Quiz

Correct answer to the quiz. Check your diagnosis

Case report

Thoracic SMARCA4-deficient undifferentiated tumour – a case of an aggressive neoplasm

Gizem Teoman

Karadeniz Technical University, Faculty of Medicine, Department of Pathology, Trabzon, Turkey

SMARCA4-deficient undifferentiated tumours exhibit undifferentiated and rhabdoid features. These highly aggressive neoplasms pose significant diagnostic challenges. They are characterised by an inactivating mutation of SMARCA4, leading to the loss of expression of Brahma-related gene 1 (*BRG1*). Despite their rareness and poor differentiation as thoracic tumours, it is important to recognise these tumours because, despite being highly aggressive, there are potential treatment options for the future, such as immunotherapy and SMARCA4-targeted therapies. This case presentation aims to raise awareness of this rare neoplasm when evaluating cases presenting undifferentiated morphology.

Key words: SMARCA4, BRG1, lung, thorax.

Introduction

SMARCA4-deficient undifferentiated tumour (SMARCA4-UT) was first discovered and recorded as a pathological entity by Loarer *et al*. in 2015. This tumour is distinguished by the inactivation of the *SMARCA4* gene located at *19p13*, which encodes the Brahma-related gene-1 (*BRG1*) protein. This protein is a critical component of the switch/sucrose-nonfermenting (SWI/SNF) chromatin remodeling complex [1]. SMARCA4-UT is newly added to the 2021 World Health Organisation Classification of Lung Tumours [2]. It was previously called SMARCA4-deficient thoracic sarcoma [3].

SMARCA4-UT is generally more common in young to middle-aged men. SMARCA4-UT typically arises in the thoracic region. Frequently, it presents as masses in the mediastinum, lung, or pleura. Characteristically, it exhibits poorly differentiated morphology, and the presence of cells with rhabdoid features is also quite common. Immunophenotypically, tumour cells do not express thymic, lung, or mesothelial markers. They may show CD34 and SOX-2 expression and occasionally focal keratin expression. The most valuable diagnostic marker is the complete loss of BRG1 protein immunohistochemically [4].

Since SMARCA4-UT is a newly defined entity, it is not yet well recognised, and an optimal treatment strategy has not been determined. Immunotherapy and SMARCA4-targeted treatment strategies are increasingly important in treating this disease [5]. Therefore, the awareness and recognition of this pathological entity are precious.

Herein, a case of SMARCA4-UT is presented. This case exhibits the typical morphological and immunophenotypic characteristics of SMARCA4-UT. This case report also provides a review of the literature.

This is an Open Access journal, all articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International (CC BY-NC-SA 4.0) License (http://creativecommons.org/licenses/by-nc-sa/4.0/)

Case report

A 61-year-old male patient presented to the hospital with complaints of cough and haemoptysis. His past medical history was remarkable for smoking. A chest computed tomography (CT) revealed multiple masses, the largest being 3.5 cm in diameter, located in the left lung lower lobe superior segment, pleura, and mediastinum. Positron emission tomography (PET) imaging showed multiple masses in the right paratracheal, subaortic, right lower paratracheal-carinal area, and left lung lower lobe. Additionally, multiple LAPs in the abdomen and pathological 18-F-fluorodeoxyglucose (FDG) uptake in both scapulae, sternum, vertebrae, pelvis, and femur were detected.

A thoracoscopic biopsy was performed under general anaesthesia on a 2-cm pleural-based nodule in the left lung lower lobe of the patient. Macroscopically, the tissue samples, sent in fragmented form, were collectively 2.5 cm in diameter and cream-coloured. Microscopic examination revealed a neoplasm composed of neoplastic cells arranged in discohesive layers, exhibiting both epithelioid, undifferentiated, and rhabdoid morphology, with round-oval nuclei, vesicular chromatin, prominent nucleoli, and frequent mitotic activity. Focal necrosis areas were observed (Fig. 1). Gland formation, cytoplasmic vacuolisation, or keratinisation were not identified. Considering the morphological features and the location of the mass, differential diagnoses included poorly differentiated carcinoma, rhabdomyosarcoma, malignant melanoma, lymphoma, and malignant mesothelioma. Immunostaining showed that the tumour cells lacked expression of multiple keratins, including pankeratin, CAM5.2, and EMA, excluding carcinoma and malignant mesothelioma because of negativity with WT-1 and calretinin. For lymphoma, it was also negative for CD45, CD3, CD20, and CD43. Malignant melanoma was ruled out due to negativity for S100 and HMB45, while rhabdomyosarcoma was excluded for myogenin, SMA, and desmin. The tumour cells were also negative for TTF1, p40, SALL4, CD38, CD56, CD117, CD99, and Bcl2. While tumour cells were diffusely strongly positive for CD34, they were weakly positive for synaptophysin and focally positive for vimentin. Weak and focal staining was observed in the tumour cells with SOX-2 (Fig. 2).

