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TOPIC REVIEW

Atypical teratoid/rhabdoid tumor in adults: a systematic review of the literature with meta-analysis and additional reports of 4 cases

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Abstract

Introduction Atypical teratoid/rhabdoid tumor (AT/RT) is a highly aggressive embryonal CNS neoplasm, characterized by inactivation of SMARCB1 (INI1) or rarely of SMARCA4 (BRG1). While it is predominantly a childhood tumor, AT/RT is rare in adults.

Methods We provide a comprehensive systematic review of literature with meta-analysis; 92 adult cases were found from 74 articles. We additionally present 4 cases of adult AT/RTs (age ranging from 19 to 29 years), located to cerebellum in 2 cases, to ponto-cerebellar angle in 1 case and to spinal cord in the remaining case.

Results Microscopic features of our 4 cases showed a highly cellular tumor with rhabdoid morphology and high mitotic activity. All tumor cells lacked nuclear SMARCB1/INI1 protein expression. In case no. 3 we also performed methylation profiling which clustered the tumor with pediatric AT/RT-MYC subgroup. Prognosis remains poor in both pediatric and adult population with a median overall survival of 11 months. Our review demonstrated median overall survival of 15 months among the adult populations. However, consistent with a recent review, adult AT/RT seems to have highly variable prognosis and some patients reach long term survival with 22.9% of 5-year survival without evidence of disease and mean follow up time of 35.9 months (SD = 36.5). 27.1% of dissemination was also reported among the adult population.

Conclusions Adult AT/RTs predominantly arise in female patients and in supratentorial location. Midline structures, including the sellar region, are the most affected sites, especially among females aged > 40 years. Male gender is more prevalent between the age of 18 and 40 years and more frequently associated with non-midline tumors. Factors significantly associated with better prognosis are patient's age (< 40 years), combined radio-chemotherapy adjuvant approach and Ki-67 score < 40%.

Keywords Atypical teratoid/rhabdoid tumor · AT/RT · Adults · Systematic review · Meta-analysis

Introduction

Atypical teratoid/rhabdoid tumor (AT/RT) is a highly aggressive central nervous system (CNS) embryonal neoplasm, first described by Rorke et al. in 1996 [1]. According to the World Health Organization (WHO), the diagnosis of AT/RT can be rendered in presence of a poorly-differentiated neoplasm that frequently exhibits, at least focally, rhabdoid morphology, with inactivation of SMARCB1 (INI1) or rarely of SMARCA4 (BRG1) [2, 3]. WHO assigns to this entity a grade 4. The histologic spectrum of AT/RT is quite wide, as it is composed of poorly differentiated cells, mainly with rhabdoid morphology, exhibiting mesenchymal, epithelial and neuroectodermal differentiation. Rhabdoid features in the CNS are not specific nor sensitive of AT/RT. Interestingly, cells with rhabdoid morphology are the exclusive or predominant histopathologic finding in only a minority of cases of AT/RT. In fact, pediatric CNS embryonal tumors without rhabdoid features, but with loss of SMARCB1 expression in tumor cells, may qualify as AT/RTs as well [3]. Other CNS tumors with rhabdoid histology include epithelioid glioblastoma with rhabdoid component, as well as the rhabdoid variants of more common tumors, such as meningiomas, metastatic carcinomas, chordomas and sarcomas. AT/RT is predominantly a childhood tumor. It is the most common malignant brain tumor in children younger than 6 months [4] and it is believed to account for 1–2% of pediatric brain tumors and over 10% of CNS tumors in infants [3].

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Adult cases (i.e. age > 18) are rare and, to the best of our knowledge, only 92 cases have been confirmed and reported to date [4–91].

Recently, some studies found that AT/RTs belonged to three different molecular subtypes (AT/RT-TYR, AT/RT-SHH, and AT/RT-MYC), characterized by distinct DNA methylation profiling, gene expression patterns, and clinico-pathologic features [30, 92]. The main correlations between molecular and clinico-pathologic features of AT/RT are summarized in Table 1.

Tumor location of pediatric AT/RT is mainly related to specific molecular subtype and the tumor shows an overall male preponderance [30, 36], while in adults it is often supratentorial with female preponderance [19]. As many cases are misdiagnosed because of the polyphenotypic profile of the tumor cells, as well as the absence of specific radiologic findings, a standardized treatment [16] for these tumors currently lacks. Prognosis is poor, although adults with AT/RT tend to have longer overall survival than children. Treatment generally consists of surgical resection in combination with chemotherapy and radiotherapy [19]. Currently, management of AT/RT in adults is based on data extrapolated from pediatric literature [19]. Little is known on the optimal treatment of adult population. Given the limited number of AT/RT cases in adults, most of them reported in the form of single case reports or small case series, patient and tumor characteristics, overall prognosis, and impact of extent of resection and adjuvant therapy remain indeterminate in this patient population. In addition, other previously published systematic reviews and meta-analysis have also included tumors that did not exhibit INI1 or BRG1 alterations, resulting in analyses of heterogeneous populations that may contain tumors that are not molecularly defined as AT/RT. As far as we are aware, there have been 92 reported cases of AT/RT in adults [4–91]. A previously published review by Chan et al. [19] in 2018 presented quantitative and qualitative analysis of 50 recognized cases of AT/RT and, as our work included 92 cases, a significant increase in data is available (+ 86%). In addition to case by case in depth analysis and comprehensive data synthesis, we also compared our findings with quantitative and qualitative studies of both pediatric and adult AT/RT. Considering the rare incidence of this tumor and its highly malignant nature, our work can elaborate the current data in literature and demonstrate more extensively the characteristics and impact of AT/RT in adults, and potentially serve as a reference tool for further studies and therapeutic decisions.

We herein provide a comprehensive systematic review of literature with quantitative analysis and present 4 additional cases of adult AT/RTs.

Materials and methods

Study design

We performed a review of the literature in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to identify reported cases of AT/RT in adults. All cases of AT/RTs, arising in patients aged ≥ 18 years and with a histopathologic diagnosis confirmed by *SMARCB1*/INI1 or *SMARCA4*/BRG1 alterations by immunohistochemistry and/or molecular tests were considered as relevant to this research; 4 unpublished adult cases from our institution were included in the study.

