Neurology®

The most widely read and highly cited peer-reviewed neurology journal
The Official Journal of the American Academy of Neurology

Neurology Publish Ahead of Print
DOI: 10.1212/WNL.0000000000200196

Pearls & Oy-sters: Pivoting Treatment Regimens of Pediatric Atypical Teratoid Rhabdoid Tumors to Optimize Care in Adult ATRT: A Case Report

Author(s):

Rohan Rao, BS¹; Abigail Koehler, BS¹; Yehudit Rothman, PA¹; Brandi Turner, RN²; Jamie Denlinger, RN²; Melissa Erickson, MD³; Matthew Hagen, MD, PhD⁴; Timothy S. Braverman, MD⁵; Abdelkader Mahammed, MD⁶; Karl Golnik, MD, M.Ed⁷; Mario Zuccarello, MD⁸; Yair M. Gozal, MD, PhD⁹; E. Randolph Broun, MD¹⁰; Susan N. Chi, MD¹¹; Soma Sengupta, MD, PhD¹

Corresponding Author:

Soma Sengupta, sengupsm@ucmail.uc.edu

Neurology® Published Ahead of Print articles have been peer reviewed and accepted for publication. This manuscript will be published in its final form after copyediting, page composition, and review of proofs. Errors that could affect the content may be corrected during these processes.

Affiliation Information for All Authors: 1. Department of Neurology and Rehabilitation Medicine, University of Cincinnati College of Medicine, Cincinnati, OH 45267 USA; 2. Barrett Cancer Center, University of Cincinnati, Cincinnati, OH 45219 USA; 3. Department of Family and Community Medicine, University of Cincinnati College of Medicine, Cincinnati, OH 45267 USA; 4. Department of Pathology & Laboratory Medicine, University of Cincinnati College of Medicine, Cincinnati, OH 45267 USA; 5. Department of Anatomy & Clinical Pathology, Jewish Hospital, Cincinnati, OH 45236 USA; 6. Department of Radiology, University of Cincinnati College of Medicine, Cincinnati, OH 45267 USA; 7. Department of Ophthalmology, University of Cincinnati College of Medicine, Cincinnati, OH 45267 USA; 8. Department of Neurosurgery, University of Cincinnati College of Medicine, Cincinnati, OH 45267 USA; 9. Mayfield Clinic, Cincinnati, OH 45209 USA; 10. Department of Hematology Oncology, Jewish Hospital, Cincinnati, OH 45236 USA; 11. Department of Pediatric Neuro-Oncology, Dana Farber/Boston Children's Cancer and Blood Disorder Center, Boston, MA 02215 USA

Equal Author Contribution:

Contributions:

Rohan Rao: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data

Abigail Koehler: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data

Yehudit Rothman: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Brandi Turner: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Jamie Denlinger: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Melissa Erickson: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data

Matthew Hagen: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data

Timothy S. Braverman: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data

Abdelkader Mahammedi: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data

Karl Golnik: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data

Mario Zuccarello: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data

Yair M. Gozal: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data

E. Randolph Broun: Drafting/revision of the manuscript for content, including medical writing for

content; Analysis or interpretation of data

Susan N. Chi: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data

Soma Sengupta: Drafting/revision of the manuscript for content, including medical writing for content;

Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data

Figure Count:

2

Table Count:

0

Search Terms:

[120] MRI, [194] Diplopia (double vision), [214] Primary brain tumor, [218] Chemotherapy-tumor, [219] Radiation therapy-tumor

Acknowledgment:

We wish to thank the patient for agreeing to participate in the case report.

Study Funding:

This work is supported by the Harold C. Schott Endowment, awarded to S.S.

Disclosures:

The authors report no disclosures relevant to the manuscript.

Handling Editor Statement:

Submitted and externally peer reviewed. The handling editors were Renee Shellhaas, MD, MS and Roy Strowd III, MD, Med, MS.

