Atypical teratoid/rhabdoid tumor

- Measles oncolytic virus as an immunotherapy for recurrent/refractory pediatric medulloblastoma and atypical teratoid rhabdoid tumor: results from PNOC005
- Importance of symptoms acuity for clinical diagnosis of primary sellar atypical teratoid/rhabdoid tumor
- Specific imaging features of sellar atypical teratoid/rhabdoid tumor or the lack of thereof
- Expression of LTR and LINE1 transposable elements defines atypical teratoid/rhabdoid tumor subtypes
- Malignant Rhabdoid Tumors of Cranial Nerves-A Clinically Distinct Group With Characteristic Neuroradiological, Histopathological, and Molecular Features
- Elevated Bromide Levels Due to Tazemetostat Therapy Treated With Salt and Water Supplementation in Two Children With Atypical Teratoid Rhabdoid Tumor
- Pediatric Atypical Teratoid Rhabdoid Tumor of Central Nervous System: A Case Series with Review of Literature
- Navigating the complexity of atypical teratoid/rhabdoid tumor (ATRT) in pediatric neuro-oncology: Insights from clinical spectrum to therapeutic challenges

---

Definition

Atypical teratoid/rhabdoid tumor (AT/RT) is a highly malignant tumor comprising poorly differentiated constituents, which often includes rhabdoid cells, with inactivation of SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily b, member 1; SMARCB1 (integrase interactor 1; INI1) or rarely SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily a, member 4; SMARCA4 (Brahma-related gene 1; BRG1) [1].

Histologically similar tumors lacking these molecular genetics should be classified as CNS embryonal tumors with rhabdoid features.

Many of these tumors were probably previously misdiagnosed as MDBs. Occurs primarily in infants and children (> 90% are < 5 years of age, with most age < 2 years). A minority are associated with primary renal rhabdoid tumor. The ratio of supratentorial to infratentorial AT/RTs is 4:3. Posterior fossa AT/RTs may occur in the cerebellar hemispheres, cerebellopontine angle (CPA) and brainstem. 33% have CSF spread at presentation. Althogh the prognosis is poor, not all AT/RTs have the same behavior, and at least 2 different molecular classes have been identified.

Atypical teratoid rhabdoid tumor (AT/RT) is a rare, highly malignant, true rhabdoid tumor in the central nervous system predominantly presenting in young children.

It was originally described a histological variant of Wilm’s tumor in 1978.

Atypical teratoid rhabdoid tumors (ATRTs) comprise at least two transcriptional subtypes with different clinical outcomes; however, the mechanisms underlying therapeutic heterogeneity remained unclear. In a study, Torchia et al., analyzed 191 primary ATRTs and 10 ATRT cell lines to define the genomic and epigenomic landscape of ATRTs and identify subgroup-specific therapeutic targets.

They found ATRTs segregated into three epigenetic subgroups with distinct genomic profiles, SMARCB1 genotypes, and chromatin landscape that correlated with differential cellular responses to a panel of signaling and epigenetic inhibitors. Significantly, they discovered that differential methylation of a PDGFRB-associated enhancer confers specific sensitivity of group 2 ATRT cells to dasatinib and nilotinib, and suggest that these are promising therapies for this highly lethal ATRT subtype [2)].

Classification

AT/RT can occur anywhere in the central nervous system (CNS) including the spinal cord. About 60% will be in the posterior cranial fossa (particularly the cerebellum). One review estimated 52% posterior fossa, 39% sPNET (supratentorial primitive neuroectodermal tumors), 5% pineal, 2% spinal, and 2% multi-focal.

In the United States, three children per 1,000,000 or around 30 new AT/RT cases are diagnosed each year. AT/RT represents around 3% of pediatric cancers of the CNS.

Around 17% of all pediatric cancers involve the CNS; it is the most common childhood solid tumor.

see Adult sellar atypical teratoid rhabdoid tumor.

see Cerebellopontine angle atypical teratoid rhabdoid tumor.

Spinal Atypical teratoid rhabdoid tumor

see Spinal Atypical teratoid rhabdoid tumor.