A search flow diagram is provided in Fig. 1. We searched PubMed using the following Medical Subject Headings (MeSH): "adult" AND "atypical teratoid rhabdoid tumor". Results were restricted to English language only. Search results yielded 138 articles. The titles and abstracts were reviewed to identify potentially eligible articles. Of the 138 results, 74 articles were deemed as relevant to this study. In addition, Google Scholar was utilized with the same search terms. 342 references from relevant articles were used to supplement the systematic review. 153 duplicate publications were removed. 181 full texts of potentially eligible articles were obtained and reviewed for eligibility. Data was extracted from all eligible articles. A total of 74 articles and 92 cases were selected. The following data were collected: (i) patient demographics, (ii) tumor characteristics, (iii)

Table 1 Summary of the correlations between molecular and clinico-pathologic features of AT/RT

Molecular subtype	AT/RT-TYR	AT/RT-SHH	AT/RT-MYC
Age distribution	Infant (< 1 year)	Toddler (2–5 years)	Older than 3 years
Tumor location	Mainly infratentorial	Mainly supratentorial	Mainly supratentorial (spinal in a subset of cases)
Chromosome 22 copy number variations	Monosomy	Diploid	Diploid
SMARCB1	Point mutations/focal deletions	Point mutations/focal deletions	Wide deletions
Genes involved	TYR, TYRP, MITF, OTX2, BMP4, PDGFRB	GLI2, BOC, PTCHD2, CBL, ASCL1, MYCN, HES1	MYC, HOX
Pathologic features	Epithelial morphology	Small round blue cell morphology	Mesenchymal/ rhabdoid morphology

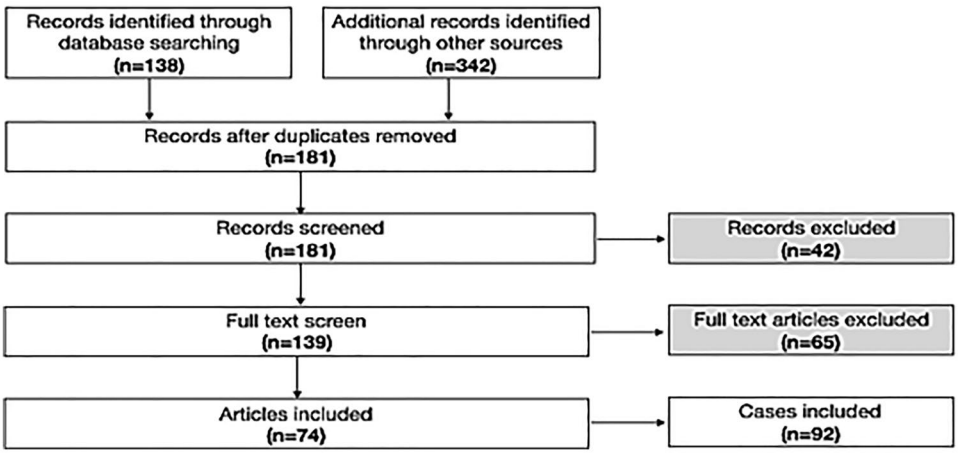


Fig. 1 Search flow diagram of the systematic literature review

survival times, (iv) treatment. Categorical variables were compared using the chi-square test, and continuous variables were compared using Student's t-test and analysis of variance. Kaplan–Meier analysis was used to compare long-term actuarial survival between groups. By adding our 4 unpublished cases to the patient cohort, a total of 96 cases were included in the analysis.

Results

Systematic review and meta-analysis

The results from the systematic review of the literature are summarized in Table 2 and Supplementary Table. We found 92 adult patients who were diagnosed with AT/RT from the 74 articles included in this study (Fig. 1). We also included our 4 cases into the patient cohort.

Clinical features

Of the 96 patients, the mean age at the diagnosis was 38.3 years, ranging from 18 to 80 years. 70 out of 96 (72.9%) were female, while 25 out of 92 (26%) were male. In 1 case (1.1%) a specific gender was not reported in the original article (Fig. 2a). Overall F:M ratio was 2.8:1. A comparison between age groups (18–40, > 40) (Fig. 2b) and gender revealed significant differences (Chi-Square = 4.8, p = 0.02). Male gender was significantly more prevalent between the age of 18 and 40 (Fig. 2c).

Signs and symptoms were related to tumor location. The most common symptoms were headache (n = 46, 47.9%) and visual disturbances (n = 43, 44.8%), followed by cranial nerve deficit (n = 18, 18.8%), altered consciousness (n = 7, 7.3%) and seizures (n = 6, 6.3%) (Fig. 2d).

Only 7 (7.3%) cases were in the spinal cord while the remaining 89 (92.7%) were intracranial. Intracranial tumors were far more common in the supratentorial region (n = 78, 81.3%) when compared to infratentorial region (n = 11, 11.5%) (Fig. 2e). The most common intracranial location was the sellar region (n = 45, 46.9%), followed by cerebral hemispheres (n = 21, 21.9%). Other reported locations were pineal region (n = 8, 8.3%), cerebellopontine (CP) angle (n = 4, 4.2%), cerebellum (4 = 4.2%), tectum (n =1, 1%) trigeminal nerve (n = 1, 1%), thalamus (n= 1, 1%) and intraventricular (n =1, 1%); 2 cases (2.1%) with intracranial location did not include a specific site (Fig. 3a).

Regarding tumor location and age, a sellar location was significantly more prevalent (Chi-Square = 22.9, p = 0.006) above the age of 40 years, while hemispheral, pineal and CP angle locations were more common among patients younger than 40 years (Fig. 3b). In addition, a highly significant difference was identified between centrality/laterality of tumor location and age (Chi-Square = 16.4, p = 0.0002). Midline tumors arose predominantly in patients above the age of 40, while laterally located tumors were more prevalent in younger than 40 (Fig. 3c). Centrality/laterality assessed with gender was found to be significantly different as well (Chi-Square = 22.4, p < 0.0001). Male gender presented with a similar degree of left, right and midline lesions while female gender presented far more commonly with a midline lesion (Fig. 3d).

