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ORIGINAL RESEARCH

SMARCA2 Deficiency While Preserving SMARCA4 in Lung Adenocarcinoma Combined with Abnormal β-Catenin Expression

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Background: The SWI/SNF complex is comprised of ATPase catalytic subunit SMARCA4/SMARCA2, evolutionarily conserved core subunits including SMARCB1, SMARCC1, and SMARCC2, as well as functionally specialized accessory subunits PBRM1 and ARID1A. Deletion or mutation of the catalytic subunit can lead to inactivation of the encoded protein and impaired overall function of the complex, contributing to tumorigenesis.

Methods: In this study, we conducted a retrospective analysis of seven cases of poorly differentiated lung adenocarcinoma from our institution that exhibited SMARCA2 deficiency while retaining SMARCA4 expression, and systematically evaluated the clinical characteristics, histological features, genetic alterations, and survival outcomes.

Results: Among the seven cases of SMARCA2-deficient lung adenocarcinoma, five were male and two were female, with an average age of 68.7 years. Four patients had a smoking history averaging 35 years, all seven patients exhibited respiratory symptoms. Histologically, these tumors displayed diverse features, including rhabdoid morphology, giant cells, and necrotic areas. The tumor cells exhibited eosinophilic cytoplasm, large nuclei with prominent nucleoli. Immunohistochemically, the tumor cells revealed SMARCA2 negativity with SMARCA4 expression. P53 staining revealed diffuse strong nuclear expression in 5 cases and complete absence expression in 2 cases. β-catenin expression was partially abnormal in 3 cases, with positive nuclear and cytoplasmic staining. PD-L1 expression was detected as positive in 5 cases. Next-generation sequencing identified mutations in driver genes KRAS, MET, and EGFR in 4 cases, and TP53 mutations in 7 cases. Clinical follow-up revealed that 2 patients died of tumor progression, 5 patients achieved complete response within a follow-up period of 10 to 33 months (median = 18.3 m).

Conclusion: SMARCA2-deficient with SMARCA4-preserved lung adenocarcinomas demonstrate substantial histological heterogeneity and may dedifferentiate into high-grade adenocarcinomas harboring TP53 mutations. In the assessment of poorly differentiated lung adenocarcinoma, immunohistochemical detection can identify this subtype for more precise clinical treatment strategies.

Keywords: lung adenocarcinoma, SMARCA2, SMARCA4, β-catenin, gene mutation

Background

The SWItch/Sucrose NonFermentable (SWI/SNF) chromatin-remodeling complex is an evolutionarily conserved, ATP-dependent multi-subunit assembly, plays a critical role in fundamental cellular processes such as cell proliferation, lineage-specific differentiation, and DNA repair.[1] Inactivation of subunits within this complex has emerged as a key molecular driver in the development and progression of both benign and malignant tumors.[2] Mutations in one or more subunits and the corresponding loss of protein expression have been observed in approximately 20% of cancer cases.[3] Notably, core subunits of the SWI/SNF complex, including SMARCA2 (BRM), SMARCA4 (BRG1), and SMARCB1 (INI1), have been found to be lost in various malignancies characterized by rhabdoid or undifferentiated morphology. Specifically, alterations in nasal and paranasal tumors predominantly involve SMARCB1 and SMARCA4,[4] while soft tissue tumors are primarily associated with SMARCB1 mutations,[5] and thoracic tumors exhibit mainly SMARCA2 and SMARCA4 deletions.[6] Thoracic SMARCA4-deficient undifferentiated tumor was included in the 5th edition of the WHO Classification of Thoracic Tumors, exhibiting undifferentiated histological features and highly aggressive biological behavior.[7] Recently, three cases of undifferentiated thoracic tumor have been documented, each characterized by

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a deletion of SMARCA2 while retaining SMARCA4 and SMARCB1 expression.[8] This suggests that a more precise classification of tumors with deficiencies in the SWI/SNF complex within the thoracic region could significantly enhance clinical management strategies.

In addition, the deletion of the SWI/SNF complex subunit was observed in 5.4% of non-small cell lung cancer cases.[9] SWI/SNF complex-deficient non-small cell lung cancer (NSCLC) exhibit aggressive clinicopathological characteristics, PD-L1 positivity, high tumor mutation burden (TMB), and exhibit favorable responses to both immunotherapy and platinum-based chemotherapy.[10] SMARCA2 deficiency was identified in 6.4% of lung adenocarcinomas and 1.7% of squamous cell carcinomas within a large cohort study, indicating a potential role for SMARCA2 in the dedifferentiation process of NSCLC.[9] However, the expression status of SMARCA2 is not routinely assessed in the pathological diagnosis of poorly differentiated lung adenocarcinoma, and the subtype of lung adenocarcinoma characterized by isolated SMARCA2 deficiency remains underrecognized. Studies have indicated that the Wnt/β-catenin signaling pathway is dysregulated in various solid tumors and plays a role in the process of tumor dedifferentiation, which is characterized by the abnormal accumulation of β-catenin protein within the cell nucleus.[11] This study aims to characterize the clinicopathological, immunohistochemical, and molecular features of SMARCA2-deficient lung adenocarcinoma with preserved SMARCA4 expression, as well as to explore its potential correlation with abnormal expression of β-catenin.

