International Journal of Life Sciences, Biotechnology and Pharma Research Vol. 13, No. 6, June 2024 Online ISSN: 2250-3137
Print ISSN: 2977-0122

DOI: 10.69605/ijlbpr_13.6.36

REVIEW ARTICLE

Comprehensive Overview of SMARCA4-Deficient Thoracic Neoplasms

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Received date: 20 April, 2024 Acceptance date: 22 May, 2024

ABSTRACT
Recently, SMARCA4, an important part of the SWI/SNF chromatin remodeling complex, was found to play a major role in the development of some thoracic cancers. SMARCA4-deficient thoracic tumors are a special type of cancer because they don't produce SMARCA4 proteins. These tumors have been linked to aggressive behavior in patients and a unique histopathological profile. The goal of this review is to give a full picture of thoracic tumors that don't have SMARCA4, giving us clues about possible ways to target these tumors and make patient results better.
Keywords: SMARCA4 deficiency, thoracic tumors, who entity

INTRODUCTION
SMARCA4 deficient thoracic tumor is a new entity in who recent classification.[1]
The SMARCA4 protein, which is also known as BRG1, is an important part of the SWI/SNF chromatin remodeling complex. This complex changes the structure of chromatin to make it easier for transcriptional machinery to reach it and control gene expression. Recently, new discoveries have shown that SMARCA4 genes play a big part in many types of cancer, such as those in the thorax, uterus, and intestines [2, 5]. Notably, thoracic tumors that don't have SMARCA4 are very aggressive and have unique clinical and histological features that make normal treatment methods more difficult [4, 6].

MOLECULAR PATHOGENESIS
Finding SMARCA4 as a tumor suppressor gene is very important for learning about the genetic processes that cause some types of cancer. Lack of SMARCA4 is often linked to changes in genetic and epigenetic regulation in thoracic cancers, which impacts important biological functions such as DNA repair, cell division, and differentiation [7,8]. Some changes in the BAF chromatin remodeling complex are what cause SMARCA4-deficient thoracic tumors to grow, especially aggressive thoracic sarcomas [7, 8].

CYTOLOGY
A close look at the cells of SMARCA4-deficient thoracic tumors, such as non-small cell lung carcinomas (SMARCA4-dNSCLCs) and thoracic sarcomas (SMARCA4-dTSs), shows that they are different in several ways [13, 24]:

1. SMARCA4-dNSCLCs are usually poorly differentiated carcinomas that have cohesive groups of large tumor cells with a lot of pale cytoplasm. This helps doctors tell them apart from other carcinomas[3].
2. There is a rhabdoid trait for SMARCA4-dTS. This means that tumor cells have perinuclear cytoplasmic condensations, which are often set against an inflammatory or necrotic background. Because of these factors, a high level of concern and the right extra tests are needed to make a correct diagnosis [13, 24].

CLINICAL AND HISTOLOGICAL FEATURES
SMARCA4-deficient thoracic sarcomas are highly aggressive, poorly differentiated tumors that often display rhabdoid features. They predominantly occur in male smokers, are large, and are typically located in the mediastinum, pleura, or lung. The median survival rate is about 6 months, underscoring their aggressive nature [9].

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DIAGNOSIS

1. Immunohistochemical Profile: The "SMARCA4-DTS immunohistochemical signature" is very important for identification because it shows that both SMARCA4 and SMARCA2 are missing at the same time, while SOX2 is overexpressed. This helps set these tumors apart from other intrathoracic cancers [10, 11, 14]. Also helpful are markers like CD34 and SALL4, especially in tough cases [9].
2. Cell Block Examination as a Diagnostic Tool: Cell block analysis is very important when regular biopsy samples are not enough. Along with immunohistochemical tests [24], it shows polyhedral to round tumor cells with unique nuclear and cytoplasmic traits.
3. Genetic and molecular insights: To prove SMARCA4 mutations, genetic testing is a must. Targeted therapies work best when this gene is turned off, which is a feature of these cancers [10,11].

THERAPEUTIC APPROACHES AND RESPONSE

Therapeutic Approaches and Response New ways of treating lung cancers that don't have SMARCA4 show promise. Immunotherapy, like nivolumab, has been shown to work in recent case reports, especially when standard cytotoxic chemotherapy has not [16]. Drug combinations like atezolizumab with bevacizumab, paclitaxel, and carboplatin also seem to work, which suggests that targeted treatment might be possible [20, 21].

