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Review

Clinicopathological and molecular perspectives on thoracic SMARCA4-deficient undifferentiated tumors and SMARCA4-deficient non-small cell lung carcinomas

Sumanta Das[1,2], Pallavi Mishra[3], Sunita Ahlawat[1]

[1] Department of Pathology, Agilus Diagnostics Ltd, Fortis Memorial Research Institute, Gurugram, India; [2] Department of Pathology, North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences, Shillong, India; [3] epartment of Cellular Pathology, Queen Elizabeth Hospital, Lewisham and Greenwich NHS Trust, London, United Kingdom

Summary

SMARCA4-deficient tumors of the thoracic cavity represent a newly emerging group of aggressive neoplasms driven by inactivation of the SMARCA4 gene, a key member of the SWI/SNF chromatin remodeling complex. These tumors are broadly classified into thoracic SMARCA4-deficient undifferentiated tumors (SMARCA4-UT) and SMARCA4-deficient non-small cell lung carcinomas (SMARCA4-dNSCLC). Despite some overlap in genomic alterations, especially smoking-related mutations like TP53, KRAS, and KEAP1, these entities differ in histomorphology, immunoprofile, and biological behavior. SMARCA4-UTs are undifferentiated, often rhabdoid in appearance, with loss of epithelial markers and gain of stem cell markers such as SOX2 and SALL4, while SMARCA4-dNSCLCs retain some epithelial differentiation. Radiologically, these tumors often present as large central thoracic masses with high metabolic activity and early metastases. Both tumor types show poor prognosis, with limited response to conventional therapies. Immunotherapy, particularly immune checkpoint inhibitors, shows promise even in PD-L1–negative cases, and emerging epigenetic and molecular targeted therapies are under investigation. It is crucial to distinguish SMARCA4-UT and SMARCA4-dNSCLC by appropriate use of histopathology, immunohistochemistry, and molecular studies, considering the prognosis and treatment response. Our review focuses on the advancement of understanding the clinicopathological spectrum of both entities, their genetic landscape, and current treatment options.

Key words: SMARCA4-deficient tumors, Thoracic neoplasms, Non-small cell lung carcinoma, Chromatin remodeling, Immunotherapy

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Correspondence
Sumanta Das
E-mail: sumantad755@gmail.com

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Introduction

The SWI/SNF (switch/sucrose nonfermenting) chromatin remodeling complex plays a crucial role in various key biological functions, including gene expression and chromatin-based processes like transcription, and the repair of DNA [1]. Genetic alterations in the components of the SWI/SNF chromatin remodeling complex are found in around 20% of solid tumors, and growing evidence indicates that particular changes within this complex may influence prognosis in some solid malignancies [2,3,4]. SWI/SNF family is of the ATP-dependent remodellers, which have a bromo domain and bind acetylated histone [5]. The core members of this SWI/SNF family include SMARCB1 (also known

as BAF47, SNF & INI1), SMARCC1 (also known as BAF155 & BAF170), SMARCA4 (also known as BRG1) and SMARCA2 (also known as BRM) [6]. SMARCB1 mutation has been postulated in a number of malignancies like a malignant rhabdoid tumor, atypical teratoid/rhabdoid tumor (AT/RT), epithelioid sarcoma, renal medullary carcinoma, sinonasal undifferentiated carcinoma, poorly differentiated chordoma, myoepithelial tumors of soft tissue, epithelioid malignant peripheral nerve sheath tumor, etc [7-15]. Compared to SMARCB1, mutation of SMARCA4 is seen in a lesser number of high-grade malignancies. SMARCA4, a key tumor suppressor, is found to be altered in roughly 5-7% of human cancers. Class I alterations – including truncating mutations, gene fusions, and homozygous deletions cause a complete loss of function. On the other hand, Class II alterations, typically missense mutations, may act in a dominant-negative manner, impart gain-of-function characteristics, or result in partial or complete loss of function [16]. SMARCA4 mutation is commonly seen in small cell carcinoma of ovary hypercalcemic type, undifferentiated uterine carcinoma, uterine sarcoma, undifferentiated colonic carcinoma, undifferentiated esophageal carcinoma etc. [17-21].

SMARCA4, together with SMARCA2, represents one of two mutually exclusive DNA-dependent ATPase proteins that play a role in controlling gene expression through transcriptional regulation [22]. SMARCA-4 mutation is seen in approximately 10% of non-small cell lung carcinomas where tumor cells show solid, mucinous patterns [23,24]. At the same time, thoracic SMARCA-4 deficient undifferentiated tumor (SMARCA4-UT) is a recently described entity that is different from SMARCA4-dNSCLC [25]. Regardless of great advances in precision oncology, a significant subset of thoracic malignancies, especially those lacking actionable genomic alterations, have limited therapeutic options. Standard chemotherapeutic regimens generally offer minimal benefits in such cases, emphasizing a critical gap in effective, personalized treatments. SMARCA4-deficient tumors, in particular SMARCA4-UT and SMARCA4-dNSCLC, epitoimizes this challenge because of their persistent absence of targetable driver mutations like EGFR, ALK, or ROS1 [26]. This therapeutic gap demands research beyond customary paradigms. Under these circumstences, novel and emerging biomarkers, such as chromatin remodelling deficiencies, novel targeted therapies (KRAS inhibitors, KEAP1 inhibitors etc), and tumor immune sigatures (anti-PDL1 therapies), offer an encouraging path for therapeutic hierarchies [27]. This review aims to critically explore all the parameters, including terminology, radiological characteristics, microscopic pathology, immunohistochemical profiles, molecular alterations, prognostic implications, and emphasis on therapeutic strategies with recent treatment updates of both entities.