Methods

Cases

The study was performed with the approval of Institutional Review Board of Zhejiang Hospital, and informed consent of the subjects has been waived. Inclusion criteria for the patient cohort were pathologic diagnosis of lung adenocarcinoma characterized by SMARCA2-deficient and SMARCA4-preserved between 2019 and 2024 for which the patients have consented to molecular testing. The specific diagnostic criteria were defined as follows: a diagnosis of lung adenocarcinoma in accordance with the 5th edition of the World Health Organization classification criteria, the absence of SMARCA4 and SMARCA2 is defined as either a complete and unequivocal absence or a diffuse and markedly reduced expression within the tumor cell nuclei. These cases included fine needle aspiration, bronchial biopsy specimens, and surgical resections. Additionally, we reviewed the electronic medical records of the study patients to document their clinical characteristics.

Histopathologic Analysis

The tissue samples were fixed in 3.7% neutral formaldehyde solution, subjected to routine dehydration, paraffin embedding, and sectioned at a thickness of 4 μm for hematoxylin and eosin (H&E) staining and subsequent light microscopic examination. Immunohistochemical staining was conducted as part of the clinical evaluation for each case. The staining procedure was performed using the EnVision two-step technique. Detailed information regarding the antibodies used in this study is provided in Table 1. Two pathologists independently and uniformly evaluated the immunohistochemical expression and intensity. Positive internal control cells (benign epithelial cells or inflammatory cells) were used for SMARCA4, SMARCA2, and INI1 staining to facilitate comparative analysis. The evaluation was performed using a two-tier scoring system based on the absence or retention of nuclear expression. The assessment of the remaining antibody for immunohistochemical staining is interpreted as positive (+) when tumor cells exhibit nuclear, cytoplasmic, and/or membrane expression in no less than 10% of the cell population. For PD-L1 (22C3), the results were interpreted in accordance with established guidelines, and the tumor proportion score (TPS) was defined as the percentage of PD-L1 positive tumor cells among the total number of PD-L1 positive and PD-L1 negative tumor cells.

Mutations Analyses

Genomic DNA was isolated from formalin-fixed, paraffin-embedded (FFPE) tissue using the DNeasy Tissue Kit (Qiagen, Hilden, Germany) according to the manufacturer's protocol. All tissue samples underwent pathological assessment to confirm adequacy of the tumor tissues, which required a minimum of 20% tumor content. Sequencing libraries were constructed using a KAPA DNA Library kit (Kapa Biosystems, Wilmington, MA, USA). The libraries were hybridized to

Table 1 List of Primary Antibodies Used in the Study

Antibody	Manufacturer	Species	Clone	Dilution
TTF-1	ZSGB-BIO	Mouse	8G7G3/1	Predilute
Napsin A	CELNOVTE	Mouse	C2C2	1:1
CK7	ZSGB-BIO	Mouse	UMAB161	1:200
P40	CELNOVTE	Mouse	C3B4	Predilute
SMARCA2	Abcam	Mouse	EPR23103-44	1:1000
SMARCA4	ZSGB-BIO	Rabbit	E8V5B	Predilute
P53	ZSGB-BIO	Mouse	D0-7	1:500
CD34	ZSGB-BIO	Mouse	10C9	1:200
SALL4	ZSGB-BIO	Mouse	OTI4D7	Predilute
SOX2	ZSGB-BIO	Rabbit	EP103	Predilute
ALK	Roche	Rabbit	D5F3	Predilute
INI-1	ZSGB-BIO	Rabbit	OTIR4G9	1:1
Ki67	ZSGB-BIO	Mouse	UMAB107	1:400
β-catenin	ZSGB-BIO	Mouse	UMAB15	1:200
E-cad	ZSGB-BIO	Mouse	EP6	1:200
PD-L1	DAKO	Mouse	22C3	1:50

a custom-designed panel containing 18 cancer-related genes, including ALK, EGFR, MET, RET, ROS1, KRAS, NRAS, BCL2L11, TP53, NTRK1, NTRK2, NTRK3, ERBB2, BRAF, PIK3CA, AXL, PNET, and RB1. Prepared libraries were sequenced on the Gene+Seq-2000 apparatus (GenePlus-Suzhou, Suzhou, China) using a paired-end read protocol. Single nucleotide variants (SNVs) were identified using MuTect (Broad Institute, Cambridge, MA, USA), and small insertions and deletions (indels) were called by GATK (Broad Institute, Cambridge, MA, USA). Copy number variations (CNVs) were detected using Contra (Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia). All final candidate variants were verified using an integrative genomics viewer browser. Germline variants were removed from variants in the tumor samples.