Pathology

Typically shows rhabdoid cells which can also be seen in other tumors, but it is differentiated from other tumors by the specific genetic alteration involving the SMARCB1 gene. Only a few cases of AT/RT arising in low-grade glioma have been reported. A 13-year-old girl presented with headache, dizziness, nausea and vomiting.A 4.7 cm cerebellar mass was found on MRI.The mass was totally removed. Histologically, the tumor revealed two distinct morphologic appearances: central areas of AT/RT containing rhabdoid cells and sarcomatous component in the background of pleomorphic xanthoastrocytoma(PXA). Immunohistochemically, PXA areas retained nuclear expression of INI-1 and low Ki-67 proliferation index, whereas AT/RT component showed loss of INI-1 nuclear expression and markedly elevated Ki-67 proliferation index. Epithelial membrane antigen (EMA), smooth muscle actin (SMA), and p53 protein were positive only in AT/RT. BRAF V600E mutation was identified in PXA by real-time polymerase chain reaction.We report a rare case of AT/RT arising in PXA which is supposed to progress by inactivation of INI-1 in a pre-existing PXA [3)].

Diagnosis

The standard work-up for AT/RT includes:

Magnetic resonance imaging (MRI) of the brain and spine

Lumbar puncture to look for M1 disease

Computed tomography (CT) of chest and abdomen to check for a tumor

Bone marrow aspiration to check for bone tumors. Sometimes the physician will perform a stem cell transplant

Bone marrow biopsy

Bone scan

The initial diagnosis of a tumor is made with a radiographic study (MRI[20] or CT-). If CT was performed first, an MRI is usually performed as the images are often more detailed and may reveal previously undetected metastatic tumors in other locations of the brain. In addition, an MRI of the spine is usually performed. The AT/RT tumor often spreads to the spine. AT/RT is difficult to diagnose only from radiographic study; usually, a pathologist must perform a cytological or genetic analysis.

Examination of the cerebrospinal fluid is important (CSF), as one-third of patients will have intracranial dissemination with involvement of the CSF. Large tumor cells, eccentricity of the nuclei, and prominent nucleoli are consistent findings.[21] Usually only a minority of AT/RT biopsies have rhabdoid cells, making diagnosis more difficult. Increasingly it is recommended that a genetic analysis be performed on the brain tumor, especially to find if a deletion in the INI1/hSNF5 gene is involved (appears to account for over 80% of the cases). The correct diagnosis of the tumor is critical to any protocol. Studies have shown that 8% to over 50% of AT/RT tumors are diagnosed incorrectly.

Treatment

Atypical teratoid rhabdoid tumor treatment.

Outcome

Patient age at the time of diagnosis, supratentorial location of the mass and fewer complications with adjuvant treatments seem to be factors yielding good prognosis for AT/RT tumors.

AT/RT is a rare and highly progressive malignancy in the children population. This tumor aggressively grows after the first surgery. The INI-1 gene has been found as a diagnostic tumor marker in AT/RT. The characteristic of AT/RT is an absence of INI-1 staining in tumor cells. The treatment in AT/RT serves as palliative treatment, aiming to improve patient's quality of life. The poor prognosis is associated with MR imaging evidence of disseminated leptomeningeal tumor [4].

Case series

Data from 6 pediatric patients with atypical teratoid/rhabdoid tumors, which mainly contained the features of magnetic resonance imaging (MRI) and positron emission tomography (PET)/computed tomography (CT), was retrospectively analyzed. Follow-up was conducted in all patients through clinic services and/or telephone consultation.

The patients included 4 males and 2 females, aged from 3.2 to 83.1 months at the initial diagnosis. All patients had MRI scans. Two patients underwent 18F-fluorodeoxyglucose PET/CT scintigraphy preoperatively and 4 postoperatively. All primary lesions were located in the cranial cavity and the average diameter of lesions was 37.2 mm. Cerebrospinal fluid spread on enhanced T1-weighted images were found in 2 patients. Multiple metastases were found on MRI and PET/CT scans, which were located at cranial cavity, spinal cord, lung and lymph node. The primary and metastatic lesions showed evident uptake of 18F-fluorodeoxyglucose. Two patients underwent total tumor removal, and 4 patients underwent subtotal removal. None of the patients received shunt surgery. Follow-up was performed in all 6 patients. One patient survived event-free 38.4 months after resection. The mean overall survival of the remaining 5 patients was 5.1 months.

They identified specific PET/CT and MRI features that can facilitate the recognition of atypical teratoid/rhabdoid tumors prior to biopsy [5)].