Prognostic factors

Over the entire course of the disease, 26 (27.1%) patients exhibited dissemination of disease. 3 (3.1%) patients were reported to have evidence of dissemination at the time of diagnosis. 23 (24%) patients experienced dissemination later in the course of the disease. 43 (44.8%) patients experienced recurrence throughout the course of the disease; the mean time to recurrence was 11.4 (SD = 18.3) months and median time to recurrence was 4 months. 30 (31.3%) patients were reported to have a degree of local invasion. 13 (13.5%)

Table 2 Patient and tumor features from the systematic review

Patients	
Adult AT/RT patients	96
Mean age at diagnosis—year (SD, range)	38.3 (15.3, 18–80)
Age group 18–40—no (%)	53 (55.2%)
Female gender—no (%)	70 (72.9%)
Tumors	
Location—no (%)	
Supratentorial	78 (81.3%)
Infratentorial	11 (11.5%)
Spinal	7 (7.3%)
Intracranial	89 (92.7%)
Sellar	45 (46.9%)
Hemispheric	21 (21.9%)
Pineal	8 (8.3%)
Cerebellum	4 (4.2%)
Cerebellopontine angle	4 (4.2%)
Thalamus	1 (1%)
Intraventricular	1 (1%)
Tectum	1 (1%)
Trigeminal	1 (1%)
Not reported	2 (2.1%)
Dissemination—no (%)	
Distant dissemination	26 (27.1%)
At diagnosis	3 (3.1%)
Later in course of disease	23 (24%)
Local invasion	30 (31.3%)
At diagnosis	15 (15.6%)
Local and distant	13 (13.5%)
Recurrence	43 (44.8%)
Composite	5 (5.2%)
Treatment	
Surgery—no (%)	
Gross total resection	28 (29.2%)
Incomplete resection	45 (46.9%)
Biopsy only	3 (3.1%)
Not reported/Unclear	20 (20.8%)
Adjuvant—no (%)	
Chemotherapy and radiotherapy	55 (57.3%)
Radiotherapy only	13 (13.5%)
Chemotherapy only	1 (1%)
Stereotactic surgery	2 (2.1%)
No adjuvant	8 (8.3%)
Not reported	7 (17.7%)
Prognosis	
Alive at follow up	42 (43.8%)
Without evidence of disease	22 (22.9%)
With evidence of disease	13 (13.5%)
Mean follow up—months (SD, range)	35.9 (36.5, 4–204)
Death	49 (51%)
Mean time to death—months (SD, range)	16.8 (29.5, 0–168)
Median overall survival—months	15
Mean overall survival—months (SD, range)	25.3 (34.1, 0–204)

patients experienced both local and distant dissemination. Cerebrospinal fluid (CSF) dissemination was reported in 18 (18.8%) cases (Fig. 4a, b).

17 out of 45 (37.8%) patients with a sellar site as primary location demonstrated local invasion. 13 (28.9%) had cavernous sinus invasion, of which 12 (26.7%) involved the left cavernous sinus, and 3 (6.7%) involved the cavernous sinuses bilaterally. In 1 case (2.2%) the side of the cavernous sinus invasion was not reported. In 5 (5.4%) patients, the tumor was a composite tumor exhibiting components of AT/RT and another primary CNS tumor.

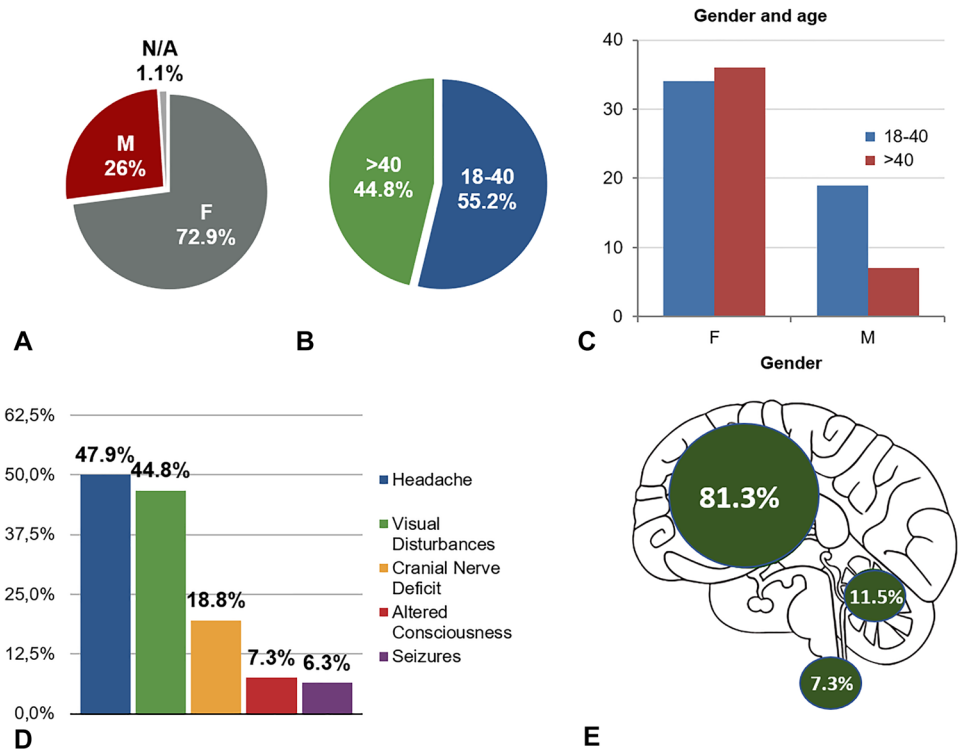
Effects of different therapies on outcome

Among the 96 cases, 28 (29.2%) had gross total resection (GTR), 45 (46.9%) had subtotal or partial resection, and 3 (3.1%) had a biopsy. Extent of resection was not reported or indeterminate in 20 (20.8%) cases.

With regard to adjuvant therapy, 55 (57.3%) received combined radiotherapy and chemotherapy, 13 (13.5%) received radiotherapy alone, 1 (1%) received chemotherapy alone, 2 (2.1%) received stereotactic radiosurgery alone, and 8 (8.3%) did not receive adjuvant therapy. Of the 68 patients who underwent radiotherapy, 18 (26.5%) received craniospinal irradiation.

