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Journal of Cancer Research and Cellular Therapeutics

Siham Mesmoudi *

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Case Report

SMARCA4-Deficient Undifferentiated Thoracic Tumor: A Case Report

Siham Mesmoudi [1]*, Mohammed Aharmim [2], Sabrine Derqaoui [1], Taha Yassine Aaboudech [1], Reguig Nezha [2], Ahmed Jahid [1], Zakia Bernoussi [1], Bourkadi Jamal Eddine [2], Kaoutar Znati [1]

[1]Department of Pathology, Ibn Sina Teaching Hospital, Rabat 10170, Morocco.

[2]Moulay Youssef university hospital Rabat 10170, Morocco.

***Corresponding Author:** Siham Mesmoudi, Department of Pathology, Ibn Sina Teaching Hospital, Rabat 10170, Morocco.

Received Date: May 14, 2025; Accepted Date: May 22, 2025; Published Date: May 29, 2025

Citation: Siham Mesmoudi, Mohammed Aharmim, Sabrine Derqaoui, Taha Y. Aaboudech, Reguig Nezha, et al., (2026), SMARCA4-Deficient Undifferentiated Thoracic Tumor: A Case Report, *J. Cancer Research and Cellular Therapeutics*. 10(2); **DOI:10.31579/2640-1053/264**

Abstract

The patient is a 63-year-old man, a chronic smoker, who presented with cervical masses and a decline in general health. Imaging revealed an invasive mediastinal-hilar process with cervical, mediastinal, and axillary lymphadenopathy. Lymph node biopsy showed a largely necrotic malignant tumor consisting of large, epithelioid-appearing but undifferentiated cells. Initial immunohistochemical testing was negative for epithelial (AE1/AE3, CK7, P40), lymphoid, and melanocytic markers. Positivity for SALL4 and SOX2 subsequently raised suspicion of a germ cell tumor, but negativity for OCT3/4 and weak, focal positivity for synaptophysin and CD34, coupled with complete loss of BRG1 expression, led to a diagnosis of SMARCA4-UT. Despite oncological management, the course was marked by rapid metastatic progression and the patient's death. SMARCA4-UT is an aggressive malignant tumor that occurs primarily in adult males with a history of chronic smoking. Its definitive diagnosis is histopathological and is based on the loss of BRG1 as detected by immunohistochemistry (IHC). The phenotypic profile is often misleading due to the expression of synaptophysin and "stemness" markers (SALL4 and SOX2), leading to confusion with neuroendocrine or germ cell tumors. This entity must be distinguished from SMARCA4-deficient non-small cell lung carcinoma (NSCLC), which retains an epithelial morphology and phenotype. Awareness of this entity is crucial for the pathologist. The pathologist must systematically consider it in the presence of any undifferentiated thoracic tumor with a "negative" or atypical IHC profile in order to guide prompt therapeutic decisions. To report on and describe a rare and aggressive entity "SMARCA4-deficient undifferentiated thoracic tumor (SMARCA4-UT)," newly included in the 5th edition of the WHO Classification of Thoracic Tumors with the aim of highlighting the diagnostic challenges and pitfalls encountered by pathologists.

Keywords: SMARCA4-UT; histopathology; immunohistochemistry; differential diagnosis

1.Introduction

SMARCA4 deficient undifferentiated thoracic tumor (SMARCA4-UT) is a high-grade malignant neoplasm that originates in the thorax [5, 13]. It was recently described in the 5th edition of the WHO Classification of Thoracic Tumors as a distinct clinicopathological entity [16]. It is characterized by undifferentiated or rhabdoid morphology and loss of SMARCA4 protein expression [5, 11]. A positive diagnosis is based solely on histopathology [5, 16]. We report a case of SMARCA4-UT to encourage pathologists to consider this diagnosis and to optimize IHC requests so as not to exhaust the biopsy material and to be able to provide a rapid and accurate diagnosis.

2. Case Presentation:

This was a 63-year-old male patient who presented with cervical masses and a marked decline in general health, characterized by weight loss. A chest CT scan was performed and revealed a left mediastinal-hilar mass measuring 19 cm in longest axis, with irregular margins and heterogeneous contrast enhancement. It was associated with mediastinal, cervical, and axillary lymphadenopathy (Figures 1).