Results

Clinical Findings

The study cohort comprised seven patients, including five males and two females (Table 2). The age range of the patients was between 52 and 79 years, with a mean age of 68.7 years. None of the patients had a history of other malignancies. Smoking history was present in four patients (57.1%), with smoking durations ranging from 20 to 55 years (mean

Table 2 Clinical Findings of SMARCA2-Deficient with SMARCA4-Preserved Lung Adenocarcinomas

Case No.	Age(y)	Sex	Smoking (Pack-years)	CT Findings in Nontumor Lung	Primary Tumor Location	Primary Tumor Size (mm)	Metastatic	Stage at Diagnosis	Treatment	Follow-up (m)
1	74	M	55	Emphysema, bullae	LUL	25	(-)	IA	Lobectomy, Chemotherapy plus ICI	CR at 33
2	58	M	25	Emphysema, bullae	RUL	59	LN	IIIB	Lobectomy, Chemotherapy	CR at 24
3	68	M	40	Fibrotic Lesion	LUL	55	MPE	IV	Chemotherapy plus ICI	PD at 15 (Died of tumor)
4	77	F	0	Fibrotic Lesion	RUL	50	LN	IIB	Lobectomy, ICI	CR at 17
5	73	M	0	Emphysema, bullae	LLL	28	(-)	IIA	Lobectomy Chemotherapy	CR at 17
6	79	M	20	Emphysema, bullae	LUL	35	(-)	IIIA	ICI	PD at 12 (Died of tumor)
7	52	F	0	Fibrotic Lesion	LLL	46	MPE	IV	Lobectomy, Chemotherapy plus Targeted therapy	CR at 10

Abbreviations: F, female; M, male. LUL, left upper lobe; LLL, left lower lobe; RUL, right upper lobe; LN, Lymph node; MPE, Malignant pleural effusion, ICI, Immune checkpoint inhibitor; m, months; CR, complete response; PD, progressive disease.

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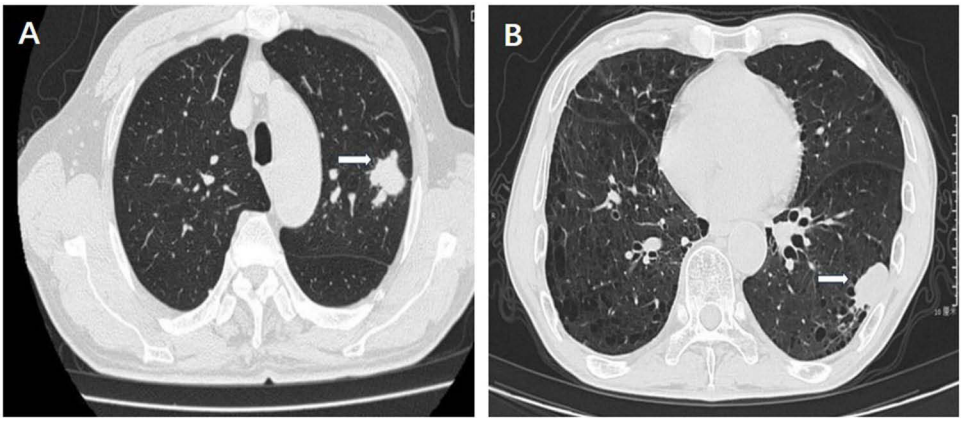

Figure 1 Computed tomography scan of SMARCA2-deficient lung adenocarcinoma. An irregular nodule exhibiting a lobulated morphology and spiculated margin was identified in the left upper lobe of the lung (**A**, white arrow). Nodular high-density opacities are observed in the lower lobe of the left lung, exhibiting lobulated features with poorly defined margins (**B**, white arrow).