49 out of the 96 patients (51%) died of their disease with a mean time to death of 16.8 (SD = 29.5) months (range: 0 to 168 months). 42 (43.8%) were alive at last follow-up with mean follow-up time of 35.9 months (SD = 36.5) (Fig. 4c). The range was 4 to 204 months. Of the 42 patients, 22 (52.4%) had no evidence of recurrence at follow-up, with follow-up time ranging from 4 to 204 months. Of the 28 patients who underwent GTR, 13 (46.4%) had passed away with time to death ranging from 1 month to 14 years after surgery. Of the 45 that had incomplete resection, 24 (53.3%) died with time to death ranging from postoperative to 2.5 years after surgery. The 3 patients that had a biopsy only died 8, 25, and 27 months after the diagnosis, respectively. When comparing patients who received gross total resection, incomplete resection, and biopsy, no significant difference on the log-rank test (Chi-square = 2.9, p = 0.2) was found.

Among the 55 patients who underwent combined radiotherapy and chemotherapy, 34 (61.8%) were alive at follow-up times, ranging from 6 months to 17 years. Time to death for the remaining 21 (38.2%) ranged from 1 month to 3 years after diagnosis. Only 2 of the 13 patients (15.4%) who received radiotherapy alone were alive at follow-up times, ranging from 6 to 9 months. Time of death for the remaining patients treated with radiotherapy alone ranged



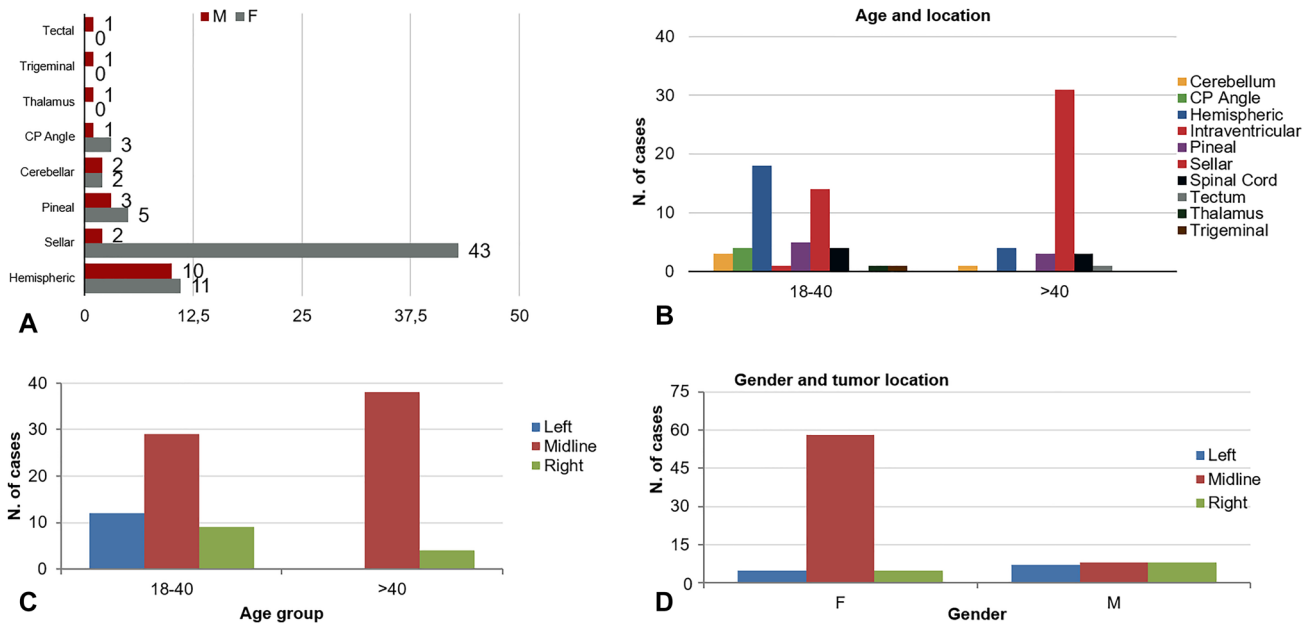


Fig. 2 **A** Gender distribution; **B** Age group; **C** Distribution between gender and age groups; **D** Signs and symptoms at presentation; **E** Tumor locations

Fig. 3 **A** Tumor location and gender of intracranial cases; **B** Distribution between tumor location and age; **C** Distribution between age and midline/lateral location; **D** Distribution between gender and midline/lateral location

from 1.5 months to 14 years. There were no patients alive at follow-up within the chemotherapy alone, stereotactic radiosurgery alone, and no adjuvant therapy groups. The patient who underwent chemotherapy died 10 years after diagnosis. The two patients treated with stereotactic radiosurgery died 6 and 27 months after diagnosis, respectively. Of the 8 patients who did not receive adjuvant therapy, time to death ranged from the immediate postoperative period to 8 months after surgery. When comparing those patients who received both radiotherapy and chemotherapy, radiotherapy alone,

