

# SMARCA2 and SMARCA4 expression in epithelioid pleural mesothelioma: association with inflammatory microenvironment

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## ABSTRACT

**Aims:** To investigate the frequency of SMARCA2 and SMARCA4 loss in epithelioid pleural mesothelioma (pleural mesothelioma) and to evaluate their clinicopathologic correlates, with particular attention to the inflammatory tumor microenvironment.

**Methods:** This retrospective study included 64 patients who underwent surgery for epithelioid pleural mesothelioma between January 2007 and October 2019. Cases with biphasic histology, unavailable clinical data or tissue blocks, and early postoperative mortality were excluded. Clinicopathologic parameters (age, sex, stage, histologic pattern, necrosis, inflammation) were reviewed. Immunohistochemistry for SMARCA2 and SMARCA4 was performed using tissue microarrays using anti-SMARCA4 (clone EPNCIR111A, 1:100) and anti-SMARCA2 (clone D9E8B, 1:100). Loss of expression was defined as complete absence of nuclear staining in tumor cells in the presence of an internal stromal positive control. Statistical analyses were conducted using R (version 3.5.1). Associations between categorical variables were assessed using Chi-square or Fisher's exact tests; continuous variables were compared using Student's t-test or one-way ANOVA. Vendor and catalog number (SMARCA4): Abcam (Cambridge, UK), cat. no. orb513921. Vendor and catalog number (SMARCA2): Abcam (Cambridge, UK), cat. no. orb575109.

**Results:** The cohort comprised 51 men (79%) and 13 women (21%), with a mean age of 57.1±12 years (range, 30–91). Fifty-three patients (82.8%) underwent decortication and 11 (17.2%) extrapleural pneumonectomy. Most tumors were stage I (n=60, 94%), with 4 (6%) at stage II. Histologic patterns were tubulopapillary (n=33, 50%), trabecular (n=2, 3%), adenomatoid (n=11, 18%), solid (n=3, 6%), and micropapillary (n=15, 23%). Inflammation was mild in 58 cases (91%) and severe in 6 (9%); necrosis was present in 8 cases (12.6%). Loss of SMARCA2 and SMARCA4 expression was detected in 4 patients each (6% for both markers). SMARCA2 loss was significantly associated with severe inflammation (p=0.02), whereas no significant relationships were observed between SMARCA4 loss and age, sex, stage, histologic pattern, necrosis, or inflammation. Mean overall survival was 22 months; 2-year and 5-year overall survival rates were 35% and 6%, respectively. Neither SMARCA4 loss (p=0.33) nor SMARCA2 loss (p=0.88) had a significant impact on survival.

**Conclusion:** SMARCA2 and SMARCA4 loss are uncommon events in epithelioid pleural mesothelioma. However, in this small surgical cohort, SMARCA2 deficiency was associated with a more pronounced lymphocytic/inflammatory infiltrate; this observation should be considered exploratory and hypothesis-generating, and its clinical/biomarker relevance requires confirmation in larger, multi-institutional cohorts with survival and immune profiling.

**Keywords:** Mesothelioma, pleural neoplasms, chromatin remodeling, SMARCA2, SMARCA4, tumor microenvironment

## INTRODUCTION

The mammalian SWI/SNF (BAF) chromatin-remodeling complex is a multi-subunit assembly that uses ATP-dependent nucleosome mobilization to regulate chromatin accessibility and gene transcription, thereby playing key roles in cell differentiation, DNA repair, and tumor suppression.<sup>1,2</sup> Two mutually exclusive ATPase subunits, SMARCA4 (BRG1) and SMARCA2 (BRM), together with accessory subunits such as SMARCB1 and ARID1A, define distinct complex variants and confer tissue-specific functions.<sup>1,2</sup> Recurrent alterations in

SWI/SNF components have been documented across a broad spectrum of human malignancies and collectively account for a substantial fraction of cancers.<sup>1,2</sup>