Terminology

SMARCA4-deficient thoracic/lung tumors are classified as thoracic SMARCA-4 deficient undifferentiated tumor (SMARCA4-UT) and SMARCA-4 deficient non-small cell carcinoma (SMARCA4-dNSCLC) [28]. Whereas SMARCA4-UT has been recently added to WHO Thoracic Tumors 5th edition, SMARCA4-dNSCLC is not considered a distinct entity [25]. SMARCA4-UT is a high-grade malignant thoracic cavity tumor comprising undifferentiated rhabdoid or epithelioid cells and SMARCA-4 mutation [29]. Loarer et al. while performing RNA-sequencing in unclassified round cell sarcomas of the thoracic cavity, found that 19 of 32 cases had a SMARCA-4 mutation. The mutations were nonsense, frameshift, missense, and splice-site mutations [30]. Histopathology of those cases revealed poorly cohesive sheets of monomorphic tumor cells with eosinophilic nuclei. The authors called it SMARCA-4 deficient thoracic sarcoma. Later, similar case series were published by Yoshida et al. (n=12) and Sauter et al. (n=12 [31,32]. Another study by Perret et al. described 30 cases of this entity with similar histopathology comprising ovoid to polygonal cells in desmoplastic stroma and extensive necrosis. Considering the primary lung as a rare location, no preneoplastic condition and similar genomic profiles to the rhabdoid tumor in some cases, prompted the nomenclature of “Thoracic SMARCA-4 deficient sarcoma” as a distinct clinicopathological entity [33]. However, Rekhtman et al. have shown that these tumors are actually “SMARCA-4 undifferentiated carcinoma” rather than sarcomas [34]. The authors have concluded from the findings of conventional NSCLC in some patients, focal expression of NSCLC markers (e.g., TTF1, p40) in some cases, heavy smoking history in all patients, the genomic smoking signature of NSCLC type (KRAS, STK11, KEAP1), high mutation burden and metastatic pattern typical of carcinomas (lymph node, bone, adrenal glands etc.). However, due to significant phenotypic and clinical differences from NSCLC, they are separately classified as “Thoracic SMARCA-4 deficient undifferentiated tumor”.

The other entity, SMARCA-4 deficient NSCLC, is defined by SMARCA-4 mutation in a conventional NSCLC [35]. Reisman et al. first showed that loss of BRG1/BRM expression in NSCLC patients was associated with poor prognosis [36]. Agaimy et al. described a dis-

tinct SMARCA-4 deficient adenocarcinoma with morphology of solid pattern, rhabdoid pattern, and mucinous pattern and characteristic immunohistochemistry of CK(+), TTF1(-), Hep Par1 (+), and SMARCA-4 (loss of expression) [24]. NGS revealed SMARCA-4 mutation and TP53 mutation predominantly. No EGFR mutation or ALK/ROS rearrangement was seen. Herpel et al. also showed that 5.1% cases of NSCLC cases with glandular and squamoid morphology have loss of SMARCA-4 in their sample of 316 cases [37]. Subsequently, Liang et al. found 6.9% (105/1520) cases of NSCLC patients had SMARCA-4 mutation and Nambirajan showed 4% cases (4/100) of NSCLC cases had SMARCA-4 mutation where these tumors were mostly TTF-1 and p40 negative on immunohistochemistry [38,39].

Overall, this group of tumors is seen in older patients with a smoking history and has a poor prognosis, with most cases presenting with advanced disease.

Radiology

Thoracic SMARCA4-deficient undifferentiated tumors mostly present as large, centrally located masses that involve mediastinum, lung, or pleura with extensive surrounding structure infiltration. Tumor sizes are generally large (usually >9 cm), and display high FDG uptake on PET-CT. Mean SUV values range from 13 to 16, which indicates intense metabolic activity. It becomes impossible many times to determine the origin of the tumor, whether it is arising from the lung or mediastinum, because of the overlapping involvement. Underlying lung abnormalilty is very common, with the most frequent findings being those of emphysematous changes and bullae.

Radiological differential diagnosis include lymphomas, germ cell tumors, or NUT midline carcinomas due to their large size and compressive behavior.

At diagnosis, most patients have advanced-stage disease with frequent metastases to lymph nodes, bones, adrenal glands, and the peritoneum. Brain metastases have been observed. Overall, these tumors demonstrate a pattern of aggressive thoracic spread, central location, and high metabolic activity, and are often associated with pre-existing smoking-related lung changes [31-34].

SMARCA4-deficient NSCLCs are usually peripheral, well-circumscribed lobulated masses with intense metabolic activity on PET-CT (high SUVmax). They are prone to early metastasis (especially to bone, lymph nodes, and adrenal glands), and often show pleural or chest wall invasion, even when small. Emphysema is a common background finding due to the strong link with smoking. Morphologically and immunophenotypically, these tumors can mimic hepatoid malignancies, which may complicate radiologic differential diagnosis. Radiological findings are compared in Table I.

Table I. Clinico-radiological comparison of SMARCA-4 dUT & SMARCA4-dNSCLC based on six major studies.