ABSTRACT

ATRT is a highly malignant embryonal tumor of the central nervous system (CNS), largely affecting pediatric patients, with exceedingly rare cases in adults at an estimated annual incidence of 1/1,000,000. We report a unique case of ATRT in a 43-year-old female patient who first presented with progressive focal headaches. Imaging revealed a sellar mass with suprasellar extensions, which was partially removed via a transsphenoidal resection. The tumor aggressively recurred just one month post-operatively. Her care team pursued a novel treatment plan by using a slightly modified COG ACNS 0332 regimen which involved radiation, followed by four cycles of monthly chemotherapy including vincristine, cyclophosphamide, and cisplatin. Hematopoietic stem cells were collected between radiation and chemotherapy in the event that the patient required stem cell salvage therapy post-adjuvant chemotherapy. The MRIs taken at 2- and 4-months post-recurrence indicated a substantial decrease in tumor volume, with corresponding clinical improvements to cranial nerve deficits. Given the scarcity of literature on adult cases of ATRT and the lack of a standard-of-care for these cases, discussing the efficacy of our patient's treatment plan may aid clinical decision-making for adult ATRT cases.

PEARLS

- Atypical teratoid rhabdoid tumor (ATRT) is an exceedingly rare diagnosis in adults with an incidence of less than 1/1,000,000.
- Adult ATRT presents in the sellar region with histological features including rhabdoid cells and primitive neuroectodermal features. However, definitive diagnosis of ATRT requires IHC identification of *INI1* or *BRG1* mutations.
- No standard of care treatment for adult ATRT exists, though a multicenter team adopted the pediatric medulloblastoma clinical trial COG ACNS 0332 for this patient which includes: resection, radiation, followed by four cycles of monthly chemotherapy including vincristine, cyclophosphamide, and cisplatin.

KEY-POINTS

- The histological features of medulloblastoma and ATRT may be commonly confused. Note that the presence of rhabdoid cells differentiates ATRT from medulloblastoma.
- Craniospinal irradiation (CSI) is indicated in adult ATRT despite potential neurocognitive impacts.

INTRODUCTION

Atypical teratoid rhabdoid tumor (ATRT) is a malignant tumor of multi-cellular lineage within the central nervous system (CNS) typically observed in patients under the age of three, but also occurring rarely in adults with an estimated annual incidence of less than 1/1,000,000 [1]. The

most common histopathological feature of ATRT is the presence of rhabdoid cells; however, this is not pathognomonic for ATRT. The 2021 WHO Classification of Tumors of the CNS favors more definitive genetic testing, defining ATRT as having mutations in either *INI1* (*SMARCB1/hSNF5*), or rarely *BRG1* (*SMARCA4*), seen via immunohistochemical staining [2]. ATRT can be further subclassified into three main molecular subgroups that are genetically and epigenetically unique – ATRT-TYR, ATRT-SHH, and ATRT-MYC [3]. Of note, recent studies of adult ATRTs suggest that these fall mostly in the ATRT-MYC group and that further clinical and molecular heterogeneity in ATRT-MYC may be revealed [3]. In this case report, we document a novel treatment plan for a rare case of adult sellar ATRT.

CASE SUMMARY

Clinical Presentation

A 43-year-old female patient presented on 6/10/20 with a one-month history of progressive left-sided headaches, diplopia, and ptosis. A consequent MRI performed in 6/22/20 revealed a sellar mass compressing the optic chiasm and invading the left cavernous sinus (**Figure 1**). A transsphenoidal approach for resection was performed on 7/1/20 (**Figure 1**). This approach resulted in an incomplete resection given that the tumor was expanding into the cavernous sinus and posterior aspect of the clivus. In conjunction with the localization, the firmness of the tumor would have necessitated resection through the cavernous sinus which is not advisable given risk of cranial nerve damage. The post-operative biopsy report detailed a background of nondescript poorly differentiated cells, with reasonably numerous karyorrhectic cells and cells with eosinophilic cytoplasmic globules, and few INI1 positive tumor cells which led to an ATRT diagnosis (**Figure 2**). Patient denied germline testing and not enough tissue was available to perform gene expression profiling for ATRT subgroup analysis.