Within the thorax, inactivating alterations of SMARCA4, frequently accompanied by SMARCA2 co-loss, define a group of highly aggressive neoplasms now termed SMARCA4-deficient undifferentiated thoracic tumors (SMARCA4-DUT), previously described as SMARCA4-deficient thoracic sarcomas.<sup>3,4</sup> The 5<sup>th</sup> edition of the World

Health Organization (WHO) Classification of Thoracic Tumours recognizes SMARCA4-DUT as a distinct entity separate from SMARCA4-deficient non-small cell lung carcinoma (NSCLC).<sup>5</sup> These tumors typically present as bulky intrathoracic masses with undifferentiated or rhabdoid morphology and carry a dismal prognosis despite multimodal therapy.<sup>3,5</sup>

Although SMARCA4-deficient thoracic tumors are an important differential diagnosis, our cases showed a mesothelial immunophenotype and lacked clinicopathologic features typical of SMARCA4-DUT sarcoma.

Malignant pleural mesothelioma (MPM) is an aggressive malignancy of mesothelial origin, strongly associated with asbestos exposure and characterized by limited therapeutic options and poor survival.<sup>6,7</sup> Genomic profiling studies indicate that MPM is driven predominantly by loss-of-function alterations in tumor suppressor genes such as BAP1, NF2, and CDKN2A, with less frequent involvement of SWI/SNF components including ARID1A and SMARCA4.<sup>6,8</sup> Standard diagnosis relies on morphology supported by immunohistochemistry, typically using mesothelial markers (calretinin, WT-1, cytokeratin 5/6, D2-40) together with carcinoma-associated exclusion markers (CEA, Ber-EP4, TTF-1).<sup>6,7</sup>

Data on SMARCA2 and SMARCA4 expression specifically in pleural mesothelioma are limited and somewhat conflicting. Perret et al.<sup>4</sup> reported SMARCA4 loss in a subset of epithelioid mesotheliomas in a series enriched for SMARCA4-deficient thoracic tumors, suggesting potential diagnostic overlap with SMARCA4-DUT. In contrast, Ahadi and Gill<sup>9</sup> found SMARCA4 loss to be very rare in thoracic mesothelioma, and Ren et al.<sup>10</sup> concluded that pleural malignant mesotheliomas generally do not show SWI/SNF complex deficiency.

In parallel, increasing evidence in other tumor types suggests that SWI/SNF deficiency may be associated with an inflamed or “hot” tumor microenvironment, characterized by increased tumor-infiltrating lymphocytes and, in some settings, enhanced sensitivity to immunotherapy.<sup>11,12</sup> In mesothelioma, chronic inflammation driven by asbestos fibers and the resulting immune dysregulation are central to pathogenesis and may influence response to treatment.<sup>6,7,12</sup>

In this context, we aimed to (i) determine the frequency of SMARCA2 and SMARCA4 loss in a single-institution cohort of epithelioid pleural mesotheliomas; and (ii) explore associations between SMARCA2/4 expression status and clinicopathologic features, with particular emphasis on the inflammatory infiltrate.

## METHODS

### Ethics

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Clinical Researches Ethics Committee of İstanbul Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital (Date: 01.07.2021, Decision No: 2021-130). Due to the retrospective design, informed consent was waived according to local regulations.

### Study Design and Patient Selection

This retrospective study included patients who underwent surgery for pleural mesothelioma at our institution between January 2007 and October 2019. A total of 107 patients with a diagnosis of pleural mesothelioma were initially identified from pathology archives.

Exclusion criteria were:

- biphasic mesothelioma (n=18);
- unavailable clinical data (n=2);
- unavailable histological material (slides or paraffin blocks) (n=20);
- death because of postoperative complications within the first 2 weeks after surgery (n=3).

After applying these criteria, 64 patients with epithelioid pleural mesothelioma and adequate clinical and pathologic data were included in the final analysis.