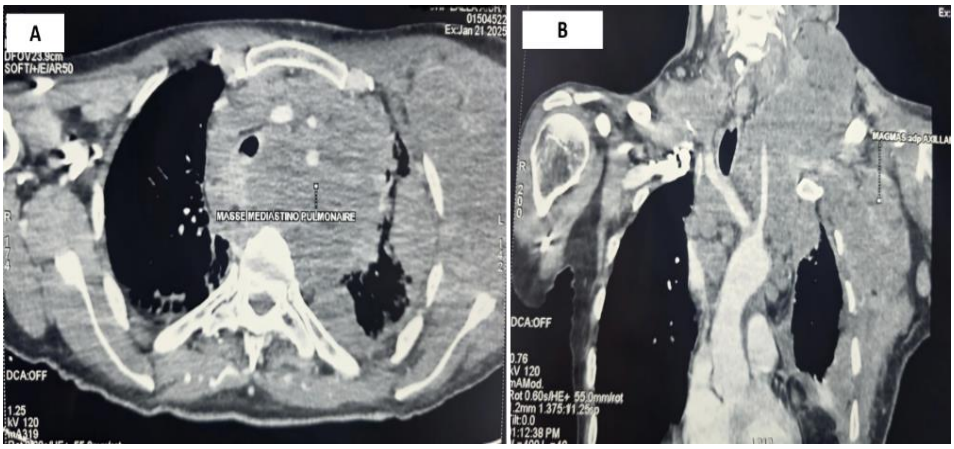

Figure 1: Thoracic CT scan: (A) heterogeneous left mediastinal mass (82 × 96 × 190 mm) with irregular margins; (B) multi-regional lymph node enlargement.

An abdominal-pelvic CT scan was performed and showed no abnormalities. A radio-guided biopsy of a cervical lymph node was performed. At the pathology laboratory, we received three paraffin-embedded sections, cut and stained with hematoxylin and eosin (HE). Microscopic examination revealed a largely necrotic malignant tumor consisting of large cells with abundant, eosinophilic cytoplasm and fairly distinct cytoplasmic borders. The nuclei are ovoid with vesicular chromatin and nucleoli (Figures 2).