An MRI taken on 8/5/20 showed tumor regrowth of a 4.5 x 4.3 x 3.0 cm non-resectable sellar mass with suprasellar extensions, and dural extension into the left middle cranial fossa and the left tentorium cerebelli. Examination revealed complete left oculomotor, trochlear and abducens nerve palsies. Trigeminal nerve function was intact with mild left facial nerve palsy.

Treatment Plan

A multi-center care team opted for the COG ACNS 0332 regimen typically used to treat elevated risk medulloblastoma/PNET patients. This treatment guideline consists of craniospinal irradiation (CSI) at 36 Gy with an 18 Gy boost to the sellar tumor and weekly vincristine, followed by four cycles of monthly chemotherapy including vincristine, cyclophosphamide, and cisplatin (St. Jude modification) [4]. Vincristine concurrent with radiation was avoided to preserve stem cell counts for the hematopoietic stem cell collection scheduled following radiotherapy (RT) completion. CSI was initiated in September 2020. During the break between radiation and chemotherapy, the patient underwent stem cell collection. Her post-radiation MRI showed a decrease in volume of the suprasellar, cavernous sinus, inferotemporal, and orbital portions of the tumor. Moreover, the optic chiasm was no longer effaced and the internal carotid arteries demonstrated less compressive effect compared to the 8/5/20 MRI. On 10/30/20, her left oculomotor, trochlear and abducens nerve palsies had improved. Her left facial weakness and hearing had also improved. The patient is currently 17 months post-diagnosis with clinicopathological stability shown on MRI and physical exam, and on maintenance tazemetostat, an EZH2 inhibitor. IRB 2019-1403 was approved by the University of Cincinnati Institutional Review Board. The patient provided written consent.

DISCUSSION

Adult ATRT is exceedingly rare thus the management is best extrapolated from pediatric cases. This case report used a multi-modal approach to treatment involving resection, radiation, and adjuvant chemotherapy. It has been shown that the extent of resection is critical to ATRT patient outcomes. Richards et al. revealed that complete total resection had a significantly higher overall survival (66.6%) compared to near-total resection (29%) or subtotal resection (12.5%) in children with newly diagnosed ATRT [5].

Pediatric ATRT is treated with aggressive intravenous or intrathecal chemotherapy rather than radiotherapy (RT), due to the possible negative neurocognitive effects. However, recent research suggests that even in pediatric populations, early RT may prolong progression-free survival [6]. In adults, craniospinal irradiation is a valuable adjunct to chemotherapy and is suggested for adult ATRT [1]. Panandiker et al. explored the effects of delayed RT on outcomes following gross total resection. Those patients who delayed RT ≥ 1 month post-operatively were more likely to experience local failure and increased progression in proportion to treatment delay time [7].

The chemotherapy plan outlined above is derived from COG ACNS 0332 and 0333, which were designed for neuroectodermal tumors. Both treatment regimens are based on the Intergroup Rhabdomyosarcoma III (IRS-III) and Children's Cancer Group 9921 (CCG 9921) studies [8]. COG ACNS 0332 with St. Jude modification and removal of chemotherapy concurrent with radiotherapy was chosen following consult with Dr. Susan Chi at DFCI. The rationale behind this treatment plan was that ATRT often resembles medulloblastoma in regards to imaging, histology, and aggressiveness which may suggest that traditional medulloblastoma treatment guidelines are applicable to ATRT [9]. Furthermore, case studies and retrospective data suggest

that HDC, PBSC rescue, early RT, and adjuvant chemotherapy have success against ATRT [10].

The COG ACNS 0332 regime is currently still active and has not been extensively tested in adults due to the low incidence of either medulloblastoma or ATRT in this patient population which further emphasizes the novelty of this case report.