### Histopathologic Evaluation and Diagnosis

All cases were reviewed by thoracic pathologists. Diagnoses were established using standard histological criteria and immunohistochemistry. Calretinin, WT-1, cytokeratin 5/6, and D2-40 were used as positive markers supportive of pleural mesothelioma, whereas thyroid transcription factor-1 (TTF-1), carcinoembryonic antigen (CEA), and Ber-EP4 were used as negative markers to exclude metastatic carcinoma.

Histologic patterns in epithelioid mesothelioma were categorized as tubulopapillary, trabecular, adenomatoid, solid, or micropapillary. The presence and severity of inflammation (mild vs severe) and the presence of tumor necrosis (yes vs no) were recorded. Inflammation was assessed on hematoxylin-eosin sections as lymphoplasmacytic infiltrates within and/or surrounding tumor nests; mild inflammation was defined as scant to moderate, patchy infiltrates without dense aggregates, whereas severe inflammation was defined as brisk, diffuse or band-like infiltrates and/or prominent lymphoid aggregates. Scoring was performed by two pathologists blinded to SMARCA2/4 status; discrepancies were resolved by consensus.

Mitoses were counted per 2 mm<sup>2</sup>, and cases were stratified into three groups according to the mitotic count-based scoring system. A score of 1 was assigned to low mitotic activity, a score of 2 to intermediate mitotic activity, and a score of 3 to high mitotic activity. Specifically, the presence of a single mitosis was assigned a score of 1; two to four mitoses were assigned a score of 2; and five or more mitoses were assigned a score of 3.

TNM staging was performed according to the 8th edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual.

### Tissue Microarrays and Immunohistochemistry

Two 1 mm cores of representative tumor were taken from each case to construct tissue microarrays (TMAs). SMARCA4 and SMARCA2 immunohistochemistry was performed using a Ventana Benchmark platform using standardized protocols

provided by the manufacturer, with appropriate positive controls on each slide. Given the known heterogeneity of mesothelioma, representative regions were selected on review of whole sections prior to TMA construction, and cases showing loss on TMA were re-checked on whole-tissue sections when available to minimize sampling bias.

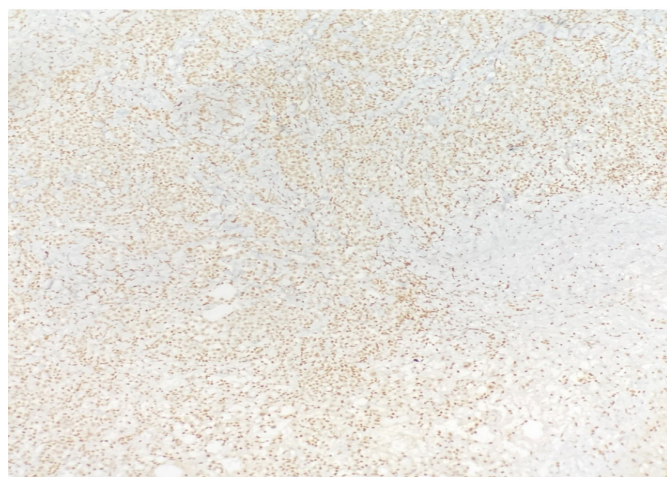
The following primary antibodies were used:

- anti-SMARCA4 (clone EPNCIR111A, 1:100 dilution);
- anti-SMARCA2 (clone D9E8B, 1:100 dilution).

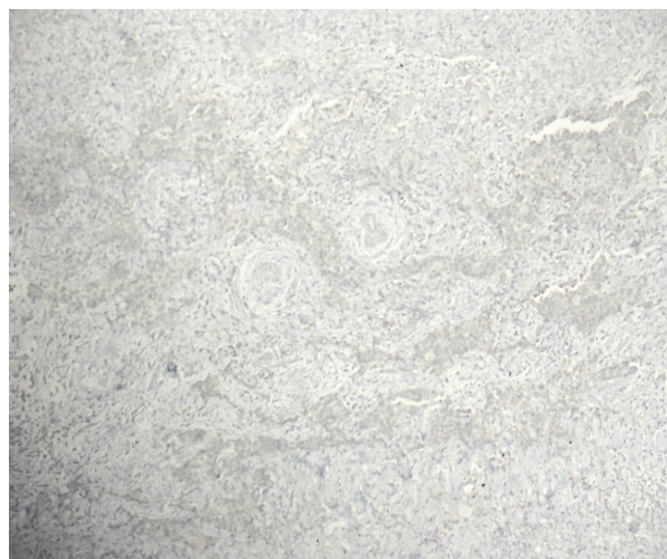
#### Interpretation of SMARCA2 and SMARCA4 Staining