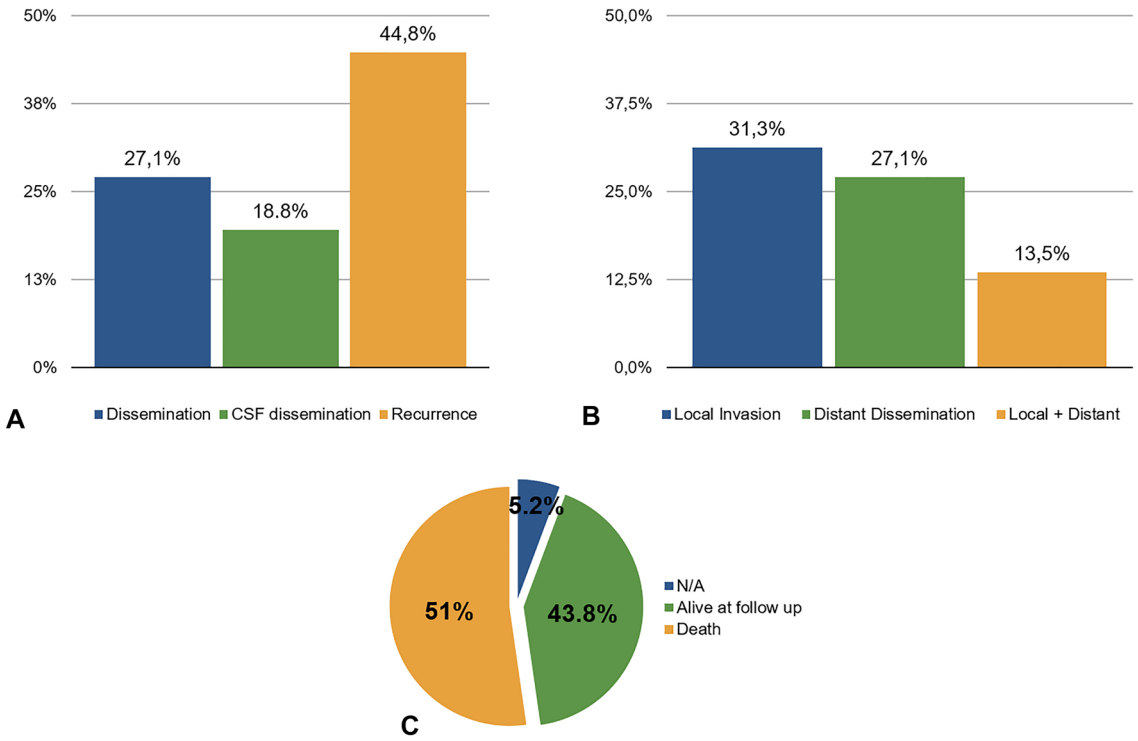


Fig. 4 **A** Percentage of disseminating and recurring adult AT/RTs; **B** Percentage of locally invasive and distant disseminating adult AT/RTs; **C** Prognosis of adult AT/RTs

chemotherapy alone, stereotactic radiosurgery alone and no adjuvant therapy, there was a highly significant difference in survival (log-rank = 66.8, $p < 0.0001$) (Fig. 5a). Patients who received a combined radiotherapy and chemotherapy approach had a significant increase in survival when compared with patients that received radiotherapy alone (HR 0.33, CI 0.13–0.83) and with those who did not receive any adjuvant therapy (HR 0.07, CI 0.009–0.56). Surgical intervention in addition to a combined chemo-radiotherapy had a highly significant effect on survival (log-rank= 67.2, $p < 0.0001$) when compared to surgical resection with radiotherapy or surgical resection alone. Increased survival time was observed in surgical resection with combined chemo-radiotherapy, independently whether GTR or an incomplete resection was performed (Fig. 5b,c). Incomplete resection and combined chemo-radiotherapy showed an improvement in survival when compared to incomplete resection with no adjuvant therapy (HR 0.06, CI 0.004–0.84). (Figure 5d).

Correlation between age and Ki-67 score on outcome

Overall survival was found to be significantly affected by age (log-rank = 4.1, $p = 0.04$) (Fig. 5e). Patients above the age of 40 (n = 43, 44.8%) experienced reduced overall survival compared to patients aged between 18 and 40 (n = 53, 55.2%). The median overall survival among the older than 40 group was 9 months, and the mean was 14.7 (CI 9.6–19.9) while the 18–40 age group demonstrated a higher median overall survival of 18 months and mean overall survival of 32.6 (CI 19.7–45.4) ($F = 5.8$, $p = 0.01$).

Ki-67 was reported in 48 cases. Numerical entries only were used for assessment (7 eliminated). Ki-67 expression was found to be a significant predictor of survival (log-rank = 14.2, $p < 0.0001$). Ki-67 score of below 40% was associated with increased survival (HR 0.22, CI 0.06–0.75) (Fig. 5f). Interestingly, Ki-67 did not show significant relationship with recurrence and dissemination.

Case presentations

We herein present 4 additional cases of AT/RT arising in young adults; our series included 1 male and 3 female patients with age ranging from 19 to 29 years old. Written informed consents were acquired from all the subjects involved in the present case series. Tumors were located to the cerebellum in 2 cases (case no.1 and case no.2), cerebellopontine angle in 1 case (case no. 3) and spinal cord in the remaining case (case no. 4).