Parameters	SD-UT Yoshida et al. 2017 & Rekhtman et al. 2020	SD-UT Le Loarer et al. 2015 & Sauter et al. 2017	SD-NSCLC Agaimy et al. 2017	SD-NSCLC Kim et al. 2024
Tumor size	Mean - 9.2 cm (2.2-18.3 cm)	Typically large (Often >10 cm)	Often large, some >7-9 cm	Median 4.2 cm (0.8-6.2 cm)
Tumor location	Central, mediastinal +/- Lung	Central or mediastinal with lung infiltration	Peripherak or central	Peripheral (78%)
Margins and shape	Lobulated, compresive	Lobulated or infiltrative, often ill-defined	Not specified in detail	Well-defined, lobulated (89%)
Pleural/chest wasll invasion	Very common	Common, often extensive	Often present	78% (even in small tumors)
Metastasis at diagnosis	91% had stage IV	Very common, aggressive spread	78% had M1 disease	44% (bone, lung)
Lymphadenopathy	59% had lymph node metastasis	Frequent	Common, not detailed	56% (sometimes necrotic)
Emphysema/ smoking Link	76% had emphysema, median age lower	Almost all are heavy smokers	Smoking hsitory common	56% had mild emphysema
PET-CT findings	High uptake (SUVmax 16) : diffuse pattern	Strong FDG uptake, hypermetabolic masses	Not described	Intense FDG uptake (SUVmax 13.5) : diffuse
Radiological pitfalls	Mimics lymphoma, germ cell tumors	May resemble sarcoma or NUT carcinoma	Mimics hepatocellular or hepatoid tumors	Mimics other adenocarcinomas

Abbreviations: SD-UT - Thoracic SMARCA4 deficient undifferentiated tumor; SD-NSCLC - SMARCA4 deficient non-small cell carcinoma; LN - Lymph node; M1 – Metastasis.

Histopathology & immunohistochemistry

Thoracic SMARCA4-Deficient Undifferentiated Tumor

These lesions show sheets of dyscohesive tumor cells arranged in sheets (Figs. 1A & 1B). Tumor cells are often present in perivascular location (Fig. 1C). Tumor cells comprise undifferentiated round to ovoid and polygonal cells. Epithelioid and rhabdoid morphology tumor cells are seen often (Fig. 1D). Rhabdoid cells show eccentric nuclei with abundant eosinophilic cytoplasm (Fig. 1D). Individual tumor cell nuclei show moderate pleomorphism with vesicular nuclei and prominent nucleoli. Cytoplasmic inclusion is seen sometimes. Desmoplastic or myxoid stroma is described. Brisk mitotic activity is seen. Extensive necrosis is seen often. No glandular or squamoid differentiation is seen.

Histopathological findings are highlighted in the Summary box 1.

On immunohistochemistry, tumor cells show focal positivity for cytokeratin (Fig. 1E) and epithelial membrane antigen (EMA). SOX2 (Fig. 1F) is uniformly positive in all cases. SALL4 and CD34 (Fig. 1G) are often positive in tumor cells. SMARCB1 is retained in tumor cells.

The diagnostic marker is SMARCA-4 (BRG1) which shows loss of expression in tumor cells (Fig. 1H). For the diagnostic marker SMARCA-4 (BRG1), a severe reduction should also be considered. Co-loss of SMARCA2 is often seen, but is not a diagnostic marker [31-34].

Architecture
Solid growth in irregular sheets, nests, or syncytial islands.
Focal alveolar, reticular-myxoid, or desmoplastic patterns.

Cell Morphology
Epithelioid to round, discohesive cells.
Rhabdoid features: eosinophilic cytoplasm, eccentric nuclei, hyaline inclusions.

Cytological Features
Monotonous cells, mild/moderate pleomorphism.
Vesicular chromatin, prominent nucleoli, occasional giant cells.

Mitotic Activity
Brisk mitotic figures (3-12/HPF).
Indicates high proliferative index.

Necrosis
Extensive, geographic necrosis.
Apoptotic debris commonly seen.

Stromal Features
Focal desmoplastic or myxoid stroma.
Induces reticular or cord-like arrangements.

Differentiation
No glandular, squamous, neuroendocrine, or mesenchymal features.
Confirms undifferentiated nature.

Summary box 1. Histopathological findings of SMARCA4-dUT.

Immunohistochemistry findings are highlighted in the Summary box 2.