Twenty-eight pediatric patients with CNS AT/RT who were treated with radiation therapy (RT) as part of multimodality treatment regimens at a single institution (1996-2015) were reviewed. Survival outcomes were analyzed in relation to possible prognostic factors.

The 28 patients analyzed were followed up for a median 48-month period. Median progression-free survival (PFS) was 11 months, and overall survival (OS) was 57 months. Patients < 3 years old had RT delayed for a longer period after surgery ($p = 0.04$), and the mean RT dose to tumor bed was lower ($p < 0.01$) than in patients ≥ 3 years old. In multivariate analysis, a higher primary tumor bed RT dose was identified as a favorable prognostic factor for both PFS (hazard ratio [HR] = 0.85 per gray, $p < 0.01$) and OS (HR = 0.92 per gray, $p = 0.02$). In addition, an interval between surgery and RT initiation > 2 months, with disease progression observed before RT, as compared with an interval ≤ 2 months without disease progression prior to RT, was associated with worse PFS (HR = 8.50, $p < 0.01$) and OS (HR = 5.27, $p < 0.01$).

Early and aggressive RT after surgery is critical for successful disease control in AT/RT patients. Conversely, a delay in RT until disease progression is observed that leads to unfavorable outcomes [6)].

In a study, Torchia et al. analyzed 191 primary Atypical teratoid rhabdoid tumor ATRTs and 10 ATRT cell lines to define the genomics and epigenomic landscape of ATRTs and identify subgroup-specific therapeutic targets. They found ATRTs segregated into three epigenetic subgroups with distinct genomic profiles, SMARCB1 genotypes, and chromatin landscape that correlated with differential cellular responses to a panel of signaling and epigenetic inhibitors. Significantly, they discovered that differential methylation of a PDGFRB-associated enhancer confers specific sensitivity of group 2 ATRT cells to dasatinib and nilotinib, and suggest that these are promising therapies for this highly lethal ATRT subtype [7)].

Case reports

A 10-month-old child presented with complaints of drowsiness and intractable vomiting. Imaging showed multifocal supra- and infratentorial lesions with obstructive hydrocephalus. The child underwent a ventriculoperitoneal shunt followed by surgical removal of the posterior fossa lesion. Histopathological features were consistent with AT/RT.

Multifocal AT/RT is very rare. The impact of multifocality on the outcome is not known as very few reports are available. Newer targeted therapies may offer insight into improving outcomes in the future [8)]

Two cases of primary spinal atypical teratoid/rhabdoid tumor (AT/RT), which rarely occurs in adults marked by SMARCA4 inactivation, and SMARCB1 inactivation for pediatric cases. AT/RT represents a highly malignant neoplasm comprising poorly differentiated constituents and rhabdoid cells, with SMARCB1(INI1) or infrequently SMARCA4 (BRG1) inactivation. These tumors are predominantly found in children but are rare in adults. While AT/RT can arise anywhere in the central nervous system, spinal cord localization is comparatively scarce. Despite mutation or loss of SMARCB1 at the 22q11.2 locus serving as the genetic hallmark of AT/RTs, infrequent cases of SMARCA4 inactivation with intact SMARCB1 protein expression are significant. We present each case of primary spinal tumors in a child and an adult, showing loss of the SMARCB1 and SMARCA4 proteins, respectively. Both tumors met the AT/RT diagnostic criteria. The histopathology demonstrated the presence of rhabdoid cells in both cases. Diagnosing primary spinal AT/RT with SMARCB1 protein loss remains a challenge. Nevertheless, the presence of SMARCB1 positivity alone must be noted to be insufficient to exclude the possibility of AT/RT diagnosis. In cases in which the diagnosis of AT/RT is highly suspected clinically, additional testing is warranted, including SMARCA4 analysis [9)].

A 7-year-old girl with recurrent tumor mass in the left parieto-occipital region after performing craniotomy surgical resection. The tumor mass aggressively grew within a month after surgery [10)].

References

[1)]
Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, Ohgaki H, Wiestler OD, Kleihues P, Ellison DW. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol. 2016 Jun;131(6):803-20. doi: 10.1007/s00401-016-1545-1. Epub 2016 May 9. PMID: 27157931.

