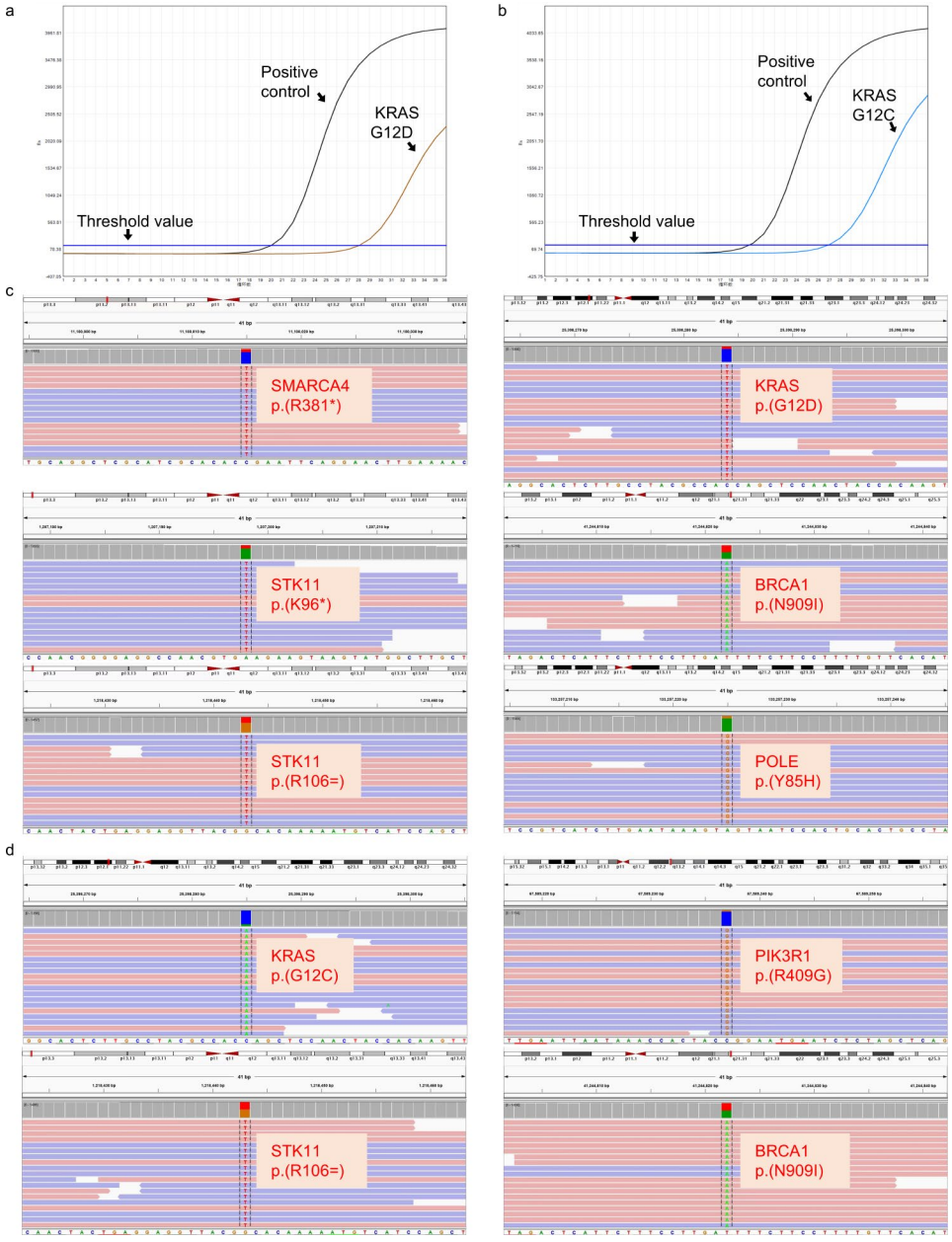

Fig. 4 Molecular analysis. (**a**) qPCR amplification plot shows that *KRAS* G12D mutations were found in SMARCA4-dADC. (**b**) qPCR amplification plot shows that *KRAS* G12C mutations were found in the poorly differentiated adenocarcinoma. (**c**, **d**) Images of the reads aligned to the reference genome as provided by the Integrative Genomics Viewer. (**c**) The mutations *SMARCA4* p.(R381*), *KRAS* p.(G12D), *STK11* p.(K96*), *BRCA1* p.(N909I), *STK11* p.(R106=), and *POLE* p.(Y85H) were detected by NGS in the SMARCA4-dADC. (**d**) The mutations *KRAS* p.(G12C), *PIK3R1* p.(R409G), *STK11* p.(R106=) and *BRCA1* p.(N909I) were detected by NGS in poorly differentiated adenocarcinoma

5th edition of its 2021 classification of thoracic tumors, renamed this entity SMARCA4-UT and categorized it under "Other epithelial tumors of the lung" [4].