Nuclear staining in tumor cells of any intensity was considered retained expression (positive) (Figure 1). Complete loss of expression was defined as total absence of nuclear staining in tumor cells in the presence of positive nuclear staining in adjacent non-neoplastic stromal or inflammatory cells, serving as an internal positive control (Figure 2).

Cases in which both tumor and internal control elements lacked nuclear staining were considered non-interpretable and were excluded from marker-specific analyses.



**Figure 1.** SMARCA4-positive nuclear staining in tumor cells of epithelioid pleural mesothelioma (immunohistochemistry, 20×)



**Figure 2.** Complete loss of SMARCA2 nuclear staining in tumor cells, with severe inflammatory infiltrate in the stroma (immunohistochemistry, 20×).

#### Clinicopathologic Parameters

Demographic data (age, sex), type of surgery [decortication (DC) vs extrapleural pneumonectomy (EPP)], and pathologic stage were retrieved from patient records. Histologic growth patterns, grade (where applicable), presence of necrosis, and inflammation (mild vs severe) were documented.

#### Statistical Analysis

All analyses were performed using R software (version 3.5.1; Bell Laboratories, Lucent Technologies, New Jersey, USA). Categorical variables were compared using Chi-square or Fisher's exact test, as appropriate. Continuous variables were analyzed using Student's t-test or one-way ANOVA. A p value <0.05 was considered statistically significant.

#### Survival Analysis

Overall survival (OS) was defined as the interval from the date of surgery to death from any cause or last follow-up. Progression-free survival (PFS) was defined as the interval from surgery to documented recurrence/progression or death, whichever occurred first. OS and PFS were estimated using the Kaplan–Meier method and compared using the log-rank test; because of the small number of SMARCA2-/SMARCA4-loss cases, subgroup comparisons were considered exploratory.

## RESULTS

#### Clinicopathologic Characteristics

Among the 64 patients included, 51 (79%) were male and 13 (21%) female. The mean age at diagnosis was  $57.1 \pm 12$  years (range, 30–91). Fifty-three patients (82.8%) underwent pleural decortication, and 11 patients (17.2%) had extrapleural pneumonectomy.

Forty-four patients (68.7%) were 65 years of age or younger, and 20 (31.3%) were older than 65 years. Most tumors were stage I (n=60, 94%), while 4 (6%) were stage II. Neither T category nor overall TNM stage was significantly associated with overall survival in univariate analysis, likely because of the highly homogeneous stage distribution of the cohort, in which 94% of patients had stage I disease.

Histologically, the predominant pattern was tubulopapillary in 33 cases (50%). Other patterns included trabecular in 2 (3%), adenomatoid in 11 (18%), solid in 3 (6%), and micropapillary in 15 (23%).

Inflammatory infiltrates were present in all cases and graded as mild in 60 patients (94%) and severe in 4 (6%). Tumor necrosis was identified in 8 cases (12.6%).

#### SMARCA2 and SMARCA4 Expression

Loss of SMARCA2 nuclear expression was observed in 4 of 64 cases (6%), while loss of SMARCA4 nuclear expression was also observed in 4 cases (6%) (Table 1). No case showed combined complete loss of both SMARCA2 and SMARCA4 in interpretable cores. Non-interpretable cases for a given marker were excluded only from that specific analysis.

