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Lumbar Atypical teratoid/rhabdoid tumor in an adolescent: Integrated histopathological and molecular diagnosis, a case report

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Case Report

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Abstract

Background: Atypical teratoid rhabdoid tumor is a rare, highly aggressive embryonal neoplasm of the central nervous system, and primary spinal presentations in older adolescents are exceptionally uncommon, with very limited comparative data in the literature.

Case Summary: We report a 17-year-old male with cauda equina syndrome due to an intradural lumbar mass initially interpreted radiologically and intraoperatively as myxopapillary ependymoma or schwannoma. Histopathological findings revealed a highly cellular small round blue cell tumor with rhabdoid morphology, high proliferative activity and complete loss of nuclear SMARCB1/INI1 expression.

DNA methylation profiling assigned the lesion to the atypical teratoid rhabdoid tumor MYC molecular subgroup with biallelic SMARCB1 inactivation. The patient received intensive multimodal therapy including craniospinal irradiation and multi-agent chemotherapy.

Conclusion: This case highlights the diagnostic value of integrated histopathological and molecular classification in an unusual spinal tumor occurring in an adolescent. In particular, DNA methylation profiling was crucial for confirming the diagnosis and assigning the tumor to the ATRT-MYC subgroup.

Introduction

Atypical teratoid rhabdoid tumors (ATRTs) are rare, highly malignant embryonal CNS tumors, accounting for approximately 1–2% of pediatric brain tumors[1]. In adults (> 18 years), ATRTs are uncommon[2]. The brain is the most frequent site, involving the posterior fossa, cerebral hemispheres, and sellar region. Primary spinal ATRTs are exceedingly rare, representing approximately 2% of CNS ATRTs and occurring predominantly in children [3–5].

Histologically, ATRTs are heterogeneous and may contain rhabdoid cells, small round blue cells, epithelial differentiation, and mesenchymal components, and thereby complicate diagnosis[6]. Immunohistochemistry and DNA methylation profiling have improved diagnostic precision. ATRTs are characterized by inactivation of SMARCB1, resulting in loss of nuclear INI1 expression, or, less commonly, by SMARCA4 inactivation with loss of BRG1 expression. Complete SMARCB1/INI1 loss also occurs in selected sarcomas and neuroepithelial tumors [7]. DNA methylation profiling distinguishes these entities and improves diagnostic accuracy. Moreover three molecular subgroups of ATRT - ATRT-SHH, ATRT-TYR, and ATRT-MYC have been delineated, each with distinct transcriptional, clinical and histopathological features[6].

Here, we present a case of a primary lumbar ATRT in an adolescent, initially suspected to represent myxopapillary ependymoma or schwannoma. However, histopathological evaluation combined with DNA methylation profiling confirmed the diagnosis of ATRT belonging to the ATRT-MYC molecular subgroup, Highlighting the diagnostic value of integrated histopathological and molecular assessment like DNA methylation profiling in anatomically and clinically atypical SMARCB1-deficient CNS tumors.

Clinical summary

A 17-year-old male presented with a one-month history of progressive lower extremity pain, followed by a rapid worsening of symptoms. His symptoms progressed to significant weakness in the lower limbs and he developed urinary incontinence. Neurological examination revealed clinical signs consistent with cauda equina syndrome, including bilateral sensory deficits in the feet and lower legs, reduced muscle strength in the lower extremities, saddle anesthesia and urinary retention.

Magnetic resonance imaging (MRI) of the entire spine demonstrated a relatively homogeneous, expansive intradural lesion located posterior to the L4 and L5 vertebral bodies, with only minimal contrast enhancement. Additional, less well-defined lesions were suspected cranially and caudally to the primary lesion (Fig. 1). The radiological findings were suggestive of a myxopapillary ependymoma. Based on clinical and radiological findings, emergency surgery was performed. Intraoperative findings revealed involvement of the L4 nerve root, and schwannoma was considered by the surgeons. The intradural tumor, with associated nerve root involvement, was resected, formalin-fixed and submitted to the Department of Pathology for histopathological evaluation. Gross total resection was achieved at surgery. Postoperative MRI did not show any residual tumor. CSF taken 13 days postoperative, was without tumor cells and no ctDNA was found in the CSF.