Upon revisiting the clinical and radiological findings of the case, we recognised that we were dealing with a highly aggressive and metastatic tumour. Given the epithelioid and rhabdoid morphology and the immunophenotype showing positivity only for CD34, vimentin, synaptophysin, and focal SOX2, we considered SMARCA4-UT. When we performed the BRG1 immunohistochemical study, we detected a loss of BRG1 expression. No loss of INI-1 expression was observed (Fig. 2). With these characteristics, we diagnosed the case as SMARCA4-UT. At the time of diagnosis, the patient's general condition worsened, and he was admitted to the oncology service. The patient, for whom chemotherapy was planned, passed away due to cardiac arrest before treatment could be started.

Discussion

SMARCA4-UT are rare, aggressive neoplasms, with approximately 141 cases reported in the literature [6–8]. Table I summarises the clinicopathological and histomorphological features of cases in the pub-

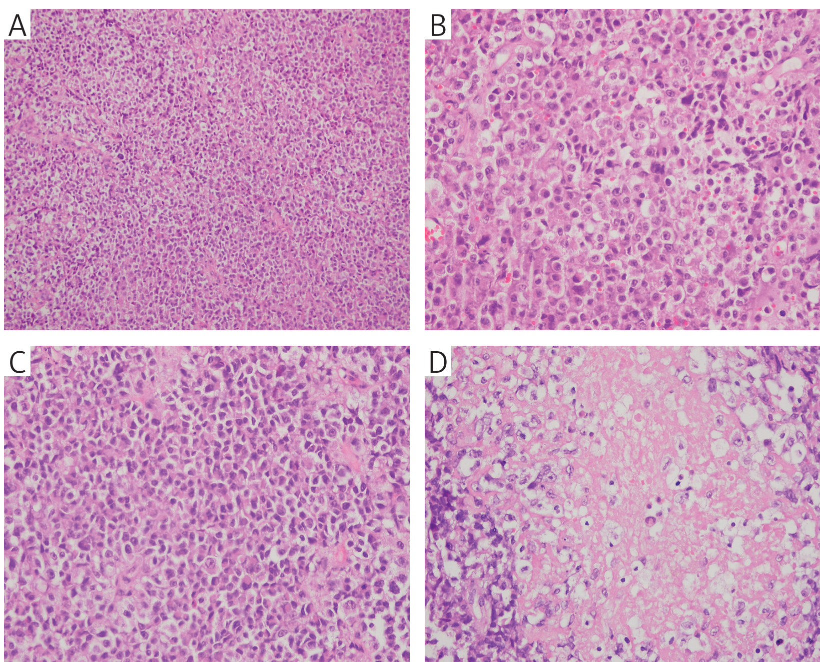

Fig. 1. Pathological features of thoracic SMARCA4-UTs. A) Tumour cells are arranged in typical solid islands and solid sheets. B) Tumour cells with epithelioid morphology occasionally show prominent nucleoli. C) Tumour cells with rhabdoid morphology, characterised by abundant eosinophilic cytoplasm and vesicular nuclei. D) Typical tumour necrosis area