#### Association with Clinicopathologic Parameters

There was no significant association between SMARCA2 loss and age, sex, follow-up time, tumor grade, type of surgery, or

**Table 1.** Demographic and clinicopathological details of the study population (n=64)

Variables	Value
Age, years <sup>a</sup>	57.1±12
<65	44 (67)
Gender, (male), n (%)	51(79)
<b>Histopathologic subtype, n (%)</b>	
Tubulopapillary	33 (50)
Trabecular	2 (3)
Adenomatoid	11 (18)
Solid	3 (6)
Micropapillary	15 (23)
The presence of necrosis, n (%)	8 (12)
The presence of SMARCA2, n (%)	60 (94)
The presence of SMARCA4, n (%)	60 (94)
<b>The presence of nuclear atypia, n (%)</b>	
Mild	14 (22)
Moderate	27 (42)
Severe	23 (36)
<b>The presence of mitosis, n (%)</b>	
Low	29 (45)
Intermediate	18 (28)
High	17 (27)
<b>The presence of inflammation</b>	
Mild	58 (91)
Severe	6 (9)
<b>The grade of mesotheliomas</b>	
Low	49 (76)
High	15 (24)
<b>Stage, n (%)</b>	
I	60 (94)
II	4 (6)
<b>Surgical procedure, n (%)</b>	
EPP	11 (17)
PD	53 (83)

a: Results given as mean±SD; n: Number of cases, SMARCA4, A2; EPP: Extrapleural pneumonectomy, PD: Pleurectomy/decortication

stage. However, SMARCA2 loss was significantly associated with severe inflammation, with SMARCA2-deficient cases more frequently displaying marked lymphocytic infiltrates compared with SMARCA2-retained tumors (p=0.02) (Table 2).

SMARCA4 loss showed no statistically significant relationships with age, sex, follow-up duration, tumor grade, type of surgery, stage, necrosis, or inflammation intensity (Table 3).

**Survival Analysis**

At the time of analysis, all patients had died. The mean overall survival (OS) was 22 months, with 2-year and 5-year OS rates of 35% and 6%, respectively. Stage-specific 5-year OS was 10% for stage I, whereas no 5-year survivors were observed in stage II.

In the SMARCA2-deficient group, the median OS was 24 months and the 5-year OS rate was 17%, while no 5-year survivors were observed among SMARCA2-retained cases; however, SMARCA2 loss was not significantly associated with OS (log-rank p=0.88) (Figure 3).

In the SMARCA4-deficient group, the median OS was 23 months and the 5-year OS rate was 13%, whereas no 5-year survivors were observed among SMARCA4-retained cases; SMARCA4 loss was not significantly associated with OS (log-rank p=0.33) (Figure 4).

**Table 2.** Univariate analysis of variables in patients with mesothelioma between SMARCA2 positive and SMARCA2 negative group

Variables	SMARCA2-positive (n=60)	SMARCA2-negative (n=4)	p value
Age, years <sup>a</sup>	57.5±12.8	52.1±9.4	0.35
Male sex, n (%)	47 (78)	4 (100)	0.39
Presence of necrosis, n (%)	8 (16)	0 (0)	0.90
<b>Nuclear atypia, n (%)</b>			0.079 <sup>+</sup>
– Mild	11 (18)	3 (75)	
– Moderate	27 (45)	0 (0)	
– Severe	22 (37)	1 (25)	
<b>Mitotic index, n (%)</b>			0.165 <sup>+</sup>
– Low	26 (44)	3 (75)	
– Intermediate	17 (33)	1 (25)	
– High	17 (33)	0 (0)	
<b>Inflammation, n (%)</b>			0.02
– Mild	57 (95)	3 (75)	
– Severe	3 (5)	1 (25)	
<b>Tumor grade, n (%)</b>			0.56
– Low	45 (75)	4 (100)	
– High	15 (25)	0 (0)	
<b>Stage, n (%)</b>			0.23
– I	57 (95)	3 (75)	
– II	3 (5)	1 (25)	
<b>Surgical procedure, n (%)</b>			0.13
– Pleurectomy/decortication (PD)	51 (85)	2 (50)	
– Extrapleural pneumonectomy (EPP)	9 (15)	2 (50)	
Follow-up time, months <sup>b</sup>	18.5 (9.0–31.7)	10.0 (4.5–56.7)	0.49

a: Results given as mean±SD, b: Results given as median (interquartile range (IQR)), n: Number of cases, +one-way ANOVA tests, SMARCA2, -; EPP: Extrapleural pneumonectomy, PD: Pleurectomy/decortication

Survival outcomes: Given the low number of SMARCA2-/SMARCA4-loss cases and limited events, subgroup comparisons should be interpreted as descriptive/exploratory.