Immunohistochemical analysis of BRG1 is a valuable tool for identifying thoracic *SMARCA4*-deficient tumors, demonstrating absent nuclear protein expression in tumor cells. This category encompasses both SMARCA4-UT and SMARCA4-dNSCLC. Generally, SMARCA4-UT tumors are larger and associated with a poorer prognosis than SMARCA4-dNSCLC [2].

SMARCA4-UT is a rare and aggressive malignancy characterized by an undifferentiated or sarcomatoid phenotype and SMARCA4 deficiency, which predominantly affects young to middle-aged males, particularly those with a significant smoking history, often with concurrent metastases. Tumor development is primarily driven by biallelic inactivation of *SMARCA4*, predominantly

through nonsense and frameshift mutations. Missense mutations, splice-site alterations, and deletions are less common [2, 3, 17, 18]. Up to 44% of SMARCA4-UT cases harbor additional mutations in *KRAS*, *STK11*, and/or *KEAP1*, genes frequently implicated as drivers in smoking-related NSCLC. The majority of these tumors exhibit frequent TP53 mutations, a genomic smoking signature, and a high tumor mutational burden, further supporting their close genomic relationship to conventional NSCLC [2]. Notably, a small proportion (~10%) of tumors occur in never-smokers, lack a smoking genomic signature, or present with a conspicuous absence of lung parenchyma, suggesting alternative pathogenic mechanisms [15]. Although approximately 10% of typical NSCLCs exhibit SMARCA4 deficiency [7, 19], the WHO classification recognizes SMARCA4-UT as a distinct entity from conventional SMARCA4-dNSCLC due to differences in histology, immunohistochemistry, clinical features, and prognosis [4]. The characteristic immunohistochemical profile of SMARCA4-UT includes co-inactivation of SMARCA4 (BRG1) and SMARCA2 (BRM), with cytokeratin expression typically focal or weak, and potentially completely absent. Furthermore, overexpression of *SALL4*, *SOX2*, and/or *CD34* may be observed [6, 16, 20]. Indeed, while accessory markers such as SMARCA2, SALL4, SOX2, and CD34 aid in differentiation, none exhibit complete sensitivity or specificity [2, 4, 17]. Additionally, three unique cases of thoracic undifferentiated tumors with isolated loss of SMARCA2 and retained expression of both SMARCA4 and SMARCB1 have been documented in the literature [19].

With the increasing use of comprehensive NGS in routine NSCLC diagnostics and the growing recognition of *SMARCA4* gene mutations, a distinct NSCLC subtype—SMARCA4-dNSCLC—has been identified. Within NSCLCs, BRG1-negative tumors tend to exhibit more aggressive clinical behavior than BRG1-positive tumors [21]. Furthermore, even at advanced clinical stages, BRG1-positive individuals demonstrate a statistically significant survival advantage compared to BRG1-negative patients receiving the same therapeutic interventions [8]. Recent research has significantly advanced our understanding of the histomorphological and molecular characteristics of SMARCA4-dNSCLC. Common morphological features include sheet-like or filamentous structures, round or oval cell shapes, enlarged nuclei, moderate to marked pleomorphism, and coarse chromatin [5, 22]. These features are consistent with the histological characteristics of undifferentiated lung tumors but differ in that SMARCA4-dNSCLCs demonstrate at least focal and definitive glandular or squamous differentiation [5, 22]. In this case, histological examination of the right lower lobe lesion revealed focal unequivocal glands in the context of SMARCA4 deficiency, supporting the diagnosis of *SMARCA4*-dADC. Consistent with the findings of Agaimy et al., SMARCA4-dADC exhibits a distinct, homogeneous immunophenotype characterized by $CK7^{+}$/HepPar-1^{+}/$TTF1^{-}$ expression (Table 1) [22]. Given that a TTF1-negative and HepPar-1-positive phenotype can be misinterpreted as metastatic non-lung cancer, we recommend including SMARCA4 in the marker panel used to evaluate TTF1-negative adenocarcinomas of potential or uncertain pulmonary origin.

Alterations in *SMARCA4* can be classified into two genomic categories: Class 1 mutations, encompassing truncating mutations, fusions, and homozygous deletions; and Class 2 mutations, consisting of missense mutations [7, 23]. Schoenfeld et al. demonstrated a significant association between protein loss and Class 1 mutations, whereas Class 2 mutations do not typically result in protein loss [7]. BRG1 protein loss has been associated with shorter survival, irrespective of tumor stage [8, 24]. Notably, BRG1 protein loss occurs more frequently in NSCLC than *SMARCA4* mutations, and therefore the terms *SMARCA4*-mutant NSCLC and SMARCA4-dNSCLC should not be used interchangeably [25–27].