duration: 35 years), three patients were non-smokers. Tumor locations included the left upper lobe in three cases (42.8%) (Figure 1A), the left lower lobe in two cases (28.6%) (Figure 1B), and the right upper lobe in two cases (28.6%). The primary lesions were measured 17 to 59 mm in greatest diameter (mean: 41 mm). Chest computed tomography revealed emphysema and bullae in all four smokers, as well as peripheral pulmonary fibrosis in other three patients. All seven patients exhibited respiratory symptoms, including cough, sputum production, chest tightness, and dyspnea, and pleural effusion was observed in two patients at the time of diagnosis. Tumor marker levels were within normal limits in one patient, while six patients demonstrated elevated levels of one or more tumor markers. Specifically, these included carcinoembryonic antigen (2/7), carbohydrate antigen 15–3 (1/7), non-small cell lung cancer-related antigen 21–1 (4/7), carbohydrate antigen 125 (2/7), serum neuron-specific enolase (2/7), alpha-fetoprotein (1/7), pro-gastrin-releasing peptide (1/7), and carbohydrate antigen 19–9 (1/7). One patient (14.3%) was diagnosed in stage I, two patients (28.6%) at stage II, two patients (28.6%) at stage III, and two patients (28.6%) at stage IV. Among the five patients who underwent lobectomy, two patients received adjuvant chemotherapy (pemetrexed plus carboplatin), two patients received immunotherapy (tislelizumab and sintilimab, respectively), and one patient received chemotherapy and immunotherapy (pemetrexed plus tislelizumab). Additionally, among those who did not undergo surgical resection, one patient received chemotherapy and targeted therapy (cisplatin plus osimertinib), while the other patient received chemotherapy and immunotherapy (pemetrexed plus tislelizumab). The follow-up data for all seven patients ranged from 10 to 33 months, with a mean follow-up duration of 18.3 months. Among the five patients who underwent lobectomy, four patients remained in complete response (CR) with no evidence of disease recurrence or distant metastasis. One patient developed progressive disease (PD), ultimately died of tumor recurrence and hemoptysis. Among the two patients who did not receive surgical intervention, one patient experienced disease progression and died of hemoptysis and pleural effusion, while the other patient remained in CR.

Pathologic and IHC Findings

The histological evaluation was conducted on seven cases, comprising five surgically resected specimens, one bronchial biopsy specimen of a primary tumor, and one CT-guided percutaneous lung biopsy specimen of a primary tumor. Seven cases were diagnosed as non-mucinous poorly differentiated adenocarcinomas characterized by typical focal adenoid differentiation, including acinar, cribriform, and papillary structures (Figure 2A). In certain regions, the tumor cells were also observed to exhibit a cable-like distribution pattern (Figure 2B), with their growth predominantly characterized by solid components (Figure 2C). The tumor cells exhibited morphological variability, ranging from oval to rhabdoid morphology (Figure 2D), with neoplastic necrosis observed in five cases, multinucleated giant cells (Figure 2E) in four cases, and hyaline changes (Figure 2F) in three cases. The cytoplasm of the tumor cells was predominantly eosinophilic, with well-defined cell borders. All cases demonstrated marked nuclear atypia, prominent nucleoli, and frequent