**DISCUSSION**

In this single-institution cohort of epithelioid pleural mesothelioma, we found that SMARCA2 and SMARCA4 loss were relatively rare events (6% each). Importantly, SMARCA2 loss, but not SMARCA4 loss, was associated with a marked inflammatory infiltrate in the tumor microenvironment.

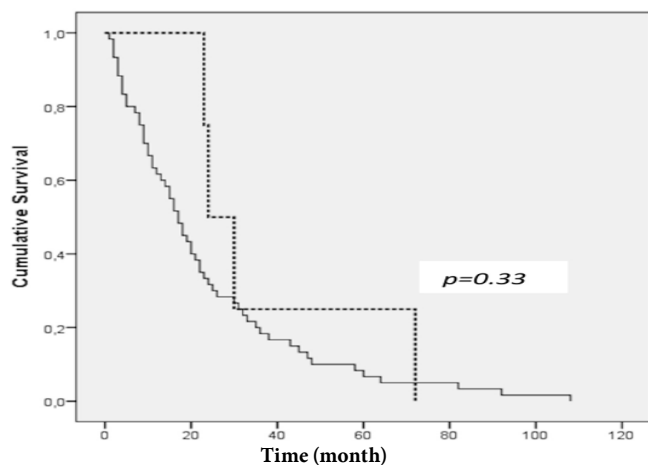
**Frequency of SMARCA2/SMARCA4 Loss**

Our findings are broadly consistent with prior work suggesting that SWI/SNF deficiency is uncommon in conventional pleural mesothelioma. Perret et al.<sup>4</sup> described SMARCA4-deficient thoracic sarcomas and reported SMARCA4 loss in a subset of mesotheliomas in a series that also included SMARCA4-DUT, raising diagnostic considerations at the interface of these entities. Ahadi and Gill,<sup>9</sup> in a larger series of 296 mesotheliomas, identified SMARCA4 loss in only two epithelioid cases (0.7%) and did not observe SMARCA2 loss. Ren et al.<sup>10</sup> subsequently reported that pleural malignant mesotheliomas generally do not demonstrate SWI/SNF complex deficiency, arguing against a major role of core SWI/SNF subunit loss in typical mesothelioma biology.

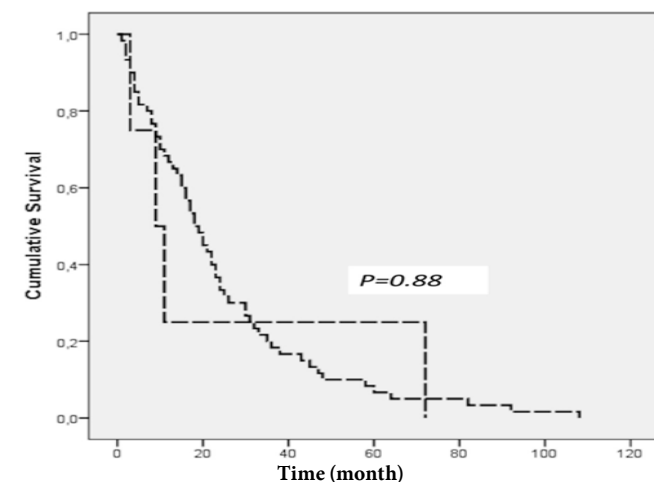
**Table 3.** Univariate analysis of variables in patients with mesothelioma between SMARCA 4 positive and SMARCA 4 negative group