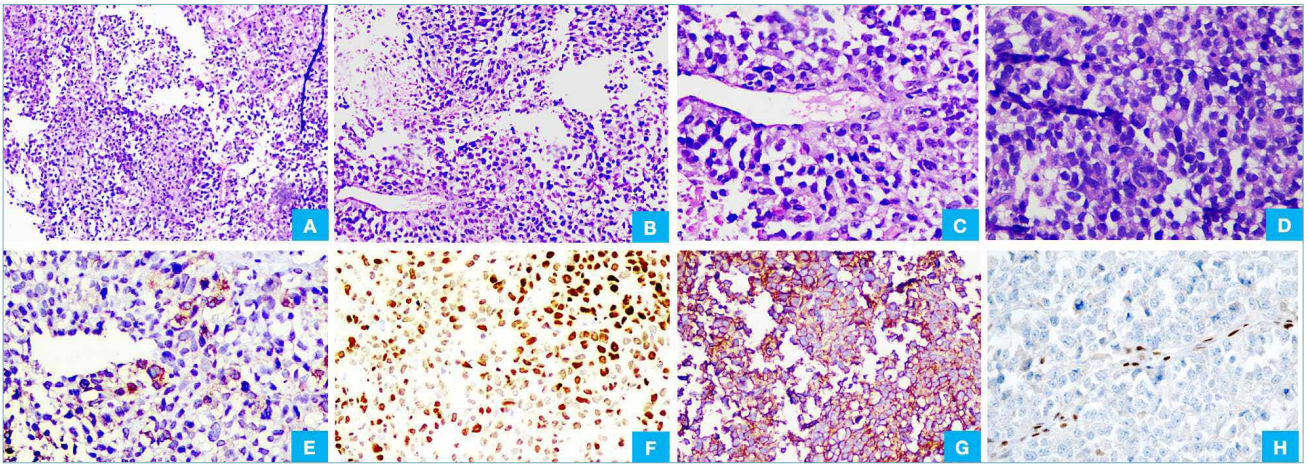

Figure 1. Biopsy from thoracic mass.(A) & (B) H&E (100X) images showing a highly cellular lesion with tumor cells arranged in sheets. (C) Tumor cells are arranged in perivascular location. (D) Individual tumor cells are round to epithelioid, they have moderate to abundant eosinophilic cytoplasm with eccentric nuclei. Rhabdoid cells with cytoplasmic inclusion is seen. (E) Immunohistochemistry for pan-cytokeratin is focally positive. (F) SOX2 is diffusely positive. (G) CD34 is diffusely positive. (H) SMARCA4 (BRG1) shows loss of nuclear expression (internal control is positive).

Core Diagnostic Markers
- SMARCA4: Complete loss or severe global reduction
- SMARCA2: Lost in most cases
- Claudin-4: Negative or very focally weak
- SOX2: Strong, diffuse expression in most cases

Epithelial Markers
- Cytokeratins (AE1/AE3, CAM5.2, KL1): Weak/focal in 60–80%
- EMA: Patchy to diffuse expression
- TTF-1/p40/p63: Rare focal positivity

Stem Cell & Other Markers
- CD34: Positive in ~60–63%, sometimes diffuse
- SALL4: Focal positivity in ~30–35%
- CD99: Variable (30–40%)
- Vimentin: Strongly positive

Neuroendocrine/Proliferation Markers
- Synaptophysin: Positive in ~18–71%, may mimic NEC
- Ki-67: High proliferation (mean 79%)
- p53: Overexpressed in ~70% (>90% nuclei)

Retained or Negative Markers
- SMARCB1 (INI1): Retained in all cases
- MMR proteins (MSH6/PMS2): Retained
- Negative: Desmin, S-100, NUT, CD56, WT1, HMB45, Melan A, CI

Summary box 2. Immunohistochemistry findings of SMARCA4-dUT.

SMARCA4-Deficient Non-Small Cell Lung Carcinoma

These tumors are characterized by predominantly solid and nested growth pattern (Fig. 2A), and frequent rhabdoid/ undifferentiated features. Focal glandular, papillary, or mucinous differentiation can be present but is typically limited. A prominent inflammatory background and stromal variability (desmoplasia, myxoid areas) may contribute to diagnostic complexity (Fig. 2B). Necrosis may be present (Fig. 2C).These tumors often show cohesive epithelioid cells with striking nuclear features and mimic various poorly differentiated neoplasms (Fig. 2D).

Histopathological findings have been highlighted in Summary box 3.

On immunohistochemistry, the tumors typically express at least one epithelial marker, most commonly pan-cytokeratin (Fig. 2E) and/or EMA, often in a diffuse and strong manner. In rare instances, rhabdoid variants lack CK7 and pan-cytokeratin but show isolated or strong EMA positivity. HepPar-1 is positive in the majority of cases, showing a granular cytoplasmic pattern typical of hepatocellular differentiation. TTF-1 is focally positive in a few cases. Notably, when HepPar-1 is positive, TTF-1 is typically absent, indicating a hepatoid-like profile in some tumors. Neuroendocrine markers like synaptophysin, chromogranin and INSM1(Fig. 2F) may be focally positive. Markers associated with hepatocyte differentiation, such as AFP, glypican-3 may be focally positive. p53 often shows diffuse strong positiv-

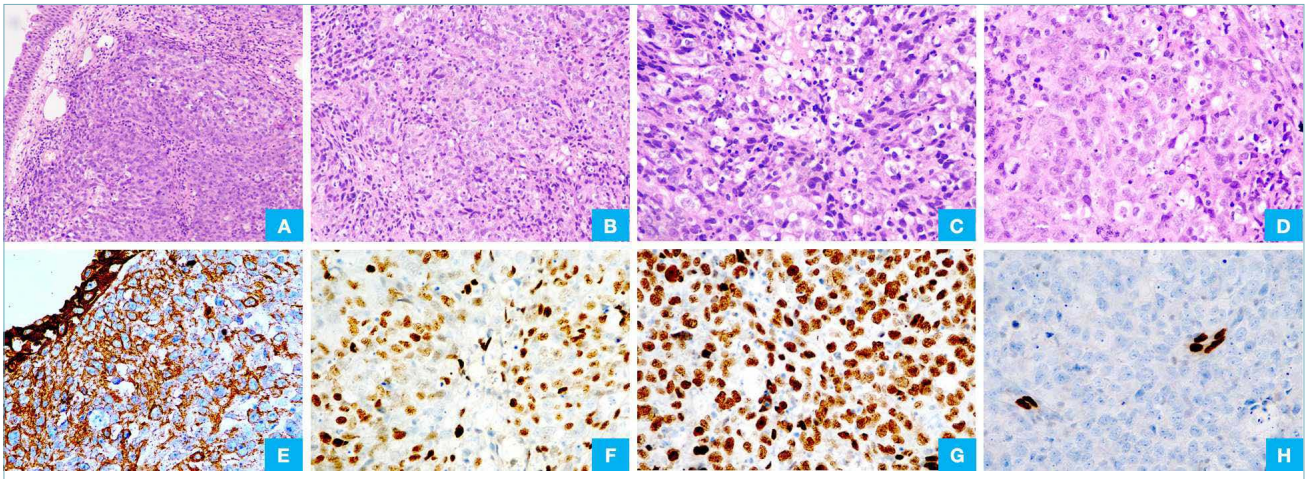

Figure 2. Biopsy from lung mass. (A) H&E (40x) image shows squamous lined epithelium with underlying area shows a cellular tumor. Tumor cells arranged in nests. (B) H&E (100X) images shows nests of tumor cells with interspersed inflammatory cells. (C) Higher magnification (200x) images showing tumor cells with cytoplasmic clearing. Necrosis and apoptotic bodies are seen. (D) Higher magnification (400x) reveals tumor cells having moderate amount of indistinct eosinophilic cytoplasm, round to polygonal nuclei and prominent nucleoli. Numerous plasma cells are also noted. (E) Pan-cytokeratin shows diffuse weak expression. (F) INSM1 is positive in tumor cells. (G) p53 is diffusely positive. (H) SMARCA4 (BRG1) shows loss of nuclear expression in tumor cells (internal control is positive).