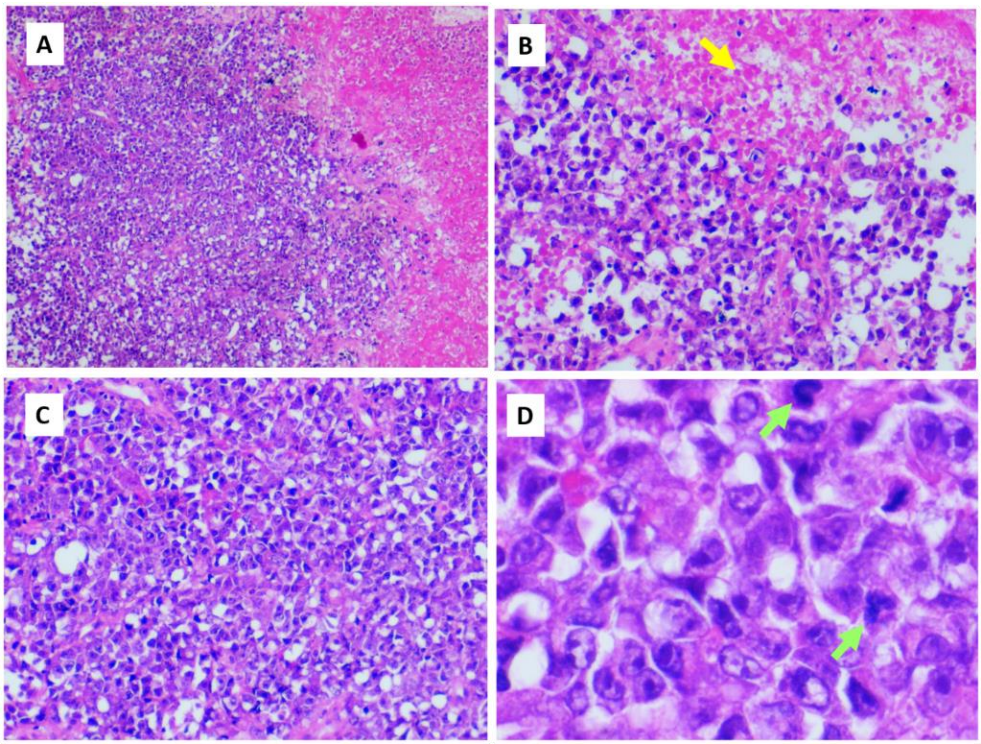

Figure 2: Histological appearance of the tumor. (**A**) Highly necrotic malignant tumor proliferation at low magnification (H&E×40); the yellow arrows indicate prominent areas of tumor necrosis. (**B–C**) Large tumor cells arranged in diffuse sheets without glandular or squamous differentiation at medium magnification (H&E×200). (**D**) Marked cytonuclear atypia with high mitotic activity at high magnification (H&E×400); the green arrows highlight typical mitotic figures.

On IHC, the tumor cells were negative for the antibodies AE1/AE3, EMA, CK7, TTF1, and P40. A second complementary panel was performed to rule out hematopoietic, melanocytic, and germ cell origins. This panel showed negativity for S100 and CD45, while SALL4 was positive. The IHC profile following these two panels pointed toward a germ cell origin or SMARCA4-UT. The third panel showed negativity for OCT ¾ and desmin antibodies with intense nuclear positivity for SOX2. The expression of synaptophysin and CD34 was heterogeneous and weak, with a loss of BRG1 expression (the protein encoded by the SMARCA4 gene) in the tumor cells (Figure 3). Consequently, based on the tumor's location, its morphological appearance, and its IHC profile, the diagnosis was SMARCA4-UT. The patient was referred to the oncology department. His course was marked by the development of extrathoracic metastases, followed by death.

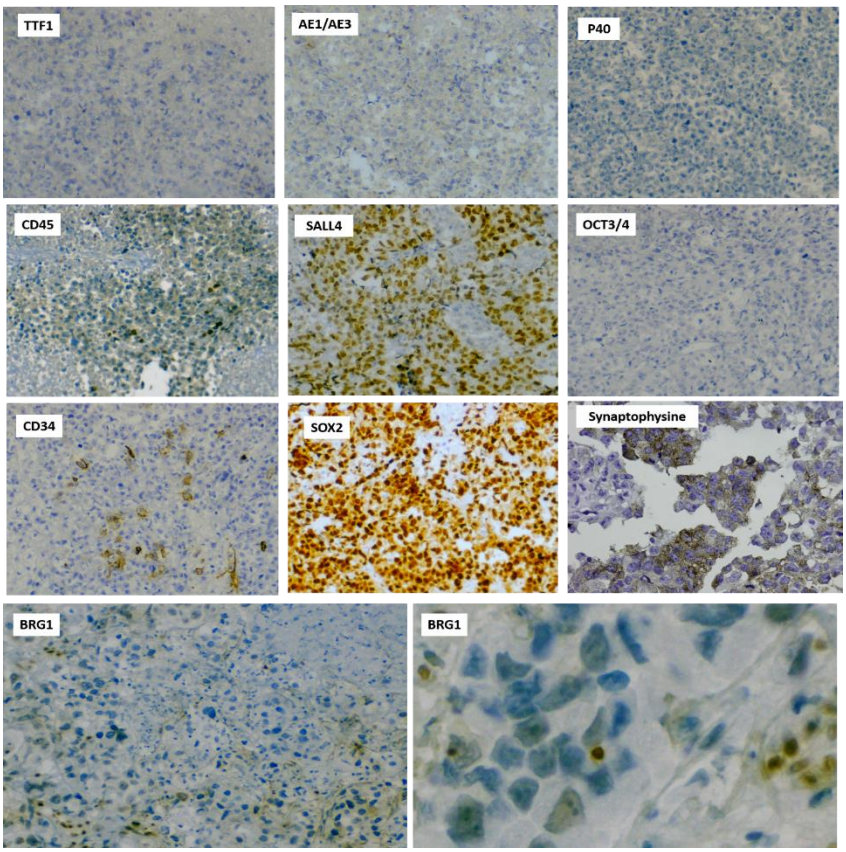

Figure 3: The tumor cells are negative for the markers AE1/AE3, TTF1, P40, and CD45. However, they express SALL4 and SOX2 diffusely and intensely. OCT3/4 expression is negative, ruling out a germline origin. Heterogeneous and focal staining for CD34 and synaptophysin is observed. The nuclei of the tumor cells show no staining with the BRG1 (SMARCA4) antibody, whereas the internal control (stromal lymphocytes) is positive.