[2)], [7)]
Torchia J, Golbourn B, Feng S, Ho KC, Sin-Chan P, Vasiljevic A, Norman JD, Guilhamon P, Garzia L, Agamez NR, Lu M, Chan TS, Picard D, de Antonellis P, Khuong-Quang DA, Planello AC, Zeller C, Barsyte-Lovejoy D, Lafay-Cousin L, Letourneau L, Bourgey M, Yu M, Gendoo DM, Dzamba M, Barszczyk M, Medina T, Riemenschneider AN, Morrissy AS, Ra YS, Ramaswamy V, Remke M, Dunham CP, Yip S, Ng HK, Lu JQ, Mehta V, Albrecht S, Pimentel J, Chan JA, Somers GR, Faria CC, Roque L, Fouladi M, Hoffman LM, Moore AS, Wang Y, Choi SA, Hansford JR, Catchpoole D, Birks DK, Foreman NK, Strother D, Klekner A, Bognár L, Garami M, Hauser P, Hortobágyi T, Wilson B, Hukin J, Carret AS, Van Meter TE, Hwang EI, Gajjar A, Chiou SH, Nakamura H, Toledano H, Fried I, Fults D, Wataya T, Fryer C, Eisenstat

DD, Scheinemann K, Fleming AJ, Johnston DL, Michaud J, Zelcer S, Hammond R, Afzal S, Ramsay DA, Sirachainan N, Hongeng S, Larbcharoensub N, Grundy RG, Lulla RR, Fangusaro JR, Druker H, Bartels U, Grant R, Malkin D, McGlade CJ, Nicolaides T, Tihan T, Phillips J, Majewski J, Montpetit A, Bourque G, Bader GD, Reddy AT, Gillespie GY, Warmuth-Metz M, Rutkowski S, Tabori U, Lupien M, Brudno M, Schüller U, Pietsch T, Judkins AR, Hawkins CE, Bouffet E, Kim SK, Dirks PB, Taylor MD, Erdreich-Epstein A, Arrowsmith CH, De Carvalho DD, Rutka JT, Jabado N, Huang A. Integrated (epi)-Genomic Analyses Identify Subgroup-Specific Therapeutic Targets in CNS Rhabdoid Tumors. Cancer Cell. 2016 Dec 12;30(6):891-908. doi: 10.1016/j.ccell.2016.11.003. PubMed PMID: 27960086.

3) Jeong JY, Suh YL, Hong SW. Atypical teratoid/rhabdoid tumor arising in pleomorphic xanthoastrocytoma: a case report. Neuropathology. 2014 Aug;34(4):398-405. PubMed PMID: 25268025.

4) , 10) Parenrengi MA, Permana GI, Suryaningtyas W, Fauziah D. The aggressive progression of primary intracranial atypical teratoid/rhabdoid tumor after surgical resection: A case report. Int J Surg Case Rep. 2022 Jan 24;91:106790. doi: 10.1016/j.ijscr.2022.106790. Epub ahead of print. PMID: 35086049.

5) Kang X, Xia H, Skudder-Hill L, Yin Y, Wang X. Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET)/Computed Tomography Features of Atypical Teratoid/Rhabdoid Tumors: Case Series and Review. J Child Neurol. 2022 Dec;37(12-14):1003-1009. doi: 10.1177/08830738221129968. PMID: 36417494.

6) Yang WC, Yen HJ, Liang ML, Chen HH, Lee YY, Wong TT, Hu YW, Chen YW. Role of early and aggressive post-operative radiation therapy in improving outcome for pediatric central nervous system atypical teratoid/rhabdoid tumor. Childs Nerv Syst. 2019 Apr 13. doi: 10.1007/s00381-019-04126-y. [Epub ahead of print] PubMed PMID: 30982172.

8) Pai A, Prasad GL, Vasudevan G, Nayak DM. Multifocal atypical teratoid/rhabdoid tumour in an infant-a rare case report. Childs Nerv Syst. 2024 Feb 2. doi: 10.1007/s00381-023-06274-8. Epub ahead of print. PMID: 38305878.

9) Morisako T, Umebayashi D, Nagai T, Yamanaka T, Hirose T, Shishido-Hara Y, Konishi E, Hashimoto N. Two Cases of Atypical Teratoid/Rhabdoid Tumor in the Spinal Cord: Loss of SMARCB1 in a Child and Loss of SMARCA4 in an Adult. NMC Case Rep J. 2024 Jan 31;11:27-32. doi: 10.2176/jns-nmc.2022-0096. PMID: 38410173; PMCID: PMC10895083.