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COMPREHENSIVE OVERVIEW OF SMARCA4-DEFICIENT THORACIC NEOPLASMS

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ABSTRACT SMARCA4, a crucial component of the SWI/SNF chromatin remodeling complex, has recently been identified as a significant player in the pathogenesis of certain thoracic tumors. SMARCA4-deficient thoracic tumors represent a unique subset of cancers, characterized by the loss of SMARCA4 protein expression, which has been observed to correlate with aggressive clinical behavior and a distinct histopathological profile. This review aims to provide a comprehensive overview of SMARCA4-deficient thoracic tumors, offering insights into potential pathways for targeted interventions and improved patient outcomes.

KEYWORDS

SMARCA4, thoracic, lung

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Introduction

SMARCA4 (also known as BRG1) is a core catalytic subunit of the SWI/SNF chromatin remodeling complex, which plays a pivotal role in regulating gene expression by altering the chromatin structure to allow access to transcriptional machinery. In recent years, mutations and deficiencies in the SMARCA4 gene have been increasingly recognized as significant contributors to the development of various cancer types, notably thoracic tumors, which include lung cancers and thoracic sarcomas. SMARCA4-deficient thoracic tumors are particularly aggressive and are associated with specific clinical and histological features that challenge traditional treatment approaches.[1,2]

The discovery of SMARCA4 as a tumor suppressor has profound implications for understanding the biology of these cancers. Its deficiency in thoracic tumors is often linked to alterations in genetic and epigenetic regulation, impacting cell cycle control, DNA repair mechanisms, and cellular differentiation pathways. The prevalence of SMARCA4 deficiency varies, but its presence is indicative of a distinct biological and clinical entity with poor prognosis[3]

Diagnosis:

The diagnosis of SMARCA4-deficient thoracic tumors is complex due to their histological similarities with other undifferentiated tumors.[4] The key diagnostic approach includes comprehensive immunohistochemical profiling, which often shows loss of SMARCA4 expression, coupled with genetic testing to confirm mutations in the SMARCA4 gene.[5] Advanced techniques such as next-generation sequencing can further identify characteristic mutations that confirm the diagnosis.[6] The immunohistochemical signature often includes co-loss of SMARCA4 and SMARCA2 with occasional overexpression of SOX2, which assists in distinguishing these tumors from other malignancies [7,8,9].

Clinical Presentation:

Patients with SMARCA4-deficient thoracic tumors typically present with symptoms related to large, invasive mediastinal masses. [10]These symptoms can include cough, chest pain, dyspnea, and superior vena cava syndrome due to the compressive nature of the tumors. [11]The majority of patients are male smokers in their middle age, which aligns with the demographic most at risk. The clinical course is aggressive, with rapid progression and poor prognosis commonly observed. Radiological findings often show large chest masses with invasive characteristics, such as invasion into adjacent structures like the lungs, pleura, and sometimes extending to the cervical region [12,13].

Therapeutic Approaches and Response

Therapeutic strategies for SMARCA4-deficient thoracic tumors are still evolving. Recent case reports have highlighted the potential efficacy of immunotherapy, particularly drugs like nivolumab, which have shown promise in cases where traditional cytotoxic chemotherapy failed. Additionally, some studies have reported success with combinations of drugs such as atezolizumab with bevacizumab, paclitaxel, and carboplatin, suggesting a potential for targeted therapy approaches[14].

Prognostic Outcomes

The prognosis for patients with SMARCA4-deficient thoracic tumors remains generally poor, with median survival rates often not exceeding a few months from diagnosis. These tumors are highly aggressive and metastatic, leading to rapid declines in patient condition. Identifying biomarkers for prognosis and treatment efficacy is an area of ongoing research, with a focus on understanding the genetic underpinnings that drive tumor aggressiveness[15,16].

Conclusion

SMARCA4-deficient thoracic tumors are a devastating diagnosis with limited treatment options and poor outcomes. Their distinct molecular and histological profiles require specialized diagnostic approaches and highlight the need for continued research into more effective therapeutic strategies. Clinicians and researchers must work together to better understand and combat this formidable cancer type.

REFERENCES:

1. 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.
2. 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.

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3. 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.
4. 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
5. 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
6. 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
7. 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
8. 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
9. 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
10. Iijima Y, Sakakibara R, Ishizuka M, Honda T, Shirai T, Okamoto T, Tateishi T, Sakashita H, Tamaoka M, 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
11. 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
12. 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
13. 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
14. 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
15. 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
16. 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