3. Discussion:

SMARCA4-UTs are rare neoplasms [5]. According to the literature, between 100 and 150 cases have been reported to date[7, 10]. They are characterized by a striking male predominance, with an estimated sex ratio of 9:1 [11, 16]. They affect middle-aged individuals, with a median age ranging from 40 to 60 years depending on the study [5, 13]. The main risk factor is chronic smoking [5, 12]. No germline mutations in the SMARCA4 gene have been reported in these tumors [5, 11]. Initial clinical manifestations vary and are related to compression, such as dyspnea, pain, hemoptysis, superior vena cava syndrome, or significant weight loss [5, 11, 13]. The disease progresses rapidly, leading to symptoms associated with lymph node or distant metastases [5, 13, 16]. Lymph node metastases are the most common and are seen in 60% to 90% of cases. Distant metastases can involve the adrenal glands, bone, lung, liver, and brain, and, unusually, sometimes the gastrointestinal tract or skin [5, 11]. Imaging often reveals a large, poorly defined, invasive mediastinal-pulmonary mass that is hypermetabolic on PET scan [5, 11]. Mediastinal involvement alone is very rare [5]. The clinical and radiological presentation of our case is consistent with the characteristics described in the literature. The carcinogenesis of SMARCA4-UT is linked to biallelic inactivation of the SMARCA4 gene located on chromosome 19q, resulting in the loss of BRG1 protein expression [9, 10]. The mutational profile leading to this inactivation is complex, involving loss of heterozygosity and frequent inactivation of the TP53 protein [9, 14]. SMARCA4-UT tumors are characterized by a high mutational burden and genomic signatures associated with smoking [9, 16]. It is noted that approximately 44% of cases exhibit the same co-mutations involved in tobacco-related non-small cell lung cancer (NSCLC) [3, 16]. These co-mutations affect the KRAS, STK11, and/or KEAP1 genes [9, 16]. This explains the presence of a proportion of SMARCA4-deficient NSCLC and, in some cases, hybrid forms combining both, thus suggesting the possibility of an epithelial dedifferentiation process [1, 3, 16]. This is the key examination for establishing the diagnosis [5, 16]. Histologically, these tumors consist of diffuse sheets of large round to epithelioid cells that are sometimes non-cohesive. The nuclei are fairly monomorphic with vesicular chromatin and prominent nucleoli [6, 9, 16]. Rhabdoid differentiation may be observed [9, 16]. The absence of glandular or squamous differentiation is typical [9, 13]. These tumors are rich in mitoses and show geographic necrosis, indicating tumor aggressiveness [6, 13]. In rare cases, the cells exhibit a spindle-shaped, alveolar, or clear-cell appearance mimicking a mesenchymal tumor or metastasis [9]. Immunohistochemical analysis confirms the loss of BRG1 expression; this is the key antibody for diagnosing this entity [9, 16]. In practice, the pathologist uses standard panels before proceeding to the key antibody. These tumors are often negative for or show very focal expression of epithelial markers such as AE1/AE3 and EMA, whereas claudin-4 is almost always negative [6, 9, 13]. A characteristic immunohistochemical profile includes frequent expression of SOX2 (positive in approximately 90% of cases), SALL4, and CD34 [5, 6]. The majority of SMARCA4-UT tumors also express synaptophysin in 62.5% to 70% of cases, depending on the series, in a diffuse and intense manner without expression of other neuroendocrine markers [14, 16]. Although some SMARCA4-UT tumors may exhibit