	Patients with SMARCA 4 (+) (n=60)	Patients with SMARCA 4 (-) (n=4)	P value
Age, years <sup>a</sup>	56.8±12	62.5±10	0.31
Gender (Male), n, (%)	47 (78)	4 (100)	0.39
The presence of necrosis, n (%)	8 (16)	0 (0)	0.57
<b>The presence of nuclear atypia, n (%)</b>			
Mild	13 (22)	1 (25)	0.76+
Moderate	26 (42)	1 (25)	
Severe	21 (36)	2 (50)	
<b>The presence of mitosis, n (%)</b>			
Low	28 (46)	1 (25)	0.64+
Intermediate	16 (31)	2 (50)	
High	16 (31)	1 (25)	
<b>The presence of inflammation, n (%)</b>			
Mild	55 (91)	3(75)	0.33
Severe	3 (9)	1 (25)	
<b>The grade of mesotheliomas, n (%)</b>			
Low	45 (75)	4 (100)	0.33
High	15 (25)	0	
<b>Stage, n (%)</b>			
I	57 (95)	3 (75)	0.23
II	3 (5)	1 (25)	
<b>Surgical procedure, n (%)</b>			
EPP	51 (85)	2 (50)	0.13
PD	9 (15)	2 (50)	
Follow-up period(month) <sup>b</sup>	17 (9-31.7)	27 (23-61)	0.09

a: Results given as mean±SD, b: Results given as median (interquartile rage (IQR)), n: Number of cases, +: One-way ANOVA tests, SMARCA 4; EPP: Extrapleural pneumonectomy, PD: Pleurectomy/decortication



**Figure 3.** Kaplan–Meier overall survival curves according to SMARCA2 status in epithelioid pleural mesothelioma (log-rank test).



**Figure 4.** Kaplan–Meier overall survival curves according to SMARCA4 status in epithelioid pleural mesothelioma (log-rank test).

In our series, the frequency of SMARCA4 loss (6%) is higher than that reported by Ahadi<sup>9</sup> and Ren<sup>10</sup> but still indicates that complete SMARCA4 deficiency is uncommon in epithelioid pleural mesothelioma. Differences in detection rates may reflect cohort size, selection criteria, technical factors (antibody clones, cut-offs, tissue microarray vs whole sections), or tumor sampling. Importantly, none of our SMARCA4-deficient cases showed the classic clinicoradiologic or morphological features of SMARCA4-DUT, supporting their interpretation as bona fide mesotheliomas rather than misclassified SMARCA4-DUT.

**SMARCA2 Loss and Inflammatory Microenvironment**

A novel observation of this study is the significant association between SMARCA2 loss and severe inflammatory infiltrates. Although patient numbers are small, this finding aligns with emerging evidence that SWI/SNF alterations can shape tumor-immune interactions. Experimental and translational studies have linked SWI/SNF deficiency to increased immunogenicity, enhanced tumor-infiltrating lymphocytes, and in some settings improved responses to immune checkpoint blockade.<sup>11,12</sup>

In mesothelioma, chronic inflammation caused by asbestos and other mineral fibers is a key pathogenic driver, and the crosstalk between genetic alterations and the immune microenvironment is increasingly recognized as a therapeutic target.<sup>6,8,12</sup> Our data raise the possibility that SMARCA2-deficient epithelioid mesotheliomas may represent a biologically distinct subgroup with heightened immune activation. Whether this translates into differential sensitivity to immunotherapy or other targeted approaches warrants further investigation in larger, multi-institutional cohorts with detailed immune profiling.

**Diagnostic Implications**

Because SMARCA4-deficient thoracic tumors and mesotheliomas may share some clinical and morphologic features, SMARCA4 immunohistochemistry has been proposed as a potential ancillary marker in the differential diagnosis of pleural tumors.<sup>4,9,10</sup> The low frequency of SMARCA4 loss in our cohort supports the notion that sustained SMARCA4 expression is typical of epithelioid pleural mesothelioma. If future multi-center series confirm that SMARCA4 loss remains rare in mesothelioma, SMARCA4 status—interpreted in combination with morphology and mesothelial and epithelial markers—could be useful in distinguishing mesothelioma from SMARCA4-DUT and SMARCA4-deficient lung carcinomas in challenging thoracic biopsies.