PROGNOSTIC OUTCOMES

Patients with SMARCA4-deficient thoracic tumors still have a bad outlook; the median survival time is often not more than a few months from the time of diagnosis. These tumors are very aggressive and spread quickly, which makes patient results much worse. Biomarkers that can predict and improve treatment effectiveness are the focus of ongoing studies [21, 22].

CONCLUSION

Due to their unique molecular and histological features, SMARCA4-deficient lung tumors are very challenging to treat. It is very important to get a correct evaluation and learn more about how their diseases work. To find better ways to treat this difficult type of cancer [15–19], researchers must keep working together on projects.

REFERENCES

1. Singh G, Singh A, Dave R. An update on WHO classification of thoracic tumours 2021- Newly described entities and terminologies. J Clin Diagn Res. 2023 Jun;17(6):EE01-EE05. doi: 10.7860/JCDR/2023/62583.18076.
2. Meng XP, Ma J, Meng NN, Yun T, Niu B. Case Report: SMARCA4 (BRG1)-deficient undifferentiated carcinoma of gallbladder with genetic analysis. Front Oncol. 2023;.
3. Panozzi M, Alì G, Proietti A, Melfi F, Zirafa CC, Lucchi M, Fontanini G. SMARCA4 as a support for the differential diagnosis of poorly differentiated lung carcinomas. Pathologica. 2023.
4. Al-Shbool G, Krishnan Nair H. SMARCA4-Deficient Undifferentiated Tumor: A Rare Malignancy With Distinct Clinicopathological Characteristics. Cureus. 2022;14(10):e30708. DOI: 10.7759/cureus.30708.
5. Herold N, Ernst C, Ataseven B, Blümcke B, Schömig-Markiefka B, Heikaus S, Göhring UJ, Engel C, Lampe B, Rhiem K, Harter P, Hauke J, Schmutzler RK, Hahnen E. Pathogenic germline variants in SMARCA4 and further cancer predisposition genes in early onset ovarian cancer. Cancer Med. 2023;
6. Xu MJ, Zhang J, Lu X, Liu F, Shi S, Deng X. MiR-199a-5p-Regulated SMARCA4 Promotes Oral Squamous Cell Carcinoma Tumorigenesis. Int J Mol Sci. 2023;
7. Decroix E, Leroy K, Wislez M, Fournel L, Alifano M, Damotte D, Mansuet-Lupo A. [SMARCA4-deficient thoracic tumors: A new entity]. Bull Cancer. 2020.
8. Yoshida A, Kobayashi E, Kubo T, Kodaira M, Motoi T, Motoi N, Yonemori K, Ohe Y, Watanabe S-i, Kawai A, et al. Clinicopathological and molecular characterization of SMARCA4-deficient thoracic sarcomas with comparison to potentially related entities. Modern Pathol. 2017;30:797-809.
9. Perret R, Chalabreysse L, Watson S, Serre I, Garcia S, Forest F, Yvorel V, Pissaloux D, Thomas de Montpréville V, Masliah-Planchon J, 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.
10. Okazaki T, Yokoyama K, Tsuchiya J, Honda T, Ishikawa Y, Kirimura S, Miyazaki Y, Tateishi U. SMARCA4-deficient thoracic tumor detected by [18F]FDG PET/CT . Available from: https://dx.doi.org/10.1186/s41824-021-00102-5
11. Pang L, Shi M, Zhou H, Mo S, Zhuang W, Liu J, Sun D, Fang W, Zhang L. MA08.09 SMARCA4 deficient Thoracic Tumors: Clinicopathological, Molecular Characteristics and Optimal Therapeutics Methods. Available from: https://dx.doi.org/10.1016/j.jtho.2023.09.170
12. Jain D. SMARCA4 related thoracic/pulmonary tumors: a diagnostic conundrum in cytology. Available from: https://dx.doi.org/10.1016/j.jasc.2022.04.006
13. Jiang J, Chen Z, Gong J, Han N, Lu H. Thoracic SMARCA4-deficient undifferentiated tumor. Available from: https://dx.doi.org/10.1007/s12672-023-00639-w
14. Iwakoshi A, Sasaki E, Sato M, Sugiyama K, Kogure Y, Kitagawa C, Nishimura R. Thoracic SMARCA2-deficient But SMARCA4-preserved Tumors With Undifferentiated Morphology Combined With Claudin-4 Negativity. Available from: https://dx.doi.org/10.1097/PAS.0000000000001879
15. Anžeić N, Krasniqi F, Eberhardt A, Tzankov A, Haslbauer J. Ipilimumab and Pembrolizumab Mixed Response in a 41-Year-Old Patient with SMARCA4-Deficient Thoracic Sarcoma: An Interdisciplinary Case Study. Available from: https://dx.doi.org/10.1159/000515416
16. Iijima Y, Sakakibara R, Ishizuka M, Honda T, Shirai T, Okamoto T, Tateishi T, Sakashita H, Tamaoka M,