Architecture
- Predominantly solid pattern in most cases
- Focal glandular, acinar, or papillary formations in some
- Mucinous adenocarcinoma with prominent mucin pools in rare cases

Rhabdoid Features
- Focal rhabdoid morphology with polygonal, dyscohesive cells
- Pseudo-alveolar arrangements and intermingling with glandular areas
- Completely undifferentiated rhabdoid phenotype in some tumors

Cytologic Features
- Epithelioid ovoid/polygonal cells with eosinophilic or clear cytoplasm
- Large, irregular nuclei with vesicular chromatin and prominent nucleoli
- Occasional hyaline globules and mucin-containing cells

Stroma & Inflammatory Response
- Focal desmoplastic or myxoid stromal changes in a subset
- Inflammatory infiltrates: mononuclear or granulocytic
- Emperipolesis and abundant neutrophils in some cases

Necrosis & Differentiation
- Extensive geographic necrosis universally observed
- Most tumors lacked well-differentiated features
- Rare focal mucinous or glandular differentiation

Summary box 3. Histopathological findings of SMARCA4-dNSCLC.

ity (Fig. 2G). SALL4 can also be focally positive in a few tumors (each in % of neoplastic cells). Dual loss of SMARCA4 (Fig. 2H) and SMARCA2 is observed in some cases, while others showed reduced SMARCA2 expression. SMARCB1 (INI-1) is retained in all cases. All cases are negative for NUT, ALK-V, and ROS-1, ruling out NUT carcinoma and familiar targetable oncogenic drivers [24,35,39]. Immunohistochemistry findings are highlighted in Summary box 4.

SMARCA4-dNSCLC Immunohistochemistry

Epithelial Markers
- Pan-cytokeratin and/or EMA: Diffuse and strong in most cases
- CK7: Strongly positive in 90% of cases
- Rare focal positivity or loss in rhabdoid variants

Hepatoid Features
- HepPar-1: Positive in 85% of cases with granular cytoplasmic pattern
- TTF-1: Negative in 90%, often mutually exclusive with HepPar-1
- AFP, Glypican-3 : Focal (<5%) in few tumors

Neuroendocrine & Stem Cell Markers
- Synaptophysin: Positive in 12–18%, usually focal or weak
- SALL4: Positive in ~7% of cases
- CD34: Rarely positive (~3%)

Proliferation & SWI/SNF Complex
- Ki-67: Proliferation index ranged 30–90%
- SMARCA4: Completely lost in all cases
- SMARCA2: Lost or variably reduced in most
- SMARCB1 (INI-1): Retained in all

Lineage & Driver Markers
- TTF-1, Napsin A: Expressed in a minority of cases
- p63, p40, CK5/6: Occasionally positive
- NUT, ALK-V, ROS-1: Negative in all cases

Summary box 4. Immunohistochemistry markers of SMARCA4-dNSCLC. Abbreviations: EMA - Epithelial Membrane Antigen; TTF1 - Thyroid Transcription Fcator 1; AFP - Alpha Feto Protein, HepPar1 - Hepatocyte Paraffin 1; ALK V - Anaplastic Lymphoma Kinase Ventana; ROS1 - ROS protooncogene 1, receptor tyrosine kinase.

Molecular findings

Molecular signatures

Thoracic SMARCA4-UT shows inactivating mutations or complete loss of SMARCA4 (BRG1), mainly through truncating mutations or biallelic loss. Frequent co-deficiency of SMARCA2 (BRM) is observed. SMARCA4-UT also shows freqent mutations in TP53, KRAS, KEAP1, STK11, NF1 and CDKN2A. These genetic alterations are usually seen in smoking-related NSCLC patients with typical tobacco-related mutational signatures. These tumors show a high tumor mutation burden (TMB), which supports the contribution of smoking-associated genetic change.

Transcriptomic analyses revealed a similar association between SMARCA4-UTs and other rhabdoid tumors like malignant rhabdoid tumors (MRTs) and small cell carcinoma of the ovary, hypercalcemic type (SCCOHT). However SMARCA4-UTs were molecularly distinct from conventional NSCLCs. These tumors often overexpress stemness-signature genes like SOX2 and SALL4. Germline SMARCA4 mutations are usually not seen, which helps distinguish it from pediatric rhabdoid tumors.