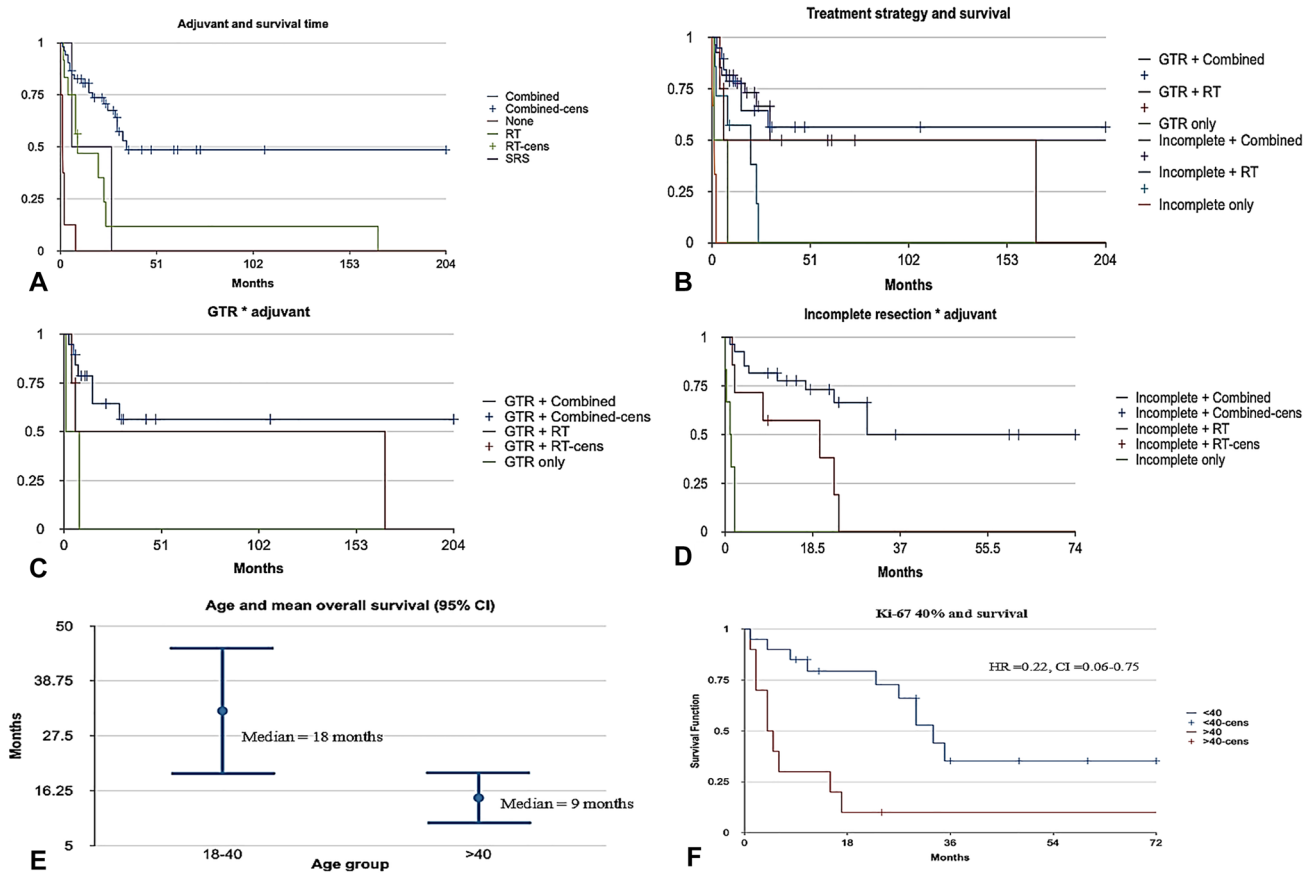


Fig. 5 **A** Kaplan Meyer survival curve showing that patients who underwent combined radiotherapy and chemotherapy exhibited higher survival times than those who underwent other treatments; **B** Correlation between survival times and different treatments; **C** Correlation between survival times and gross total resection with/without adjuvant treatments; **D** Patients who underwent incomplete resection plus combined radiotherapy and chemotherapy had better survival times than those who did not received adjuvant therapy; **E** Patients aged > 40 years had lower survival times than those aged between 18 and 40 years; **F** Ki-67 values < 40% were associated with increased overall survival

Case no. 1

The patient had previously undergone surgery for a cerebellar mass which was initially diagnosed as large cell/anaplastic medulloblastoma and was treated with craniospinal irradiation plus Packer chemotherapy regimen (lomustine, vincristine and cisplatin). One year later the patient exhibited a contrast-enhancing frontal mass on brain Magnetic Resonance Imaging (MRI) (Fig. 6a). Accordingly, a surgical resection of the mass was performed and the histologic slides were presented to our institution for a neuropathologic evaluation. Histologic examination showed a highly cellular tumor (Fig. 6b) composed of rhabdoid cells with eccentric nuclei, prominent nucleoli and eosinophilic cytoplasm (Fig. 6c). The tumor exhibited high mitotic count was (7-9 mitosis/10 HPFs) (Fig. 6c) and foci of necrosis (Fig. 6d). The tumor infiltrated the adjacent brain parenchyma. Tumor cells were diffusely positive for Vimentin (Fig. 6e), focally positive for Synaptophysin (Fig. 6f) and GFAP (Fig. 6 g) and negative for GAP, YAP1 and β-catenin (Fig. 6h–j). All tumor cells showed a loss of nuclear SMARCB1/INI1 protein expression with retained immunoreactivity in vascular endothelial cells (Fig. 6k). Ki67 index was 60% (Fig. 6l). Based on both morphological and immunohistochemical features, a diagnosis of AT/RT was rendered; in addition, the original cerebellar lesion was histologically reviewed and the diagnosis of AT/RT confirmed.

Case no. 2

A 20-year-old woman underwent emergency neurosurgery for a hemorrhage in the posterior cranial fossa; a cerebellar mass was found and surgically excised. No radiologic data were available. As for case no.1, the tumor was initially diagnosed as medulloblastoma; however, following this diagnosis, a histologic revision of the original slides was performed in our center and a diagnosis of AT/RT