Pathological findings

HE staining revealed a highly cellular tumor composed of densely packed, monomorphic small blue cells displaying round, vesicular nuclei with prominent nucleoli and a variable amount of cytoplasm. Features found in primitive neuroectodermal cells. Tumor cells exhibiting a rhabdoid phenotype was noted, with eccentrically positioned nuclei surrounded by abundant eosinophilic cytoplasm. Mitotic activity was elevated, with more than 10 mitoses per 5 high-power fields (HPF), Ki67 index in hotspots up to 50%. No significant areas of necrosis were observed (Fig. 2).

The tumor cells had a polyimmunephenotype with a diffusely positive reaction for vimentin and CD99 and a patchy reaction for ASMA. All tumor cells showed a loss of nuclear SMARCB1/INI1 protein expression (Fig. 2).

Based on the radiological, clinical and histological findings, ATRT was considered the most likely diagnosis. However, given the patients age and tumor location, further classification using DNA methylation profiling was pursued to achieve diagnostic clarification.

Molecular genetic findings

DNA methylation profiling was performed using the EPIC 936K BeadChip array (Illumina) for brain tumor classification. The sample's IDAT files were analyzed by comparison with the reference database from Heidelberg Epignostix GmbH. The tumor demonstrated a high-confidence match to the methylation class Atypical teratoid rhabdoid tumor, MYC-subtype, with a calibrated score of 0.99676, confirming the

molecular classification of the tumor, however the copy number alterations profile shows no alterations(Fig. 3).

Additionally, mutational analysis was conducted via next-generation sequencing (NGS) using the Ion Torrent Oncomine Comprehensive Assay v3 panel. A pathogenic nonsense mutation, Ser258Ter, was identified in the SMARCB1 gene, resulting in a truncated and likely non-functional protein. This finding confirms the biallelic inactivation of SMARCB1, a hallmark molecular event in ATRT.

The materials were sent to national review, and they confirmed the diagnosis and the ATRT – MYC subgroup.

Together, these molecular genetic results corroborate the histopathological diagnosis and firmly classify the tumor within the ATRT-MYC molecular subgroup.

In the differential diagnosis, epithelioid schwannoma, poorly differentiated chordoma, and epithelioid sarcoma were considered. However, the observed histopathological features and immunophenotypic profile are atypical for these entities. Furthermore, these tumor types would not be expected to cluster within the ATRT-MYC methylation class.

Treatment, prognosis and clinical outcome

In accordance with the SIOPE ATRT01 protocol (The European Society of Pediatric Oncology - Atypical Teratoid Rhabdoid Tumor 01 protocol), treatment options were discussed with the principal investigator, who recommended early initiation of radiotherapy. Thirteen days after surgery, the patient received the first cycle of ICE chemotherapy (ifosfamide, carboplatin, etoposide). No intrathecal methotrexate (IT MTX) was given to minimize CNS toxicity during radiotherapy.

Proton beam radiotherapy was initiated 11 days after the start of the first ICE cycle. Craniospinal irradiation (CSI) was delivered to a total dose of 36 Gy in 20 fractions, followed by a focal boost to the tumor bed to a cumulative dose of 50.4 Gy in 28 fractions. In accordance with the SIOPE ATRT01 protocol, no chemotherapy was given during CSI. Due to sepsis occurring three weeks into radiotherapy, chemotherapy was also withheld during the boost phase.

Following completion of radiotherapy, the second chemotherapy cycle, consisting of VCA (vincristine, cyclophosphamide, doxorubicin), was initiated on the day after the final radiotherapy fraction. The patient subsequently continued protocol-based multimodal therapy with a total of five ICE cycles, four VCA cycles, and three cycles containing doxorubicin (DOX). No dose reductions were required; however, treatment cycles were delayed by up to one week because of neutropenia, despite the use of granulocyte colony-stimulating factor (G CSF).

The patient was neurocognitive tested prior to the start of radiotherapy and again five months after completion of radiotherapy. At follow-up, the patient reported some fatigue but was able to attend

school full time and did not exhibit any overt cognitive deficits. The patient was able to walk, but still had urinary and fecal incontinence and sensory deficits.