These tumors lack oncogenic driver genes such as ALK, ROS1 and NUT (targetable genes). Overall,

Core Alterations
- SMARCA4 inactivation via truncating mutations or biallelic loss
- SMARCA2 co-loss in most cases
- SMARCB1 (INI1) retained

Mutational Profile
- Frequent mutations in TP53, KEAP1, STK11, KRAS, CDKN2A
- NF1 alterations also noted
- Associated with smoking-related mutational signature

Tumor Mutation Burden
- High TMB: Mean ~14.2 mutations/Mb
- Reflects tobacco-associated genomic damage

Transcriptomics & Expression
- Similar transcriptome to MRTs and SCCOHT
- Upregulation of stemness genes: SOX2, SALL4
- Distinct from conventional NSCLC at RNA level

Negative Markers / Other Notes
- Negative for ALK, ROS1, NUT, and MMR deficiency
- No germline SMARCA4 mutations detected
- No oncogenic driver alterations

Summary box 5. Molecular findings of SMARCA4-dUT. Abbreviations: CDKN2A-cyclin-dependent kinase inhibitor 2A; NF1- Neurofibromatosis 1; MRT- Malignant Rhabdoid Tumor; SCCOHT - Small Cell Carcinoma Of Ovary Hypercalcemic Type.

these findings reinforce this entity as genetically distinct [31-34,40,41].

Molecular findings of SMARCA4-UT are highlighted in Summary box 5.

SMARCA4-deficient NSCLCs are also characterized by inactivating mutations or complete loss of SMARCA4, through truncating mutations or biallelic deletions. TP53 mutations are present in a large number of cases, often co-occurring with SMARCA4 alterations. Additional mutations detected are KRAS, STK11, KEAP1, FGFR3, MYC, HRAS, CTNNB1, and ERBB2, reflecting a complex and smoking-related mutational landscape. Non-small cell carcinomas with SMARCA4 mutation are mutually exclusive with ALK, ROS1, EGFR, MET or RET mutation. SMARCB1 (INI1) mutation is not seen, but SMARCA2 was frequently co-losted or reduced [24,35,40,41].

Clinical Outcome Correlation With Molecular Signatures

Both thoracic SMARCA4-UT & SMARCA4-dNSCLC show truncating mutation or biallelic deletion of SMARCA4, which is associated with dismal prognosis and rapid disease progression [42]. Co-occurrence of other mutations like, TP53, STK11, amd KEAP1, are associated with therapeutic resistance, poor outcome and decreased overall survival [43]. SMARCA4 deficiency with co-deficiency of SMARCA2 or upregulation of stemmness-related genes (like SOX2, CD34, SALL4 etc) display more aggressive clinical course and shorter overall survival [44,45].

Clinical Stratification

A salient imminent parameter for clinical stratification in SMARCA4-deficient tumors is the mutant allele frequency (MAF), which reveals the allele burden/clonal burden and heterogeneity of somatic mutations [28]. Higher MAF values of SMARCA4 mutations, especially truncating variants, have been associated with more aggressive histopathologic features and adverse clinical outcomes, demonstrating a possible usefulness in prognostic scoring [42]. Integrating MAF with co-mutation profiles (e.g., TP53, KRAS, STK11) may refine risk stratification and identify patients who are less likely to benefit from immunotherapy or traditional chemotherapy [43]. Additionally, liquid biopsy, via analysis of circulating tumor DNA (ctDNA), offers a minimally invasive approach to dynamically assess MAF, monitor treatment response, and detect minimal residual disease [46]. ctDNA-based quantification of SMARCA4 MAF, alongside TMB and co-mutation signatures, could become a pivotal component of real-time patient stratification and precision oncology workflows for these otherwise treatment-refractory tumors [46].

Methodological considerations

Adherence to standard technical protocols and quality control matrics are necessary for meticulous interpretation of molecular alterations. The key parameters that are to be checked are: nucleic acid extraction purity (A260/A280 should be 1.7 to 2.0), quantification threshold (Qubit or Bioanalyzer), DNA integrity (DIN) for sequencing assays [47-50]. Next Generation Sequencing (NGS) test panels should be validated for coverage depth (≥500x for hotspot regions), uniformity, and mutation variant allele frequency (typically VAF % for reliable variant calls) [51]. Standardized variant annotation using databases such as ClinVar, COSMIC, and dbSNP is crucial for clinical interpretation [52]. In addition, integration with immunohistochemical loss of SMARCA4/BRG1 expression confirms functional deficiency and enhances diagnostic specificity [53]. Institutional or national guidelines, such as those from the College of American Pathologists (CAP), Association for Molecular Pathology (AMP), and ISO 15189-accredited laboratories, should be followed for quality assurance [54-56]. These measures are critical for ensuring the reproducibility and translational relevance of molecular data in both clinical diagnostics and therapeutic decision-making.

Differential diagnosis

The differential diagnosis for thoracic SMARCA4-UT encompasses a wide variety of tumors. It includes poorly differentiated carcinoma (including metastasis), melanoma, large cell lymphoma, germ cell tumor, high-grade neuroendocrine carcinoma, NUT carcinoma, melanoma, epithelioid sarcoma, undifferentiated sarcoma with epithelioid morphology (epithelioid MPNST, CIC-rearranged sarcoma, epithelioid inflammatory myofibroblastic sarcoma, epithelioid angiosarcoma, etc.), thymic carcinoma, epithelioid mesothelioma, etc. TTF-1 or p40 diffuse positivity will help rule out primary lung adenocarcinoma or squamous cell carcinoma [57,58,59]. LCA, CD3, CD20, and CD30 can be used for large-cell lymphoma [60]. Melanoma will express melanocytic markers like S100, HMB45, melan-A, SOX-10 etc, and germ cell tumors will express SALL4 [61,62]. Neuroendocrine carcinomas are positive for pan-cytokeratin, Synaptophysin, chromogranin and INSM1 [63,64]. Occasionally, neuroendocrine markers can be focally positive in SMARCA-4 and SMARCB1 deficient tumors, which is a pitfall [65,66]. NUT carcinoma is positive for NUTM1, p63 and p40 [67,68]. Epithelioid sarcoma shows loss of expression of SMARCB1 [69]. Epithelioid MPNST will show strong positivity for S100 and SOX10 and

show SMARCB1 loss of expression [70,71]. CIC-rearranged sarcoma show positivity for WT1, ETV4, and DUX4 [72,73]. EIMS shows positivity for desmin, CD30 and ALK [74,75]. Epithelioid angiosarcoma will be positive for ERG, CD31, CD34 and variably CK [76,77]. Thymic carcinoma will be positive for cytokeratin, CD5, CD117, and p40 [78]. Epithelioid mesothelioma will be positive for CK, WT1, calretinin, etc [79].