**Biological and Clinical Relevance**

The SWI/SNF complex acts as a tumor suppressor through context-dependent transcriptional regulation and chromatin remodeling.<sup>1,2,8</sup> Although truncal SWI/SNF mutations appear to be relatively infrequent in mesothelioma compared with other tumors, subtle alterations in complex composition or function may still contribute to disease heterogeneity and treatment response.<sup>6,8</sup> Our observation that SMARCA2 loss is associated with a robust inflammatory infiltrate suggests that even low-frequency SWI/SNF alterations may have disproportionate effects on the tumor microenvironment.

Future studies integrating next-generation sequencing, immunohistochemical panels for multiple SWI/SNF subunits, and comprehensive immune profiling (including CD8+ T-cell density, PD-L1 expression, and T-cell receptor clonality) are needed to clarify the prognostic and predictive significance of SMARCA2/4 loss in mesothelioma.

### Limitations

Adjuvant chemotherapy and/or radiotherapy was planned for all patients; however, actual treatment delivery and completion could not be reliably ascertained because of the retrospective design and incomplete treatment documentation.

Immune cell subtyping (e.g., CD3/CD8/CD68) was not performed; therefore, the cellular composition of the inflammatory infiltrate could not be characterized.

This study has several limitations. First, its retrospective, single-center design may introduce selection bias. Second, the sample size is relatively small, particularly for the subgroup with SMARCA2 and SMARCA4 loss, limiting the statistical power to detect subtle associations and precluding robust survival analysis. Third, we relied on TMA cores, which may not fully capture intratumoral heterogeneity of SMARCA2/4 expression. Fourth, molecular analyses (e.g., sequencing of SMARCA2/4 and other SWI/SNF genes) and detailed immune profiling were not available, preventing association of immunohistochemical findings with underlying genetic alterations and immune signatures. Finally, only epithelioid mesotheliomas were included; sarcomatoid and biphasic subtypes were not evaluated. Tumors were staged according to the AJCC 8th edition TNM system, in which T3 tumors may fall into stage II or III depending on nodal status; thus, the scarcity of higher-stage cases reflects surgical selection and institutional referral patterns rather than misclassification. Finally, the association between SMARCA2 loss and severe inflammation is based on very small numbers (n=4) and should be viewed as hypothesis-generating.

### CONCLUSION

In summary, SMARCA2 and SMARCA4 expression loss is rare in epithelioid pleural mesothelioma, occurring in only a small subset of cases. While SMARCA4 status did not correlate with clinicopathologic or inflammatory parameters, SMARCA2 deficiency was associated with a marked lymphocytic (inflammatory) response in this cohort; given the small number of SMARCA2-loss cases (n=4), this finding should be interpreted cautiously as exploratory. These data support the notion that alterations in SWI/SNF subunits may contribute to shaping an immunogenic tumor microenvironment and suggest that SMARCA2/SMARCA4 assessment may provide both diagnostic and potential biomarker information in pleural malignancies. Confirmation of these findings in larger, multi-institutional cohorts with integrated genomic and immune profiling will be essential to clarify the true prevalence, biological impact, and therapeutic relevance of SMARCA2 and SMARCA4 alterations in pleural mesothelioma.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

Was approved by the Clinical Researches Ethics Committee of İstanbul Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital (Date: 01.07.2021, Decision No: 2021-130).

### Informed Consent

As this was a retrospective study, formal written informed consent was not required and was therefore not obtained.

### Peer Review Process

This manuscript was subject to external peer review.

### Conflict of Interest

The author declare no conflicts of interest related to this study.

### Financial Disclosure

The author received no financial support for the conduct or publication of this research.

### Author Contributions

The preparation of the article, the analysis of the data, and the writing process were carried out entirely by the author.

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