Discussion

ATRT arising in the spinal cord or intradural spinal canal rather than brain is very rare and the prognosis is still poor [1] [8]. A total 48 cases were reported in the review by Li et al [1], with only 5 patients above 15. Three died of disease after 1–34 months and two where not specified. Two of them had radiotherapy and only one had CSI but was only subtotal resected. Based on these cases we do not have any cases to compare to.

Prognostic factors as young age, incomplete resection, metastasis, high-dose chemotherapy (HDCT) or RT have been described in literature, but molecular classification in the three distinct subgroups ATRT-TYR, - SHH and – MYC too is a prognostic factor [9] [10] [11]. As reported by M.C. Frühwald et al [9], an European cohort of 143 children with ATRT, shows children over the age of three have better prognosis, but this effect is modified by the underlying methylation subgroup. 5-year overall survival (OS) and event-free survival (EFS) were 34.7 ± 4.5% and 30.5 ± 4.2% respectively, but subgroup analysis revealed markedly better outcomes for ATRT-TYR in patients ≥ 1 year (5-years OS = 71.5 ± 12,2 %), an intermedate for ATRT –nonTYR in patients ≥1year (5 years OS 32.5 ± 8.7 % and poorest fr ATRT – nonTYR in patients ≤ 1 year.

In our case, the patient's age of 17 years would suggest a more favorable risk profile, however, the assignment to the ATRT-MYC subgroup indicates a higher risk disease. The ATRT-MYC classification provides biologically relevant prognostic context and supported management within a protocol-based, multidisciplinary treatment strategy. However, the prognostic and treatment implications of methylation subgroup assignment in spinal ATRT occurring in adolescents remain uncertain because of the very limited number of comparable cases.

Moreover, the median age at diagnosis in the referred cohort was 2.45 years, ranging from 0 to 19 years old, and only 3 had a spinal location [9], witch again make it difficult to compare and underlines the difficulties in predicting clinical outcome in ATRT, particularly in rare spinal presentation in older patients [12].

This case highlights the diagnostic value of integrated histopathological and molecular classification in an unusual spinal tumor occurring in an adolescent. The initial radiological and intraoperative findings were suggestive for myxopapillary ependymoma or schwannoma; however, the histological findings, complete loss of SMARCB1/INI1 expression, and DNA methylation profiling established the diagnosis of ATRT and assigned the tumor to the ATRT-MYC subgroup. In this anatomically and clinically atypical setting, DNA methylation profiling was particularly important for distinguishing ATRT from more common spinal and nerve-root tumors and from other SMARCB1-deficient neoplasms. As molecular classification becomes increasingly integrated into clinical practice, DNA methylation profiling may serve as an important tool to refine prognosis and may guide future treatment strategies.

Declarations

We hereby declair that the manuscript - Lumbar Atypical teratoid/rhabdoid tumor in an adolescent: Integrated histopathological and molecular diagnosis, a case report – or any part of it has not been previously published or submitted concurrently to any other journal.

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Conflict of interest

The authors have no relevant financial or non-financial interests to disclose.

Author contribution

Each author, Sarah S. R. Kragesteen, Jeanette K. Petersen and Michael T. Callsen has contributed according to the ICMJE criteria.

SK: collecting, organizing, and compiling the clinical and histopathological data, as well as conducting the literature review. - Original draft, Conceptualization.

JP: Expert analysis of the histopathological findings, and writing. - review and editing, Conceptualization.

MT**:** Clinical expert and interpretation of the clinical aspects of the case, and writing. -review and editing, Conceptualization.

All authors read and approved the final manuscript.

Data availability statement

There are no new data associated with this article.

Ethics approval

This is a case report. According to the guidelines of The National- or Regional Committee on Health Research Ethics (NVK and RVK), no ethical approval is required.

Consent to participate and publish

The authors confirm that written consent for submission and publication of this case report, including the images and associated text, have been obtained from the patient in line with.

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Figures



Figure 1

MRI, Homogeneous, expansive intradural tumour at L4-L5 (white arrow, ←).