Following radiation therapy, autologous stem cell rescue was used to counteract chemotherapy-induced myelosuppression [8]. Lastly, maintenance tazemetostat at 800 mg bid was prescribed as ATRT typically has a recurring genetic mutation in *INII/SMARCB1* that leads to constitutive activation of EZH2, a methylator of histone H3 lysine 27 (H3K27) [11]. H3K27 is a transcriptional repressor shown to be temporally expressed in cell cycle progression. Therefore, inhibition of EZH2 by tazemetostat may reverse pro-ATRT epigenetic changes.

Given the extensive treatment regimen for this patient, post-treatment side effects were carefully monitored by the treatment team. In particular, the patient experienced significant nausea following tazemetostat treatment. The symptoms persisted even after anti-emetics were prescribed, leading to a dose reduction per pharmacy recommendation. The patient is currently tolerating the reduced dose well. Additionally, following CSI, the patient noted some neurocognitive decline, in particular, bradyphrenia, attention deficits, and recall issues. Thorough neurocognitive testing is performed regularly through the University of Cincinnati brain tumor survivorship clinic in which significant deviations from baseline testing are flagged.

CONCLUSION

The above treatment plan serves as an evidenced-based framework to treat adult ATRT – early resection, craniospinal irradiation, followed by adjuvant chemotherapy and maintenance tazemetostat. Given the scarcity of adult ATRT cases, further quantitative research on optimal

treatment strategies continues to be difficult. However, ATRT remains a part of the NCI-CONNECT (Comprehensive Oncology Network Evaluating Rare CNS Tumors) which provides a forum to connect patients and physicians to a network for the optimal care management of these assortment of rare CNS tumors.

ACCEPTED

Figure Legends

Figure 1. (A) Before surgery: Pre and postcontrast images show a large sellar and suprasellar mass which demonstrates slightly heterogenous enhancement with more prominent enhancing area centrally (yellow arrows). The mass completely encases the left cavernous carotid artery with invasion of the left cavernous sinus (orange arrow). (B) Postoperative pre and postcontrast images demonstrate interval transsphenoidal pituitary surgery with resection and debulking of the large sellar and suprasellar mass with fat packing material in the inferior aspect of the sella and sphenoid sinus (yellow arrow). There is a residual peripheral enhancement which is most prominent in the left cavernous sinus consistent with residual tumor (orange arrow). Significantly improved mass effect along the undersurface of the optic nerve. (C) 1 month after surgery (before chemoradiotherapy): Interval aggressive recurrent disease centered in the left cavernous sinus with extension to the orbital apex (orange circle) and foramen ovale (yellow arrow) (D) 2 months follow-up after chemoradiotherapy demonstrate significant decrease in pituitary and left cavernous disease. No residual mass effect. (E) 1 year (most recent) follow-up after chemoradiotherapy: stable nonspecific minimal enhancement in the left cavernous sinus, which could be posttreatment changes or residual disease. Otherwise, no recurrent tumor.

Figure 2: Pathological characteristics of adult, sellar ATRT. H&E stains (A-B) of the tumor at 100x magnification (A) show the reasonably monotonous histology, with (B) mitoses (circle) and karyorrhectic cells (arrows, and also crossed by mitosis circle at 2:00) (400x), the inset (1000x oil) with discrete eosinophilic cytoplasmic globules, (C) (400x) with INI1 positive endothelial cells on the central vessel, and very few positively staining tumor cells.

References:

- [1] Dardis C, Yeo J, Milton K, et al. Atypical Teratoid Rhabdoid Tumor: Two Case Reports and an Analysis of Adult Cases with Implications for Pathophysiology and Treatment. *Front Neurol*. 2017;8: 247. doi:10.3389/fneur.2017.00247
- [2] Louis DN, Perry A, Wesseling P, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. *Neuro-Oncology*. 2021;23(8):1231-1251. doi:10.1093/neuonc/noab106
- [3] Ho B, Johann PD, Grabovska Y, et al. Molecular subgrouping of atypical teratoid/rhabdoid tumors—a reinvestigation and current consensus. *Neuro Oncol*. 2020;22(5):613-624. doi:10.1093/neuonc/noz235
- [4] Children's Oncology Group. *Efficacy of Carboplatin Administered Concomitantly With Radiation and Isotretinoin as a Pro-Apoptotic Agent in Other Than Average Risk Medulloblastoma/PNET Patients*. clinicaltrials.gov; 2020. Accessed July 27, 2021. <https://clinicaltrials.gov/ct2/show/NCT00392327>
- [5] Richards A, Ved R, Murphy C, et al. Outcomes with respect to extent of surgical resection for pediatric atypical teratoid rhabdoid tumors. *Childs Nerv Syst*. 2020;36(4):713-719. doi:10.1007/s00381-019-04478-5
- [6] Lee J, Kim DS, Han JW, Suh CO. Atypical teratoid/rhabdoid tumors in children treated with multimodal therapies: The necessity of upfront radiotherapy after surgery. *Pediatr Blood Cancer*. 2017;64(12). doi:10.1002/pbc.26663

[7] Pai Panandiker AS, Merchant TE, Beltran C, et al. SEQUENCING OF LOCAL THERAPY AFFECTS THE PATTERN OF TREATMENT FAILURE AND SURVIVAL IN CHILDREN WITH ATYPICAL TERATOID RHABDOID TUMORS OF THE CENTRAL NERVOUS SYSTEM. *Int J Radiat Oncol Biol Phys*. 2012;82(5):1756-1763.

doi:10.1016/j.ijrobp.2011.02.059

[8] Nicolaides T, Tihan T, Horn B, et al. High-dose chemotherapy and autologous stem cell rescue for atypical teratoid/rhabdoid tumor of the central nervous system. *J Neurooncol*. 2010;98(1):117-123. doi:10.1007/s11060-009-0071-6

[9] Rai S. Primitive neuroectodermal tumor (MB) versus atypical teratoid/rhabdoid tumors, an imaging dilemma! *J Pediatr Neurosci*. 2009;4(1):48-49. doi:10.4103/1817-1745.49111

[10] Tekautz TM, Fuller CE, Blaney S, et al. Atypical Teratoid/Rhabdoid Tumors (ATRT): Improved Survival in Children 3 Years of Age and Older With Radiation Therapy and High-Dose Alkylator-Based Chemotherapy. *JCO*. 2005;23(7):1491-1499. doi:10.1200/JCO.2005.05.187

[11] Chi SN, Bourdeaut F, Laetsch TW, et al. Phase I study of tazemetostat, an enhancer of zeste homolog-2 inhibitor, in pediatric pts with relapsed/refractory integrase interactor 1-negative tumors. *JCO*. 2020;38(15_suppl):10525-10525. doi:10.1200/JCO.2020.38.15_suppl.10525

Neurology®

Pearls & Oy-sters: Pivoting Treatment Regimens of Pediatric Atypical Teratoid Rhabdoid Tumors to Optimize Care in Adult ATRT: A Case Report

Rohan Rao, Abigail Koehler, Yehudit Rothman, et al.

Neurology published online March 7, 2022

DOI 10.1212/WNL.0000000000200196

This information is current as of March 7, 2022

Updated Information & Services	including high resolution figures, can be found at: http://n.neurology.org/content/early/2022/03/07/WNL.0000000000200196.citation.full
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): Chemotherapy-tumor http://n.neurology.org/cgi/collection/chemotherapytumor Diplopia (double vision) http://n.neurology.org/cgi/collection/diplopia_double_vision MRI http://n.neurology.org/cgi/collection/mri Primary brain tumor http://n.neurology.org/cgi/collection/primary_brain_tumor Radiation therapy-tumor http://n.neurology.org/cgi/collection/radiation_therapytumor
Permissions & Licensing	Information about reproducing this article in parts (figures,tables) or in its entirety can be found online at: http://www.neurology.org/about/about_the_journal#permissions
Reprints	Information about ordering reprints can be found online: http://n.neurology.org/subscribers/advertise

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2022 American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.