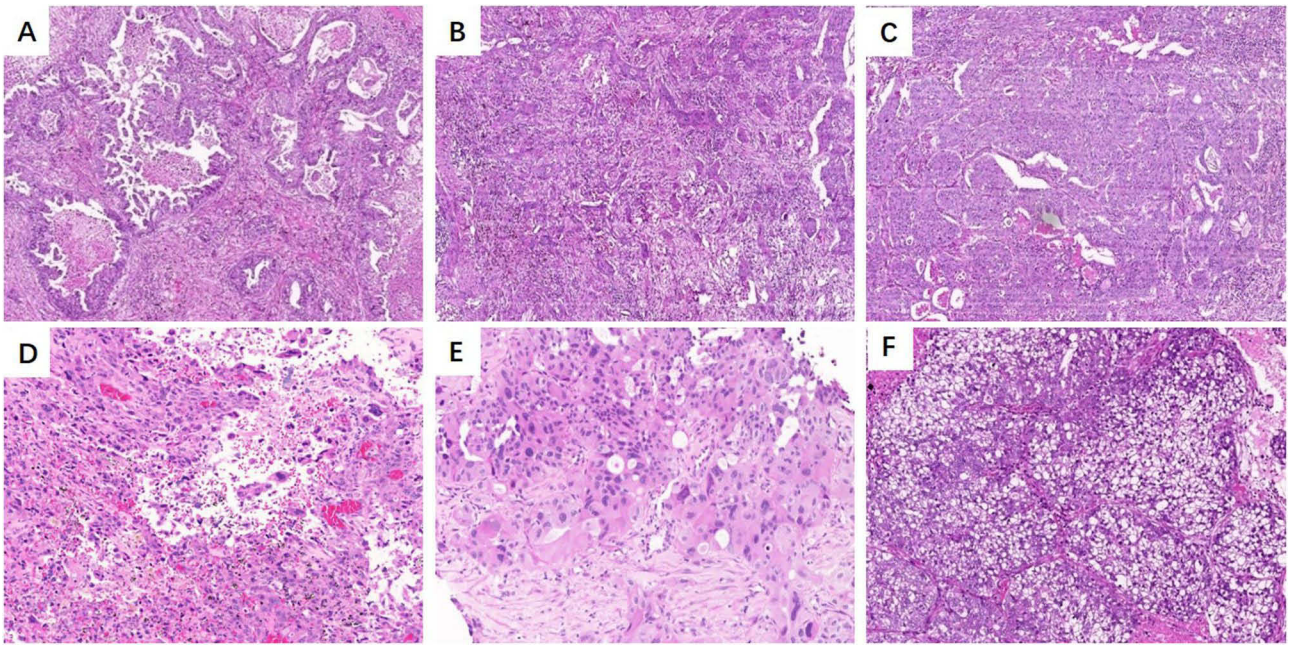

Figure 2 The histologic findings of SMARCA2-deficient lung adenocarcinoma. The tumor cells exhibited a cribriform and papillary architecture, with evident necrosis observed within the glandular cavities (**A**). The tumor cells demonstrated a cable-like structure accompanied by hyalinization of the interstitial tissue (**B**). Solid components of the tumor were present, characterized by eosinophilic globules and stromal cell infiltration (**C**). Notable features included the presence of rhabdoid morphology cells (**D**), giant cells (**E**), and solid regions with distinct clear cytoplasm (**F**).

pathological mitotic figures. Mild interstitial inflammation was noted in two cases, while moderate inflammatory cell infiltration, predominantly lymphocytes, plasma cells, and histiocytes, was observed in five cases. Extracellular mucinous secretion was identified in one case.

Key immunohistochemical (IHC) findings are summarized in Table 3. SMARCA2 expression was absent in seven tumor samples (Figure 3A), whereas SMARCA4 (Figure 3B) and INI-1 exhibited consistent positivity. TTF-1 (Figure 3C) and Napsin A showed focal expression in three cases that exhibited similar morphological characteristics, while 4 cases demonstrated diffuse positivity. CK7 and E-cadherin were expressed in seven cases, whereas P40, CD34, and ALK were consistently negative. Notably, SALL4 was partially positive in one case, 2 cases showed partial positivity for SOX2 (Figure 3D), and β-catenin exhibited abnormal cytoplasmic and nuclear positivity in three cases (Figure 3E). Immunohistochemical analysis revealed that p53 was diffusely and strongly positive (Figure 3F) in five cases and completely negative in two cases. PD-L1 (22C3) expression was negative in two cases (2/7), low expression in three cases (3/7), and high expression in two cases (2/7) (TPS<1% was defined negative, 1–49% was defined low expression, and >50% was defined high expression). MIB-1 staining indicated a significant increase in proliferative activity, with a nuclear positivity rate ranging from 40% to 80% (mean: 64.3%).

Table 3 Immunohistochemical Results in SMARCA2-Deficient with SMARCA4-Preserved Lung Adenocarcinomas

CK7	P40	SMARCA2	SMARCA4	INI-1	P53	CD34	SALL4	SOX2	ALK	E-cad	β-catenin	MIB-1	PD-L1
+	-	-	+	+	+D	-	-	-	-	+	+A	70%	<1%
+	-	-	+	+	-	-	-	+F	-	+	+N	80%	40%
+	-	-	+	+	+D	-	-	-	-	+	+N	40%	60%
+	-	-	+	+	-	-	-	-	-	+	+N	40%	20%
+	-	-	+	+	+D	-	+F	-	-	+	+A	80%	5%
+	-	-	+	+	+D	-	-	+F	-	+	+N	80%	70%
+	-	-	+	+	+D	-	-	-	-	+	+A	60%	<1%

Notes: +, indicates positive; -, indicates negative; F, Focal; D, Diffuse; N, Normal (defined as membranous staining); A, Abnormal (defined as nuclear/cytoplasm staining).