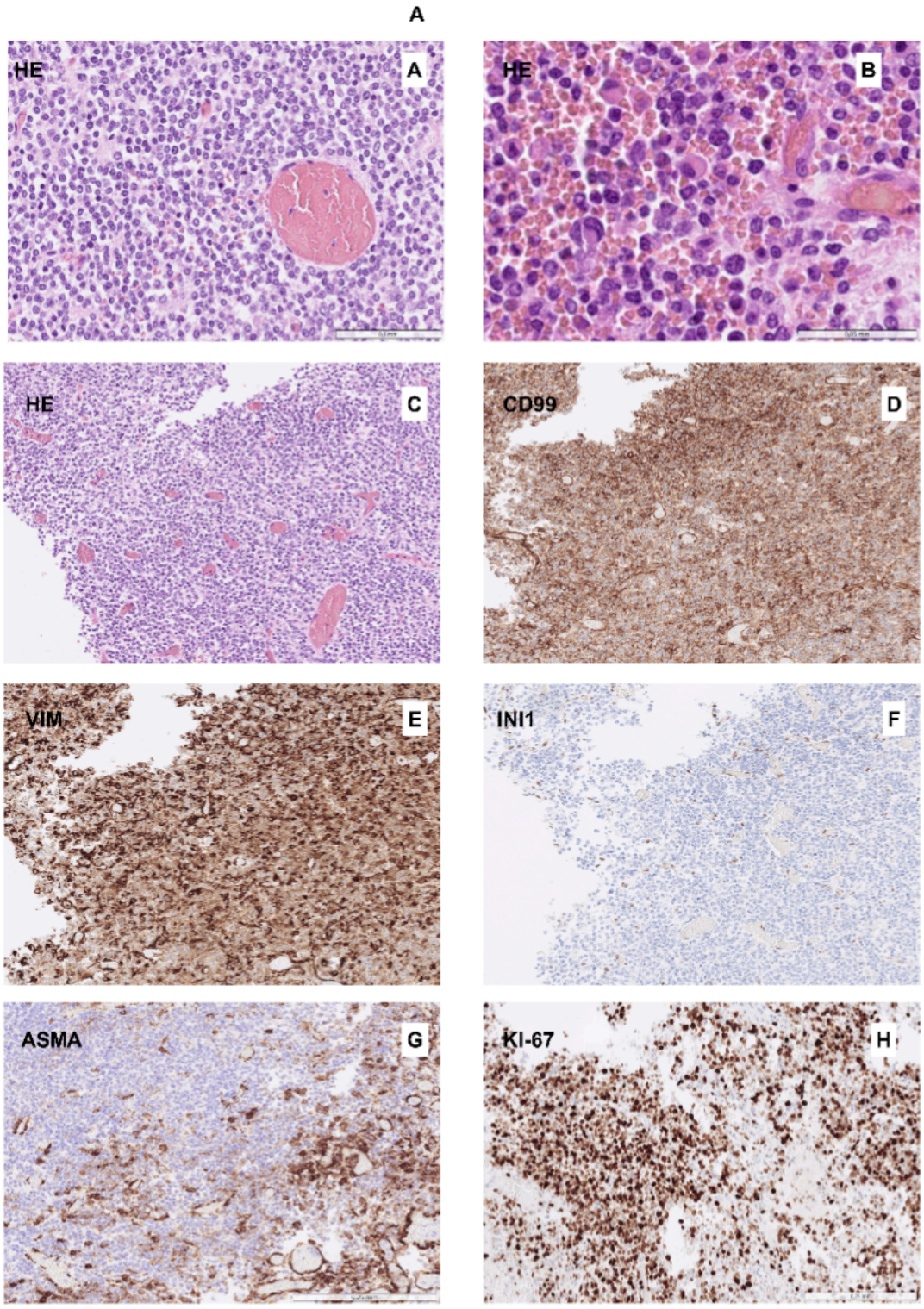


Figure 2

Microscopical evaluation of the resected tissue showed small monomorphic blue tumor cells displaying round, vesicular nuclei with prominent nuclei and tumor cells with rhabdoid features exhibiting eccentrically located nucleus surrounded by abundant eosinophilic cytoplasm (**A** 40X: **B** 40X: **C** 15X) The tumor cells are diffusely immunopositive for CD99 and Vimentin (**D** 15X: **E** 15X), immunonegative for INI-

1 (**F**), and focally immunopositive for smooth muscle actin, ASMA (**G** 20X). Ki-67 proliferation index in hotspot up to 50% (**H** 20X)