DOI: 10.69605/ijlbpr_13.6.36

Takemoto A, Kumaki Y, Ikeda S, Miyazaki Y. Notable response to nivolumab during the treatment of SMARCA4-deficient thoracic sarcoma: a case report. Available from: https://dx.doi.org/10.2217/imt-2019-0142

17. Boshara P, Hanona P, Poudel S, Jaiyesimi I, Ezekwudo D, Allen T, Nair G. AN AGGRESSIVE CASE OF THORACIC UNDIFFERENTIATED SMARCA4-DEFICIENT TUMOR WITH EXTENSIVE PLEURAL INVOLVEMENT . Available from: https://dx.doi.org/10.1016/j.chest.2023.07.2789
18. Ito A, Kawaguchi T, Shinoda M, Kaneda S, Kawaguchi K, Shimamoto A, Ito T, Fujimoto H, Yuasa H, Takao M. A Case of Thoracic SMARCA4-deficient Undifferentiated Tumor with Early Postoperative Recurrence. Available from: https://dx.doi.org/10.2482/haigan.62.417
19. Rekhtman N, Montecalvo J, Chang JC, Alex D, Ptashkin R, Ai N, Sauter J, Kezlarian BE, Jungbluth A, Desmeules P, Beras A, Bishop J, Plodkowski A, Gounder M, Schoenfeld A, Namakydoust A, Li BT, Rudin C, Riely G, Jones DR, Ladanyi M, Travis W. SMARCA4-Deficient Thoracic Sarcomatoid Tumors Represent Primarily Smoking-Related Undifferentiated Carcinomas Rather Than Primary Thoracic Sarcomas . Available from: https://dx.doi.org/10.1016/j.jtho.2019.10.023
20. Xiong Y, Zhang B, Nie L, Wu SK, Zhao H, Li D, Di J. [Thoracic SMARCA4-deficient undifferentiated tumor-pathological diagnosis and combined immune checkpoint inhibitor treatment] . Available from: https://pubmed.ncbi.nlm.nih.gov/37042149
21. Lin Y, Yu B, Sun H, Zhang H, Hu Z, Zhang Y, Wu Z, Sun S, Zhao X, Yu H, Wu X, Li Y, Wang J, Wang H. Promising efficacy of immune checkpoint inhibitor plus chemotherapy for thoracic SMARCA4-deficient undifferentiated tumor . Available from: https://dx.doi.org/10.1007/s00432-023-04806-y
22. Jiang J, Chen Z, Gong J, Han N, Lu H. Thoracic SMARCA4-deficient undifferentiated tumor . Available from: https://dx.doi.org/10.1007/s12672-023-00639-w
23. Nambirajan, A., Dutta, R., Malik, P., Bubendorf, L., & Jain, D. (2020). Cytology of SMARCA4-Deficient Thoracic Neoplasms: Comparative Analysis of SMARCA4-Deficient Non-Small Cell Lung Carcinomas and SMARCA4-Deficient Thoracic Sarcomas. *Acta Cytologica*, 65, 67 - 74. https://doi.org/10.1159/000510323.
24. Minoshima, A., Sugita, S., Segawa, K., Aoyama, T., Ito, M., Daimon, F., Takenami, T., Kido, T., Moriya, J., Nishikiori, H., & Hasegawa, T. (2023). Usefulness of cell block examination for the cytological diagnosis of thoracic SMARCA4-deficient undifferentiated tumor: A case report. *Diagnostic Cytopathology*, 51, E149 - E154. https://doi.org/10.1002/dc.25116.