SMARCA4-dNSCLC can be confused with adenocarcinoma or squamous cell carcinoma. TTF1 and p40 are negative in most of the cases, with the diagnostic marker being SMARCA4. Positive staining for Hep-Par1 may be mistaken for metastatic hepatocellular carcinoma or hepatoid adenocarcinoma.

Relation Between SMARCA4-UT & SMARCA4-dNSCLC

Both entities are characterized by SMARCA-4 mutation; there are some similarities and differences between them. SMARCA4-dNSCLC retains at least partial differentiation of epithelial origin compatible with carcinoma (e.g., glandular or squamous), whereas SMARCA4-UT is purely undifferentiated and rhabdoid or sarcomatoid in appearance [24,34]. SMARCA4-dNSCLC cases generally express epithelial markers (CK7, EMA, TTF-1), while SMARCA4-UTs show loss or minimal expression of epithelial markers and gain of stem cell markers (CD34, SOX2), suggesting dedifferentiated phenotype [33].

Table II. Comparison between thoracic SMARCA4 deficient undifferentiated tumor (SMARCA4-dUT) and SMARCA4 deficient non-small cell carcinoma (SMARCA4-dNSCLC)

Features	SMARCA4-dUT	SMARCA4-dNSCLC
WHO classification	Distinct entity in WHO 2021 Thoracic tumors	Not a distinct WHO entity
Age group	Younger to middle aged adults (40-60 years age)	Usually older adults (>60 years age)
Gender	Strong male preponderance	Not such
Smoking history	Heavy smokers	Often smokers, nonsmokers can also be affected
Symptoms	Usually rapidly progressive respiratory symptoms, chest pain, dyspnea, weight loss	Gradual onset of symptoms
Location	Mediastinal or parenchymal mass that involves chest wall, pleura, hilum etc.	Primarily intrapulmonary lesion
Appearance	Poorly circumscribed & lobulated mass with hemorrhage and necrosis	Usually solitary pulmonary nodule with well-defined borders
Pleural/chest wall invasion	Very common	Common
Metastasis	Lymph nodes, bones, adrenal glands, liver, peritoneum, soft tissue, and even brain Peritoneal and unusual soft tissue site metastasis is very common	Lymph nodes, brain, bones, adrenal glands, liver Peritoneal and unusual soft tissue metastasis is rare
Histology	Undifferentiated/Rhabdoid morphology; lacks glandular or squamoid pattern	Solid, nested, glandular or squamoid morphology is common; undifferentiated/rhabdoid is very infrequent
Immunohistochemistry	1. SMARCA4 loss of expression 2. SMARCA2 (BRM) often loss of expression 3. Positive for stemness markers (SOX2, SALL4, CD34) 4. Epithelial markers often negative/patchy positive (CK, EMA, Claudin-4) 5. TTF1, p40 negative	1.SMARCA4 loss of expression 2. SMARCA2 (BRM) often retained 3. Stemness markers maybe very focally positive 4.Epithelial markers often positive (CK, EMA, Claudin-4) 5. TTF1, p40 usually negative but focal expression/diffuse expression can be present in some cases
Genetics	TP53, KRAS, STK11, KEAP1 SMARCA2 concurent loss is seen	Similar (TP53, KRAS, STK11, KEAP1 being common) SMARCA2 concurrent loss is usually not seen
Prognosis	Vey aggressive, poor prognosis	Less aggressive than SMARCA4-dUC
Treatment	Chemoresistant; limited targeted therapy options available; Immune checkpoint inhibitors are being explored	May respond to platinum-based chemotherapy and immunotherapy depending on biomarkers

Both tumor types share a smoking-related mutational background and overlapping alterations in TP53, STK11, KRAS, and KEAP1, suggesting a shared lineage. However, the phenotypic divergence is marked by the co-loss of SMARCA2 and the emergence of a stem-like profile in UTs [24,34].

SMARCA4-UTs display a strikingly more aggressive nature, rapid progression, and resistance to therapies, emphasizing the need to be considered separately from SMARCA4-dNSCLCs.

It is proposed that SMARCA4-UTs may represent an extremely de-differentiated endpoint of SMARCA4-dNSCLCs or arise de novo from stem-like precursor cells in smokers, rationalizing their classification as a distinct yet related entity.

Comparison between these entities is highlighted in Table II.

Prognosis

SMARCA4-UTs show dismal prognosis with median overall survival averaging 4-7 months [25]. The median overall survival of SMARCA4-dNSCLC was 5.2 months in one study[80]. and 7.8 months in another [35].

Treatment and Current Perspectives

There are no standard guidelines for treatment of SMARCA-4 deficient tumors [81]. Patients have limited treatment options and poor prognosis. Surgery is only effective in early-stage (Stage I) patients, with high recurrence rates even after complete resection [82,83]. Chemotherapy, typically platinum-based regimens (paclitaxel and carboplatin), show minimal response and short survival outcomes [84]. Radiotherapy is generally ineffective. Immune checkpoint inhibitors (ICIs) like pembrolizumab, nivolumab, and ipilimumab have demonstrated promising responses, even in PD-L1–negative patients, making these ICIs as encouraging options [85,86]. Immune checkpoint inhibitors combined with chemotherapy may offer better response [86].