In NSCLC, *SMARCA4* mutations are frequently co-mutated with *TP53*, *KRAS*, and *STK11*, which are associated with poor prognosis [7], suboptimal response to conventional chemotherapy and unfavorable prognosis [28]. They also show mutual exclusivity with targetable oncogenes (e.g., *EGFR*, *ALK*, and *ROS1*) [19, 21, 29]. While there are no established standard treatment options for SMARCA4-dNSCLC, recent reports suggest that SMARCA4-dADCs derive benefit from adjuvant therapies, including platinum-based chemotherapy regimens [19, 21, 30] and immune checkpoint blockade therapies [31–33]. Additionally, preclinical studies suggest sensitivity to KDM6 inhibitors [34], Aurora kinase A inhibitors VX-680 [35] and ATR inhibitors [36]. Despite exhibiting an elevated tumor mutational burden (TMB), SMARCA4-mutant tumors often demonstrate low or negative PD-L1 expression [7]. Nonetheless, studies have shown a significant association between the use of immune checkpoint inhibitors (ICIs) and improved overall outcomes in NSCLC with *SMARCA4* mutations [29, 33, 37, 38]. In patients with metastatic NSCLC, SMARCA4 alterations were associated with shorter overall survival. However, treatment with ICIs has been associated with improved outcomes in SMARCA4-dADCs, with class 1 mutations demonstrating the most favorable response to ICIs [7, 39]. A Chinese study demonstrated that approximately 15% of Chinese patients with lung cancer harbored mutations in the SWI/SNF chromatin remodeling complex, which were mutually exclusive with *EGFR* mutations. Patients with SWI/SNFmut NSCLC receiving first-line chemoimmunotherapy experienced better survival outcomes than those who received

chemotherapy alone (median progression-free survival: 8.70 versus 6.93 months) [39]. This finding was also confirmed by external validation using the POPLAR/OAK cohort. SMARCA4-mutant NSCLC is frequently associated with a high tumor mutational burden and concurrent *TP53* or *STK11/KEAP* mutations. Further analysis indicated that *TP53* and *STK11/KEAP1* mutations may serve as stratifying factors to optimize personalized immunotherapy and guide patient selection. The study revealed superior outcomes with immunotherapy over chemotherapy in SMARCA4-mutant patients, especially in SMARCA4-mut and TP53mut subgroups [39, 40]. A Finnish comprehensive genomic analysis of the lung adenocarcinoma cohort revealed that SMARCA4 (DSS; HR 3.911, 95% CI 1.561–9.795, $P = 0.004$) exhibited independent prognostic significance alongside staging, tumor mutational burden, and major histological subtypes [41]. Therefore, assessing *SMARCA4* mutation status is warranted as a potential novel biomarker for predicting response to ICIs, complementing existing assessments, including PD-L1 expression and TMB in NSCLC.

Previous studies have reported BRM protein deficiency in 6.4–10% of lung adenocarcinomas. Moreover, BRM expression correlates with tumor differentiation, with BRM deficiency consistently observed in poorly differentiated tumors [9, 42]. Analogous to SMARCA4 deficiency, SMARCA2 deficiency has been associated with significantly decreased survival in NSCLC patients, irrespective of tumor stage [8, 43]. Notably, SMARCA4-UT frequently presents with concurrent SMARCA2 deficiency, whereas co-occurrence of SMARCA4 and SMARCA2 deficiency is exceedingly rare in NSCLC (including SMARCA4-dNSCLC) [2, 17, 44]. In this case, the patient's right upper lobe mass, diagnosed as poorly differentiated adenocarcinoma, retained BRG1 expression but exhibited complete loss of BRM protein expression. Conversely, the right lower lobe mass, diagnosed as SMARCA4-dADC, demonstrated complete loss of BRG1 protein expression and partial reduction in BRM protein levels. Rhabdomyoblast-like cells were observed in both lesions. These findings suggest that SMARCA4-UT likely represents the least differentiated (undifferentiated) variant of SMARCA4-deficient NSCLC. However, further investigation of SMARCA4-UT differentiation in larger cohorts is necessary for validation.

Studies on SMARCA2-deficient adenocarcinomas are relatively scarce compared to those on SMARCA4-dADC. However, SMARCA2 deficiency has been reported in lung neuroendocrine cancer and exhibits unique biological characteristics when SMARCA4 and SMARCB1 remain intact [45]. Chromatin accessibility may be impacted by this deficiency, accelerating the growth of tumors [45]. Further research is needed to identify precise therapeutic targets and optimize treatment strategies for SMARCA2-deficient adenocarcinomas. In a preclinical study, Xue et al. found that the loss of SMARCA4 and SMARCA2 could reduce the expression of the cell cycle protein D1, thereby conferring selective sensitivity to CDK4/6 inhibitors. This opens up possibilities for Food and Drug Administration (FDA) approved CDK4/6 inhibitors in treating such NSCLCs [46]. Furthermore, poorly differentiated adenocarcinomas often demonstrate resistance to standard therapies, necessitating novel therapeutic approaches to enhance patient outcomes. In summary, SMARCA4- and SMARCA2-deficient adenocarcinomas display unique biological and therapeutic profiles distinct from conventional poorly differentiated adenocarcinomas. Further assessment of the mechanism of these defects will facilitate the development of more accurate treatment strategies.