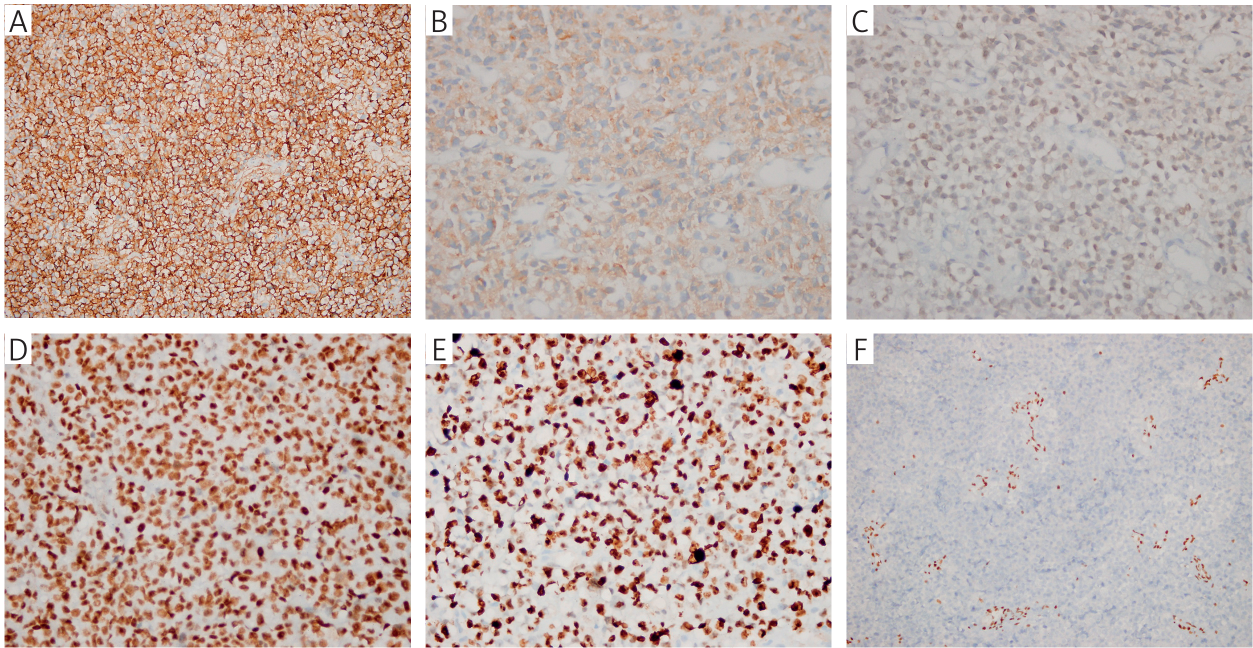

Fig. 2. Immunohistochemical staining of thoracic SMARCA4-UTs. A) Diffuse strong CD34 positivity in neoplastic cells. B) Weak synaptophysin positivity in neoplastic cells. C) Weak and focal SOX2 positivity in tumour cells. D) Preserved INI1 expression in tumour cells. E) The Ki-67 index was approximately 90%. F) In the BRG1 immunohistochemical study, there was a complete loss of expression in tumour cells, while inflammatory cells served as an internal control and were positively stained

lished literature. It is observed in individuals ranging from 27 to 90 years of age but is most often seen in the fifth and sixth decades of life and among smokers. It is more frequent in men, with a male-to-female ratio of 9 : 1 [6]. Patients are typically metastatic at the time of diagnosis. Mediastinal lymph node metastasis is frequently observed. Adrenal gland, bone, and liver metastases are commonly encountered during diagnosis [7]. Patients often present to hospitals with complaints such as dyspnoea, chest and back pain, cough, and haemoptysis [4]. Tumours are frequently large at presentation, with a reported median tumour size of 12–13 cm (range 2.2–27 cm) [7].

On radiological imaging, primary tumours typically appear as relatively well-defined masses with heterogeneous contrast enhancement in the upper and middle mediastinum, extending towards the oesophagus, bronchi, thymus, and major blood vessels [9]. Primary tumours exhibit strong FDG avidity on PET-CT scans [7].

Morphologically, as in our case, the tumour cells exhibit poorly differentiated cytological features with medium-sized epithelioid and occasionally rhabdoid cells. Some nuclei show prominent nucleoli. The tumour cells are arranged in discohesive layers and exhibit frequent mitotic activity. In 7% of tumours, focal myxoid stroma or desmoplastic small round tumour cells can be observed [7]. They generally have extensive areas of necrosis.

Regarding immune profiling, these tumours generally exhibit stem cell markers such as CD34, SOX2, and SALL4. Diffuse expression of SOX2 has been reported in nearly all cases [7]. Many of these tumours are negative for multiple keratins, like our case. In almost all cases, including ours, S100, WT1, desmin, p40, and CD45 are negative. No loss of INI1 expression was observed.

SMARCA4 encodes BRG1, a tumour suppressor and catalytic subunit of the SWI/SNF chromatin-remodeling complex. This complex regulates transcription and promotes cell differentiation [7]. SMARCA4-UT is characterised by an inactivating mutation in the *SMARCA4* gene, which results in the loss of BRG1 expression in neoplastic cells [6]. In these patients, no germline *SMARCA4* mutations were detected. Therefore, performing immunohistochemical staining for BRG1 in tumour cells is crucial for identifying *SMARCA4* mutations and diagnosing this tumour.