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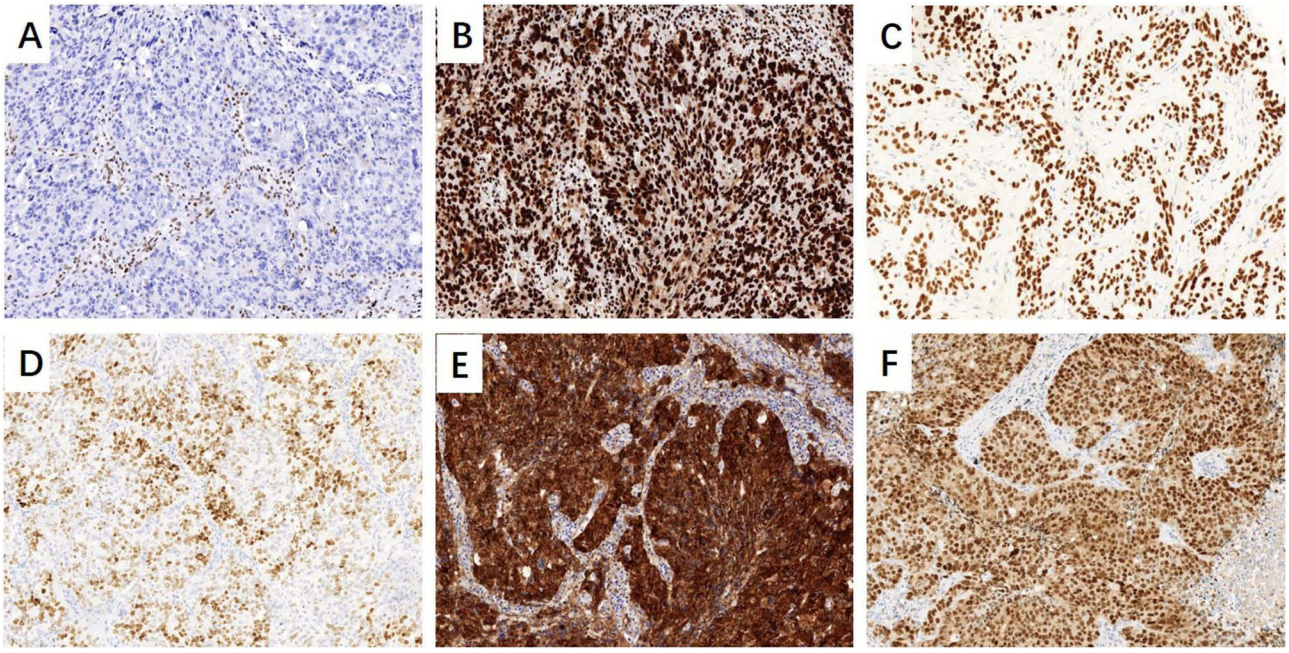

Figure 3 Immunohistochemical findings in SMARCA2-deficient lung adenocarcinoma. Immunohistochemistry for SMARCA2 is negative (**A**). SMARCA4 immunohistochemistry exhibits strong diffuse nuclear staining (**B**). The tumor cells retained expression of TTF-1 (**C**). The subset of tumor cells expressed SOX2 (**D**). Aberrant β-catenin expression in tumor cells is observed both in the nucleus and cytoplasm (**E**). The cells showed strong nuclear positivity of P53 (F).

Mutations

Next-generation sequencing (NGS) analysis revealed that four cases harbored driver gene mutations, specifically two KRAS mutations (c.35G>C p.G12A and c.34G>C p.G12R), one MET mutation (Exon14 c.3054_3082+13del p.V1019_D102 8del), and one EGFR exon 19 in-frame deletion (p.T751_I759d elinsN). Notably, TP53 mutations (c.524G>A p.R175H, c.574C>T p.Q192, c.1010G>T p.R337L, c.808T>G p.F270V, c.785G>T p.G262V, c.1114_1130deli nsG p.K372Afs45, c.469G>T p.V157F) were identified in all seven patients. Additionally, other genetic alterations were observed, including mutations in ERBB2 (c.929C>T p.S310F), PIK3CA (Exon10 c.1624G>A p.E524K), and RB1 (Exon17 c.1510C>p.Q504), as well as amplifications of EGFR and KRAS, and a deletion in CDKN2A.