Unlike BRG1 protein loss resulting from *SMARCA4* gene mutations, *SMARCA2* is rarely subject to mutation. Instead, BRM protein silencing is mediated by reversible epigenetic mechanisms [47]. In NSCLC, *SMARCA4* and *SMARCA2* silencing is largely mutually exclusive. These two genes exhibit functional complementarity at the transcriptional level, primarily related to gene activities associated with chromatin remodeling, cell cycle regulation, and cell proliferation [8]. Loss of BRG1 and/or BRM is associated with the progression of lung adenocarcinoma toward a solid-predominant phenotype characterized by epithelial-mesenchymal transition and loss of bronchial epithelial phenotypic features [9]. Tumors with loss-of-function *SMARCA4* mutations are dependent on *SMARCA2* for cell survival. Several in vitro and in vivo studies have demonstrated that inhibition of *SMARCA2* expression increases H3K9me3 levels and induces cell cycle arrest and senescence in SMARCA4-deficient NSCLC cells. This has positioned *SMARCA2* as a key synthetic lethal target in SMARCA4-deficient cancers, prompting functional epigenetic approaches to its investigation [48–51]. Given the role of epigenetic dysregulation in cancer development, continued investigation into targeting *SMARCA2* is warranted, particularly in light of recently disclosed patent applications [52]. Furthermore, investigating pathways or transcriptional regulatory mechanisms associated with target genes silenced in SMARCA4-deficient NSCLC may yield novel therapeutic strategies [28].

Conclusion

In summary, this report describes a unique case of SMARCA4-dADC and poorly differentiated SMARCA2-loss adenocarcinoma occurring concurrently in distinct locations, exhibiting similar tissue morphology but divergent immunophenotypes and genetic-molecular profiles. The exceedingly rare co-occurrence of these tumors

suggests that SMARCA4-deficient tumors may originate from epithelial precursors and represent dedifferentiated or undifferentiated cancers. However, SMARCA4-dADC exhibits significant immunophenotypic and molecular differences from conventional adenocarcinoma, establishing it as a distinct entity. SMARCA4-dADC's aggressive behavior warrants distinct diagnostic vigilance (e.g., IHC for SMARCA4 in poorly differentiated tumors) and potential immunotherapies (e.g., ICIs). Given that a TTF1-negative and HepPar-1-positive phenotype can be misinterpreted as metastatic non-pulmonary cancer, we recommend including SMARCA4 in the marker panel used to evaluate TTF1-negative adenocarcinomas of potential or uncertain pulmonary origin. Furthermore, SMARCA4-UT likely represents the least differentiated (undifferentiated) variant of SMARCA4-deficient NSCLC. However, further investigation of SMARCA4-UT differentiation in larger cohorts is necessary for validation.

Abbreviations

NSCLC	Non-small cell lung cancers
SMARCA4-dADC	SMARCA4-deficient adenocarcinoma
SMARCA4-UT	SMARCA4-deficient undifferentiated tumors
SMARCA4-dNSCLC	SMARCA4-deficient NSCLC
mSWI/SNF	mammalian Switch/Sucrose-Nonfermentable
BRG1	Brahma-related gene 1
IHC	immunohistochemistry
WHO	World Health Organization
EMA	Epithelial membrane antigen
CK-pan	Pan-Cytokeratin
CT	Computed tomography
PCR	Polymerase Chain Reaction
NGS	Next-generation sequencing
CNVs	Copy number variations ()
TMB	Tumor mutational burden
ICIs	Immune checkpoint inhibitors
ADCs	Antibody–drug conjugates
FDA	Food and Drug Administration

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12957-025-03839-6.

Supplementary Material 1

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Author contributions
All authors contributed actively to this manuscript. L.W. and Y.W. conceived the study, conducted the experiments, and drafted the manuscript. L.H. collected the experimental data. G.W. performed the analysis and contributed to the conceptualization. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics
The research was approved by the institutional ethics review board of the Fourth Affiliated Hospital, Zhejiang University School of Medicine (K2025006) and conducted in accordance with the principles of the World Medical Association's Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Beings."

Informed consent
Written informed consent was obtained from the patient to publish this paper.

Conflict of interest
The authors declare no conflict of interest.

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