In the differential diagnosis of SMARCA4-UT, malignant rhabdoid tumour, atypical teratoid rhabdoid tumour, metastatic small cell carcinoma of the ovary hypercalcaemic type, lung carcinoma, germ cell tumour, lymphoma, malignant melanoma, malignant mesothelioma, and sarcoma are included. Loss of BRG1 expression alone is not specific to this tumour, as BRG1 expression loss can also be observed in malignant rhabdoid tumours, small cell carcinoma of the ovary hypercalcaemic type, and atypical teratoid rhabdoid tumours [7]. Malignant rhabdoid tumour patients are typically young, and tumour cells are usually SOX2 negative. Additionally, there is

Table I. Clinicopathological and histomorphological features of the SMARCA4-UT cases exist in the literature

Author	Number of patients	Age (median)	Sex	Smoking (%)	Tumor size [cm]	Histomorphology	Metastatic disease
Zhou *et al.* [8]	35	61	M	88.6	N/A	Undifferentiated-rhabdoid	Present
Mundada *et al.* [6]	1	55	M	100	2.2	Undifferentiated-epitheloid	Present
Rachidi *et al.* [14]	1	42	M	100	N/A	Epitheloid	Present
Shinno *et al.* [15]	18	53	M*	100	N/A	N/A	Present – 13 patients
Kawachi *et al.* [11]	3	64	F*	100	6.4	Undifferentiated-plasmacytoid	Present
Stewart *et al.* [16]	1	59	M	100	5	Undifferentiated-rhabdoid	Absent
Lijima *et al.* [12]	1	76	M	100	N/A	Undifferentiated-rhabdoid	Present
Roden [7]	1	66	M	100	N/A	Undifferentiated-rhabdoid	Present
Perret *et al.* [4]	30	48	M*	87	1.2–24	Undifferentiated-epitheloid, rhabdoid	Present – 20 patients
Kunimasa *et al.* [17]	2	45	M	100	5–11	Undifferentiated-rhabdoid	Present
Rekhtman *et al.* [18]	22	58	M*	95	9.2	Undifferentiated-rhabdoid	Present – 20 patients
Takada *et al.* [10]	1	69	F	N/A	N/A	Polyhedral tumor cells	Present
Sauter *et al.* [3]	12	59	M*	41.6	N/A	Solid and discohesive sheets, rhabdoid	Present – 7 patients
Kuwamoto *et al.* [19]	1	30	F	100	7.8	Undifferentiated-rhabdoid	Present
Yoshida *et al.* [20]	12	39	M*	70	N/A	Epitheloid-rhabdoid	Present – 10 patients

F – female, F – female dominant, M – male, M* – male dominant*

a loss of INI-1 expression in tumour cells. Patients with hypercalcaemic type small cell carcinoma of the ovary are females. These patients often have a history of an abdominal mass and generally present with hypercalcaemia. While SOX2 expression may be observed, it is usually focal. There is a loss of INI1 expression. INI-1 immunohistochemical stain, which is another component of the SWI/SNF complex, encoded by the *SMARCB1* gene, can be used to differentiate SMARCA4-UT from many tumours with similar morphological features, such as epithelioid sarcoma [7].

SMARCA4-UT is an aggressive neoplasm with a poor prognosis. The median overall survival time is 4–7 months. Some examples in the literature show significant improvements in survival for patients undergoing immunotherapy treatment [10–12]. Notably, one documented case demonstrated a remarkable survival period of up to 22 months [13].

Conclusions

In conclusion, SMARCA4-UT is a very aggressive and poorly prognostic neoplasm typically seen in smoking men. When encountering a tumour with epithelioid, undifferentiated, and rhabdoid morphology arranged in solid nests microscopically, it is essential to perform immunohistochemical staining for BRG1. Despite its abysmal prognosis, promising results have begun to emerge with immunotherapy and *SMARCA4*-targeted treatments. This situation offers promising opportunities for the future.