Discussion

SMARCA2 and SMARCA4 constitute the two core catalytic subunits of the SWI/SNF chromatin remodeling complex and are recognized as tumor suppressors.[3] The proteins encoded by these genes, BRM and BRG1, both possess a bromodomain and an ATPase domain with approximately 75% sequence homology.[1] Notably, there are significant differences in expression and function between SMARCA4 and SMARCA2.[12] Mutations in SMARCA4 have been identified in various types of cancer, including rhabdomyosarcoma, small cell ovarian cancer with hypercalcemia, gastric cancer, and lung cancer,[13] whereas mutations in SMARCA2 are relatively rare in cancer. Multiple studies have demonstrated that the simultaneous or non-simultaneous loss of SMARCA2 and SMARCA4 may accelerate tumor differentiation and epithelial-mesenchymal transition.[14] Additionally, isolated SMARCA2 deletions have been reported in three undifferentiated tumors within the thoracic cavity[8] and two undifferentiated adenocarcinomas at the gastro-esophageal junction.[15] These cancers exhibit morphologic features similar to those observed in SMARCA4-deficient cancers. Agaimy et al have reported a notable increase in undifferentiated morphology and SMARCA2 loss in gastrointestinal cases with metastases of NSCLC.[16] To the best of our knowledge, limited studies have investigated the clinical and histopathological features of lung adenocarcinoma with SMARCA2 deletion but SMARCA4 retention. Therefore, this rare subtype of lung cancer remains inadequately understood by thoracic surgeons. In this study, we present a series of poorly differentiated lung adenocarcinoma cases characterized by SMARCA2 deletion and retained SMARCA4 expression, providing a detailed analysis of morphological features and clinical outcomes.

In this cohort, the majority of cases were male (71.4%), with a significant proportion being smokers (57.1%). The average smoking duration was 35 years, indicating a potential association between SMARCA2 deficiency and smoking. However, it remains undetermined whether smoking is a direct cause of SMARCA2 loss. All cases within this cohort were classified as poorly differentiated adenocarcinomas. Histopathological examination revealed predominantly solid structures with prominent inflammatory infiltrates. Tumor cells exhibited a nested pattern, characterized by abundant eosinophilic cytoplasm. In certain regions, the tumor demonstrated continuity with typical adenocarcinoma features, adenocarcinoma differentiation exhibited acinar, cribriform, and papillary structures. Tumor cells displayed rhabdoid differentiation, granular chromatin, prominent nucleoli, and multinucleated giant cells, often associated with necrosis. Additionally, clear cell-like morphology was observed, characterized by large tumor cells with clear cytoplasm and well-defined cell borders, indicative of intracellular or extracellular mucin production. Notably, 3 cases demonstrated aberrant β-catenin expression in the cytoplasm and nucleus of certain tumor cells, along with diminished TTF-1 expression, providing additional evidence that SMARCA2 deficiency contributes to morphological alterations, changes in cell viability, and dedifferentiation. Literature on isolated cases of SMARCA2 deletion in lung adenocarcinoma remains limited, and in-depth studies investigating the relationship between the Wnt/β-catenin signaling pathway and SMARCA2 loss have been scarce. Therefore, further elucidation of this relationship necessitates larger patient cohort studies. Additionally, in cases of poorly differentiated lung adenocarcinoma exhibiting rhabdoid morphology and tumor giant cells, immunohistochemical testing for SMARCA2 and SMARCA4 can effectively identify such tumors, which is highly significant for clinicians in selecting more precise therapeutic strategies.

The top differential diagnosis is thoracic SMARCA4-deficient undifferentiated tumor primarily involves tumor cells characterized by rhabdoid morphology, poor cellular cohesion, and a lack of epithelial differentiation. These tumors typically exhibit focal positivity or complete negativity for epithelial markers and lack immunohistochemical expression of BRG1 and Claudin-4.[17] Other differential diagnosis should be discussed with primary tumors, including poorly differentiated squamous cell carcinoma, large cell carcinoma, and sarcomatoid carcinoma. Poorly differentiated squamous cell carcinomas usually express squamous markers such as CK5/6, p40, and p63. Morphological evidence of adenocarcinoma, including intracellular mucin and glandular differentiation, can be identified using immunohistochemical markers like TTF-1 and Napsin A, as well as special stains for mucin. Large cell carcinomas may display striated muscle-like cytological features, necessitating adequate surgical specimens for definitive diagnosis. In these cases, there is no evidence of adenocarcinoma differentiation, and TTF-1 and Napsin A are negative. SWI/SNF complex-deficient cancers have been reported in various systems,[2] with the lung being a common site of metastasis for many malignancies. For SMARCA2-deficient lung adenocarcinomas, comprehensive immunohistochemical labeling combined with imaging studies is essential to rule out metastatic disease. Non-small cell carcinomas with clear characteristics of lung adenocarcinoma and positive expression of TTF-1 and Napsin A can be diagnosed as SMARCA2-deficient lung adenocarcinoma.