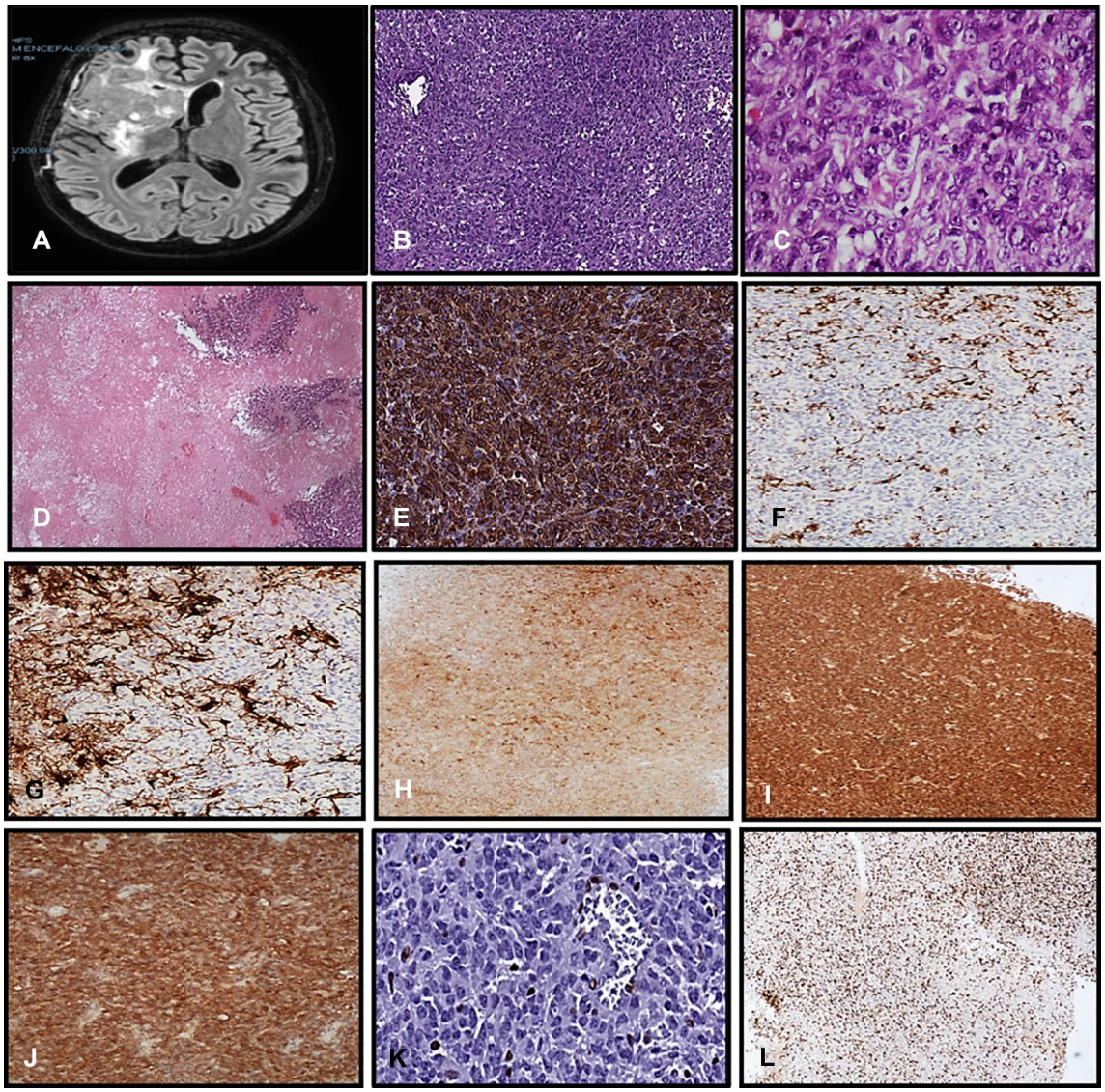


Fig. 6 Case no. 1 **A** Brain MRI showing a contrast-enhancing frontal mass. Histological examination showing a hypercellular tumor (**B**), composed of mitotically-active rhabdoid cells with eccentric nuclei, prominent nucleoli and eosinophilic cytoplasm (**C**); tumor also exhibits foci of necrosis (**D**). Neoplastic cells are diffusely stained with Vimentin (**E**) and focally with Synaptophysin (**F**) and GFAP (**G**); conversely, tumor is negative for GAP (**H**), YAP1 (**I**) and beta-catenin (**J**); neoplastic cells characteristically lack nuclear expression of SMARCB1/INI1, that is retained in vascular endothelial cells (**K**). Ki-67 is high (**L**); (**B**, **D**–**J**, **L**: original magnification ×100; **B**, **K**: original magnification ×200)

was rendered. Tumor was composed of mitotically-active, undifferentiated cells with focal rhabdoid features and immunohistochemical loss of SMARCB1/INI1 expression. Necrosis and numerous apoptotic bodies were found. Neoplastic cells also exhibited focal positivity for GFAP and α-smooth muscle actin (α-SMA). Accordingly, patient underwent combined chemo-radiotherapy with complete remission of disease after 4 months from the diagnosis and is currently alive and healthy at 7 years of follow-up.

Case no.3

Patient underwent surgery for a cerebellopontine angle mass, clinically suspicious for meningioma; brain MRI showed an extra-axial lesion with ill-defined borders and infiltrative margins that exhibited invasion of the cavernous sinus and mass effect on the adjacent structures. Histologically, a mitotically-active, hypercellular tumor, mainly composed of partially non-cohesive undifferentiated cells with nuclear anaplasia, was found. Rhabdoid features, including large,

eccentric and focally incised nuclei, prominent nucleoli and eosinophilic cytoplasm, were only a focal finding in this case. Neoplastic cells were diffusely stained with Vimentin and focally with EMA and α-SMA, while they were negative for cytokeratin AE1/AE3. A complete loss of nuclear SMARCB1/INI1 protein expression was found; accordingly, a diagnosis of AT/RT was rendered. Ki-67 proliferative rate was 15%. Methylation profiling was also performed and it clustered the tumor with pediatric AT/RT-MYC subgroup. 3 months after the diagnosis, brain MRI showed a large residual cerebellopontine angle mass with hemorrhagic infarction; patient is still alive after 18 months of follow-up.

Case no. 4

Patient underwent spinal MRI due to a rapidly worsening onset of back pain and leg paresthesia; a L4-L5 intra-axial spinal mass with homogeneous contrast-enhancement and ill-defined borders was found. Histologic examination revealed a poorly-differentiated tumor, characterized by hypercellularity, high mitotic count, nuclear anaplasia and rhabdoid morphology. Numerous apoptotic bodies were also found. Immunohistochemically, neoplastic cells were stained with cytokeratin AE1/AE3 and α-SMA and lacked nuclear expression of SMARCB1/INI1. Following the diagnosis of spinal AT/RT, the patient exhibited disease progression and passed away after 14 and 40 months of follow-up, respectively.