Disclosures

1. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki

Declaration and its later amendments or comparable ethical standards. Due to the nature of this report, the Ethical Committee waived informed consent.
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

References

1. Le Loarer F, Watson S, Pierron G, et al. SMARCA4 inactivation defines a group of undifferentiated thoracic malignancies transcriptionally related to BAF-deficient sarcomas. Nat Genet 2015; 47: 1200-1205.
2. Nicholson AG, Tsao MS, Beasley MB, et al. The 2021 WHO classification of lung tumors: impact of advances since 2015. J Thorac Oncol 2022; 17: 362-387.
3. Sauter JL, Graham RP, Larsen BT, Jenkins SM, Roden AC, Boland JM. SMARCA4-deficient thoracic sarcoma: a distinctive clinicopathological entity with undifferentiated rhabdoid morphology and aggressive behavior. Mod Pathol 2017; 30: 1422-1432.
4. Perret R, Chalabreysse L, Watson S, et al. SMARCA4-deficient thoracic sarcomas: clinicopathologic study of 30 cases with an emphasis on their nosology and differential diagnoses. Am J Surg Pathol 2019; 43: 455-465.
5. Gantzer J, Davidson G, Vokshi B, et al. Immune-desert tumor microenvironment in thoracic SMARCA4-deficient undifferentiated tumors with limited efficacy of immune checkpoint inhibitors. Oncologist 2022; 27: 501-511.
6. Mundada M, Abdul Mannan K, Vasu D, et al. Under the microscope: a case report of thoracic SMARCA4-deficient undifferentiated tumor with review of the literature. Turk J Pathol 2024; 40: 128-133.
7. Roden A. Thoracic SMARCA4- deficient undifferentiated tumor-a case of an aggressive neoplasm-case report. Mediastinum 2021; 5: 39-44.
8. Zhou P, Fu Y, Tang Y, et al. Thoracic SMARCA4-deficient undifferentiated tumor: a clinicopathological and prognostic analysis of 35 cases and immunotherapy efficacy. Lung Cancer 2024; 189: 107471.
9. Crombé A, Alberti N, Villard N, et al. Imaging features of SMARCA4-deficient thoracic sarcomas: a multi-centric study of 21 patients. Eur Radiol 2019; 29: 4730-4741.
10. Takada K, Sugita S, Murase K, et al. Exceptionally rapid response to pembrolizumab in a SMARCA4-deficient thoracic sarcoma overexpressing PD-L1: a case report. Thorac Cancer 2019; 10: 2312-2315.
11. Kawachi H, Kunimasa K, Kukita Y, et al. Atezolizumab with bevacizumab, paclitaxel and carboplatin was effective for patients with SMARCA4-deficient thoracic sarcoma. Immunotherapy 2021; 13: 799-806.
12. Iijima Y, Sakakibara R, Ishizuka M, et al. Notable response to nivolumab during the treatment of SMARCA4-deficient thoracic sarcoma: a case report. Immunotherapy 2020; 12: 563-569.
13. Nambirajan A, Dutta R, Malik PS, Bubendorf L, Jain D. Cytology of SMARCA4-deficient thoracic neoplasms: comparative analysis of SMARCA4-deficient non-small cell lung carcinomas and SMARCA4-deficient thoracic sarcomas. Acta Cytologica 2020; 65: 67-74.
14. Rachidi SL, Firmin N, Elfadli M, et al. A Case report of SMARCA4-deficient thoracic sarcoma: a rare and aggressive disease with a grim prognosis. Cureus 2023;15(5): e39571.
15. Shinno Y, Yoshida A, Masuda K, et al. Efficacy of immune checkpoint inhibitors in SMARCA4-deficient thoracic tumor. Clin Lung Cancer 2022; 23: 386-392.
16. Stewart BD, Kaye F, Machuca T, et al. SMARCA4-deficient thoracic sarcoma: a case report and review of literature. Int J Surg Pathol 2020; 28: 102-108.
17. Kunimasa K, Nakamura H, Sakai K, et al. Patients with SMARCA4-deficient thoracic sarcoma and severe skeletal-related events. Lung Cancer 2019; 132: 59-64.
18. Rekhtman N, Montecalvo J, Chang JC, et al. SMARCA4-deficient thoracic sarcomatoid tumors represent primarily smoking-related undifferentiated carcinomas rather than primary thoracic sarcomas. J Thorac Oncol 2020; 15: 231-247.
19. Kuwamoto S, Matsushita M, Takeda K, et al. SMARCA4-deficient thoracic sarcoma: report of a case and insights into how to reach the diagnosis using limited samples and resources. Hum Pathol 2017; 70: 92-97.
20. Yoshida A, Kobayashi E, Kubo T, et al. Clinicopathological and molecular characterization of SMARCA4-deficient thoracic sarcomas with comparison to potentially related entities. Mod Pathol 2017; 30: 797-809.

Address for correspondence

Gizem Teoman, Assistant Professor, MD
Department of Pathology
Faculty of Medicine
Karadeniz Technical University
Trabzon, Turkey
Phone: +905321325336
e-mail: dr.gizemcivelek@gmail.com