Novel targeted therapies are emerging in SMARCA4-deficient tumors. Sensitivity to CDK4/6 inhibitors increases in tumors with loss of SMARCA4 or SMARCA2. Abemaciclib (CDK4/6 inhibitor) is indicated in advanced breast cancer, and being tested in lung cancer. Tumors with SMARCA4 mutation show OXPHOS overexpression. OXPHOS inhibitor (IACS-010759) inhibits OXPHOS and cause cell death. $KRAS^{G12C}$ mutation is associated with poor outcome in NSCLC. KRAS inhibitors like sotorasib, adagrasib, garsorasib, and divarasib show good clinical outcomes. KEAP1 deficiency leads to sensitization to ATM inhibition. Novel ATM inhibitors are in phase I trial. AXL is a receptor tyrosine kinase that is frequently overexpressed in tumors. Bemcentinib (AXL inhibitor) restores pembrolizumab sensitivity of STK11/LKB1 mutant non-small cell lung cancer. Bromodomain and Extra-Terminal Domain Protein Inhibitor (BETi) shows antitumor activity in lung cancer. BETi also increases the sensitivity of tumor cells to $CD8^+$ T cells. BETi repressed tumor growth in SMARCA4/SMARCA2-deficient lung cancer model. Aurora kinase A (AURKA) helps in mitotic spindle assesmbly and cell survival in SMARCA4-deficient tumors. Alisertib (AURKA inhibitor) showed promising results in solid tumors. PARP inhibitor (veliparib, olaparib, nirapanib etc.)in combination with radiotherapy shows a synergistic effect in the treatment of SWI/SNF mutant tumors, and sensitizes lung cancer to PD-1 inhibitor immunotherapy. Histone deacetylase inhibitors (HDACi) can reinstate SMARCA2 expression in SMARCA2-deficient tumors. Vorinostat (HDACi) in combination with pembrolizumab enhances sensitivity to PD-1 inhibitor. Due to the inhibition of Polycomb group (PcG) proteins by the BAF complex, the loss of SMARCA4 and/or SMARCA2 leads to enhanced EZH2 activity, resulting in the activation of oncogenes and suppression of tumor suppressor genes. EZH2 inhibitors like tazemetostat JQEZ25, GSK126 have shown anti-proliferative and antitumor activity [87].

Epigenetic therapies targeting histone modification and chromatin remodeling also show therapeutic potential. Co-occurring mutations (e.g., TP53, KRAS, STK11) may impact treatment response, particularly to immune checkpoint inhibitors (resistance to treatment) [87,88]. Conversion surgery after immunotherapy has shown complete pathological responses in select cases [89]. However, standardized treatment guidelines and clinical trials for SMARCA4-UT are still lacking and urgently needed.

SMARCA4-dNSCLC patients who have truncating mutations of SMARCA4, show worse overall survival compared to SMARCA4-wild type patients and are unlikely to benefit from checkpoint therapy [90]. In SMARCA4-dNSCLC cases, the helicase domain of SMARCA4 constitutes novel missense mutations. There is strikingly reduced activity of chromatin remodeling in these missense mutants. When there is SMARC4 mutation (loss of SMARCA4), the cells depend excessively on its paralog SMARCA2. If SMARCA2 is blocked, the cells cannot grow further and will die. This is called synthetic lethality (Fig. 3) which can be used as therapeutic option in these tumors [90].

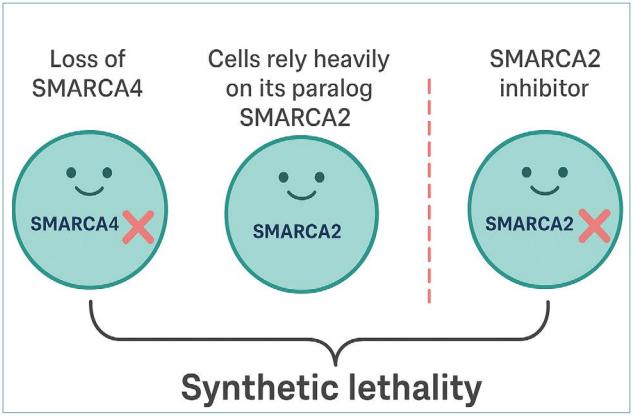

Figure 3. SMARCA4 and SMARCA2 synthetic lethality.

Conclusion

SMARCA4-deficient thoracic tumors are aggressive malignancies with distinct clinicopathological and molecular profiles. Clear distinction between SMARCA4-UT and SMARCA4-deficient NSCLC is essential due to differences in differentiation, behavior, and prognosis. Both are strongly linked to smoking-related mutations and lack effective targeted therapies. Emerging data on immunotherapy and epigenetic targets offer hope, but standardized treatment guidelines are still lacking.

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Conflict of interest statement

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Author Contributions

SD and PM were responsible for conception, design, data collection, analysis, interpretation amd writing the manuscript. SA was responsible for supervision.

Ethical consideration

As it is a review article, informed consent was waived off by the Institute Ethics Committee, Fortis Memorial & Research Institute, Gurugram.
As it is a review article and the records are retrospective, ethical approval was waived off by the Institute Ethics Committee, Fortis Medical & Research Institute, Gurugram.

Declaration Of Generative AI And AI-Assisted Technologies In The Writing Process

The authors took help of AI/AI assisted technlolgy like ChatGPT only for proper grammatical correction and for proper readability at some places.

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