rhabdoid morphology, they show no muscular differentiation. Desmin expression is absent [7, 16]. The p53 protein is overexpressed in the majority of cases, reflecting the tumor's genomic instability [5, 14, 16]. The NUT marker is consistently negative (8). INI1 expression is preserved, which allows for the exclusion of classic malignant rhabdoid tumors [5, 16]. SMARCA4 loss is often associated with concomitant SMARCA2 loss (BRM). This alteration is absent in SMARCA4-deficient NPCs [6, 8]. Testing for it remains relevant in SMARCA4-UT cases showing diffuse and significant reduction in BRG1 staining rather than complete loss. This situation is observed in approximately 25% of cases [6, 16]. The morphology of our case is consistent with the classic features reported in the literature, and the IHC profile is virtually identical. The differential diagnosis of SMARCA4-UT is complex both morphologically and by IHC, given the negative results for many standard markers and the expression of misleading markers such as SALL4 and synaptophysin [5, 16]. The distinction relies on a correlation between clinical data, histology, and the immunohistochemical profile [3]. Confusion may arise with SMARCA4-deficient NSCLC (SD-NSCLC) because both entities occur in smokers and share the loss of SMARCA4[17]. However, SD-NSCLC exhibits a carcinoma morphology consisting of cohesive cells, sometimes with glandular or squamous differentiation. On IHC, NSCLC expresses cytokeratins and Claudin-4 intensely and diffusely. In contrast, the "stemness" markers SOX2, SALL4, and CD34 are negative [5, 16, 17]. Other differential diagnoses may be considered based on the IHC profile of these tumors, primarily germ cell tumors given the expression of SALL4, large cell neuroendocrine carcinoma given the expression of synaptophysin, lymphoma, or melanoma. However, IHC in doubtful cases allows these to be ruled out [10]. It has been reported that certain extrathoracic tumors, primarily in the uterus, ovary, stomach, or pancreas, exhibit an identical phenotype of SMARCA4 deficiency. Their metastasis to the thorax can lead to diagnostic errors, hence the importance of cross-referencing with clinical and radiological data [13, 16]. In our case, IHC antibody panels allowed us to rule out the aforementioned differential diagnoses: a germ cell tumor, as well as a neuroendocrine carcinoma, a lymphoma, and a melanoma. The negativity of epithelial markers and of TTF1 and P40 allowed us to rule out NSCLC. Staging at the time of diagnosis revealed no other sites, thereby ruling out SMARCA4-deficient extrathoracic tumors. Recently, a review study carried out by Song et al [15] emphasizes that an accurate diagnosis of SMARCA4-UT can influence treatment selection and may allow enrollment in targeted clinical trials. The prognosis for SMARCA4-UT is poor. The median survival after diagnosis is 4 to 7 months [16]. The tumor progresses rapidly. According to case series in the literature, in some cases treated surgically with negative margins, recurrence has been documented within less than a month [5]. The course of our case was also marked by the development of distant metastases followed by death. From a therapeutic standpoint, given the rarity of these tumors, there are no established standards of care[5, 16]. Conventional chemotherapy shows limited efficacy according to the literature. In contrast, immunotherapy has yielded durable responses of up to two years in some cases with PD-1/PD-L1 inhibitors [8]. Targeted therapies are still under investigation and require validation through clinical trials [4]. However, the rarity of these tumors remains a limitation for reliable and valid evaluation [4, 5]. A multi-institution retrospective cohort analysis revealed a population of patients with short progression-free survival to standard therapies and poor overall survival [2].

4. Conclusion:

In conclusion, SMARCA4-UT is a rare and highly aggressive thoracic tumor recently recognized in the 5th edition of the WHO Classification of Thoracic Tumors, generally affecting male smokers. Its diagnosis is challenging for the reason that its unusual immunohistochemical profile, which may mimic neuroendocrine or germ cell tumors. Definitive diagnosis relies on histopathology and loss of BRG1 expression, after excluding SMARCA4-deficient NSCLC and extrathoracic SMARCA4-deficient tumors. Awareness of this entity is crucial for accurate diagnosis, suitable therapeutic management, and optimized use of biopsy material.

Conflict of Interest

The authors declare no conflict of interest

Funding

The authors declare that no financial support was received for this study

Consent for Publication

Written informed consent was obtained from the patient and his legal guardian for the publication of this case report and associated images. A copy of the signed consent form is available upon request.

Ethical Approval

This case report did not require approval from an ethics committee, as per institutional and international guidelines for case studies involving anonymized patient data.

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DOI:10.31579/2640-1053/264