In all seven patients, next-generation sequencing (NGS) was conducted to identify mutations in 18 genes associated with lung cancer development. These mutations encompassed point mutations, small fragment insertions and deletions, copy number variations, and known fusion genes. Driver gene mutations were identified in four patients: two harbored KRAS mutations, one had a MET mutation, and another exhibited an EGFR exon 19 non-frameshift deletion. Notably, TP53 mutations were present in all seven cases. Additional genetic alterations detected included ERBB2, PIK3CA, and RB1 mutations, as well as EGFR and KRAS amplifications, and CDKN2A deletions. SMARCA2 may represent an additional genetic event independent of EGFR and ALK mutations.[18] Further investigation is required to determine whether SMARCA2 functions as a direct driver gene, a passenger gene, or if its role is influenced by epigenetic regulatory factors.[19] Previous studies utilizing mouse models have demonstrated that the preservation of SMARCA2 deficiencies in the context of SMARCA4 mutations promotes the onset and/or progression of lung cancer.[1,20] Research has confirmed that promoter methylation results in the inactivation of SMARCA2, thereby facilitating lung cancer development. The silencing of SMARCA2 is driven by promoter polymorphisms and is associated with histone deacetylase (HDAC) activity.[21] Recent studies have demonstrated that hypermethylation of the ABCG1 gene results in reduced ABCG1 gene expression and decreased protein levels in non-small cell lung cancer (NSCLC), which is significantly correlated with overall survival in lung adenocarcinoma (LUAD) patients.[22] These findings indicate that

the alterations in SMARCA2 resulting from promoter methylation may serve as a promising epigenetic biomarker for predicting the clinical prognosis of non-small cell lung cancer.

The significant heterogeneity observed among lung cancer tumors has prompted increased research efforts directed toward the identification of cell type-specific genes. This approach holds promise for improving the classification of tumor subtypes and predicting responses to therapeutic interventions.[23] Previous studies have indicated that SMARCA2-deficient lung adenocarcinoma exhibits a poor prognosis and a significantly lower 5-year survival rate, serving as an independent prognostic factor for lung adenocarcinoma.[18] Currently, there is no specific treatment regimen established for SMARCA2-deficient lung adenocarcinoma. Protein acetyltransferase inhibitors have been shown to restore the expression levels of various mRNAs and proteins, which can be further modulated by HDAC inhibitor therapy.[1] If SMARCA2 loss co-occurs with other driver gene mutations, a combination of targeted therapies may be considered to enhance clinical outcomes. Studies have indicated that this subtype of lung adenocarcinoma demonstrates sensitivity to platinum-based chemotherapy, CDK4/6 inhibitors, and PD-1 inhibitors, all of which exhibit significant therapeutic efficacy.[10] Notably, four patients who received immunotherapy achieved complete remission during the follow-up period (12 to 33 months), suggesting a potentially favorable response to immunotherapy in this patient cohort.

One limitation of our study is the relatively small number of cases included in the retrospective analysis, which makes it difficult to conduct effective statistical analysis to establish a clear association between this rare tumor subtype and clinical treatment or patient prognosis. Importantly, this study represents the first report of abnormal β-catenin expression in SWI/SNF-deficient lung cancer, despite the absence of functional validation. Further investigation into the role of SMARCA2 in tumor dedifferentiation may yield valuable insights into the molecular heterogeneity of lung cancer. Expanding the sample size to further characterize the clinicopathological features and underlying molecular mechanisms of this subgroup of lung adenocarcinoma is crucial for advancing precision medicine in the treatment of lung cancer.

Conclusions

We present a series of seven cases of lung adenocarcinoma characterized by the absence of SMARCA2 expression while maintaining intact SMARCA4 expression. The tumors demonstrate diverse histological features, including rhabdoid morphology and the presence of tumor giant cells, with some cases exhibiting aberrant β-catenin expression. Genetically, all cases harbor TP53 mutations, and certain cases present concomitant alterations in known lung cancer driver genes. This distinct subtype of lung adenocarcinoma is predominantly observed in advanced stages, and 5 patients demonstrates favorable responses to platinum-based chemotherapy and immune checkpoint inhibitor therapy. However, two patients experienced disease progression that ultimately resulted in death, long-term monitoring remains necessary. Future studies involving larger, multi-institutional cohorts are expected to make meaningful contributions to the more comprehensive understanding of SWI/SNF complex involvement in lung cancer pathogenesis, prognosis, and potential therapeutic strategies.

Ethical Approval

This study conformed to the Declaration of Helsinki on Human Research Ethics standards and was approved by the Medical Ethics Committee of the Zhejiang Hospital, Zhejiang Province, People's Republic of China (approval ZJHIRB-014K). The requirement of patients' informed consent was waived owing to the retrospective nature of the study. And we confirmed that the data was anonymized or maintained with confidentiality.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

This paper has been uploaded to SSRN as a preprint: https://papers.ssrn.com/sol3/papers.cfm/abstract_id=5185537

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