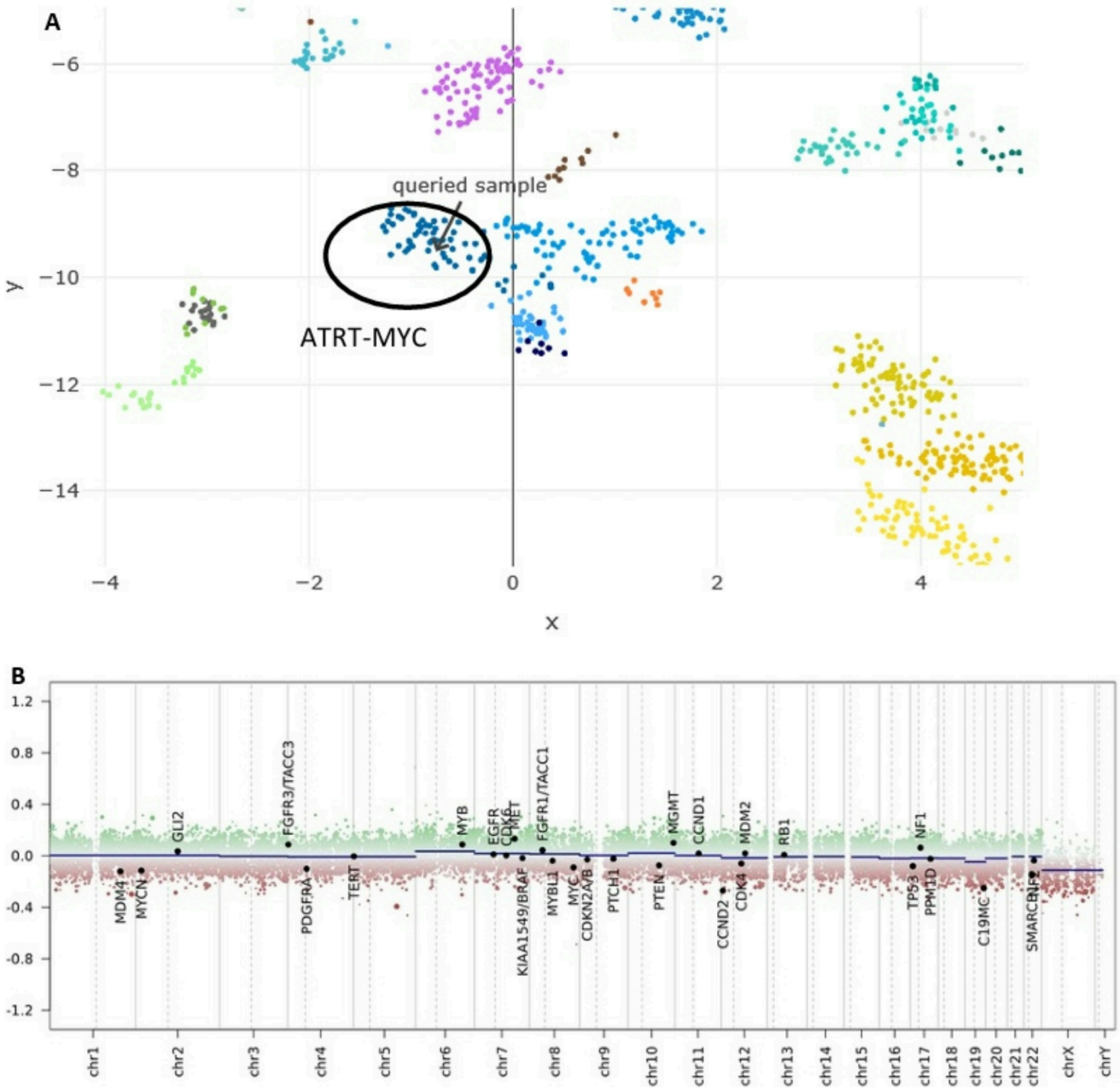


Figure 3

Uniform manifold approximation and projection (UMAP) A two-dimensional visualization of the DNA methylation reference dataset. The case groups with ATRT-MYC (**A**). Copy number variation profile analysis. The profile depicts log2 transformed copy number ratios (Y-axis) for chromosomes 1 through 22 (x-axis) Protentional gains/amplifications are represented by the positive Y-axis, while losses are

depicted by the negative y-axis. 29 CNS tumor relevant gene regions are highlighted. No detectable alterations were found (**B**).