Discussion

In accordance with the 2021 WHO Classification of Tumors of the CNS [2], only cases with confirmed mutation or loss of SMARCB1/INI1 were included in the present systematic review. The majority of AT/RTs harbor a mutation in one allele with a second allele lost due to monosomy 22, deletion of 22q11.2, or an acquired copy number neutral loss heterozygosity [3]. AT/RTs typically do not harbor recurrent mutations in addition to SMARCB1 alteration, which is the primary recurrent event [36]. Our study demonstrated that the most common location of AT/RT in adults is the supratentorial compartment, particularly in sellar region, followed by cerebral hemispheres. This is consistent with the previously reported data [19]. Sellar AT/RT encompasses nearly half of the reported cases, to date. The vast majority (43 out of 45) of patients with sellar AT/RTs were females with a mean and median age of 46 years. It has been hypothesized that this gender predilection was attributed to increased mitotic activity in female pituitary gland throughout life [23, 68]. Johann et al. [35] and Alzoubi et al. [8] demonstrated that methylation profile of 8 cases of adult AT/RTs matched with pediatric AT/RTs of the MYC subgroup. In terms of location, AT/RT-MYC is predominantly associated with a supratentorial location, followed by infratentorial and lastly the spinal cord [30], consistently with the findings of our study. Conversely, Voisin et al. reported the inability to cluster an adult sellar AT/RT with a SMARCB1 germline mutation with the pediatric MYC subgroup [85]. AT/RT in adults shows predilection for midline structures. The majority of patients in our study presented with a midline AT/RT. Sellar and pineal tumor location encompassed 55.2% of all cases. These are circumventricular organs, which are now recognized as a source of neural stem cells in adults [12]. It is postulated that these organs are capable of acquiring carcinogenic mutations throughout most of adulthood [23]. The intricate relationship of these organs to CSF circulation may explain the relative high incidence of CSF dissemination of such tumors. Despite the relatively low number of cases presenting with distant dissemination, we believe that the absence of whole neuroaxis imaging at time of diagnosis may have led to an underestimate of leptomeningeal disease rate. In our study 26 cases (27.1%) disseminated into distant sites despite tumor GTR and combined chemotherapy and radiotherapy. It is likely that such finding is a result of the aforementioned underestimation. Indeed, most of distant sites of dissemination were within the CNS but spread into thoracic and abdominal viscera has been described as well. Ingold et al. reported a peritoneal seeding of a pineal AT/RT through a ventriculo-peritoneal shunt [34]. 3 additional cases demonstrated lungs and abdominal dissemination [5, 52, 76]. Whether distant dissemination is a significant predictor for decreased overall survival, it is still highly variable and some patients demonstrated a relatively long survival despite having distant dissemination at time of diagnosis. It also remains unclear why sellar AT/RT invaded the left cavernous sinus in 12 out of 13 cases, while invasion into the right cavernous sinus was reported only in 3 cases, all of which had a concomitant left cavernous invasion.

Our review included 5 cases of AT/RT concurrent with other central nervous system tumors. These compound cases consisted of a component of AT/RT that demonstrated loss of INI1 expression and a non-AT/RT component in which INI1 was uniformly retained. These compound tumors included pleomorphic xanthoastrocytoma [17, 84], high-grade glioma [88], ependymoma [57] and prolactin-producing pituitary adenoma [11]. It has been hypothesized that a post-clonal inactivation of INI1 occurs in a cell subpopulation of the original tumor, resulting in an AT/RT component in an original non-AT/RT lesion. We demonstrated well-established differences and similarities between adult and pediatric AT/RT populations. Based on a review of 586 pediatric AT/RT cases, Ostrom et al. reported that male gender accounted for 54.2% cases [62]. Our study reported a marked female gender predominance with overall 72.9%. Pediatric AT/RT seem to have a predilection for location

based on its molecular subtype, AT/RT-TYR subgroup is strongly associated with a supratentional location while AT/RT-SHH is strongly associated with an infratentorial location, and lastly, AT/RT-MYC is associated with both locations (supratentorial 50%, infratentorial 38%, spinal cord 12%) [30, 36]. Whereas in adults there is a clear supratentorial predilection with 81.3% of tumors located in that region, 11.5% were located in the infratentorial region and 7.3% in the spinal cord. Prognosis remains poor in both pediatric and adult population. In pediatric populations life expectancy is short. This tumor is highly malignant and usually progresses quickly with a median overall survival of 11 months [62]. Our review demonstrated median overall survival of 15 months among the adult populations. However, adult AT/RT seems to have highly variable prognosis and some patients reach long term survival with 22.9% of 5-year survival without evidence of disease and mean follow up time of 35.9 months (SD = 36.5). This is consistent with a recent case series by Peng et al. [65].

In the present analysis, patient's age > 40 years and Ki-67 score > 40% were found to be significantly associated with poorer outcome in adults with AT/RT. Based on these findings, the possibility of modulating the intensity of treatment according to patient's age and/or Ki-67 could be hypothesized in the future; in particular, we emphasize the utility of performing and accurately evaluating the Ki-67 proliferative rate, as it might potentially influence outcome of this rare tumor.

AT/RT is exceedingly rare in adults. Therefore, treatment guidelines are extrapolated from pediatric AT/RT protocols. Adjuvant therapy after surgical resection has a favorable effect on survival among pediatric patients older than three years of age [13]. These guidelines have been applied to adult patients. Our analysis showed that combined adjuvant therapy that includes chemotherapy and radiotherapy has been shown to significantly improve survival among adult AT/RT when compared to surgical resection only, radiotherapy only, and to surgery and radiotherapy. No difference in survival was observed when comparing gross total resection, incomplete resection and biopsy only. It is unclear whether the extent of resection has an effect on survival. We emphasize that our analysis was focused on the differences in survival between surgery, radiotherapy alone, chemotherapy alone and combined radio-chemotherapy. Unfortunately, we did not collect data about the specific treatment regimens; however, it has been reported in literature that high-dose radiotherapy (a total dose of radiation over 50 Gy) and high-dose combinations of methotrexate, cyclophosphamide, cisplatin, vincristine, etoposide, carboplatin, and ifosfamide are currently used in adult patients with AT/RT.

We also reported 4 additional cases of AT/RT of young adults, all showing, at least focal, rhabdoid features and immunohistochemical loss of SMARCB1/INI1; for one of these cases (case no. 3), the results of DNA methylation profiling were available and the tumor was clustered with pediatric AT/RT-MYC subgroup. Interestingly, 2 cerebellar tumors from our series (cases no. 1 and 2) were initially misdiagnosed as medulloblastomas; we emphasize that the heterogeneity of AT/RT's histology and its polyphenotypic immunoprofile render the tumor difficult to recognize in certain occasions and that, due to the presence of primitive neuroepithelial elements, AT/RT can potentially be misdiagnosed as medulloblastoma [13]. However, unlike medulloblastoma, AT/RT is often a non-cerebellar tumor, diagnosed in infancy and not in childhood. In spite of the potential histological similarities, the loss of this SMARCB1/INI1 expression is often more reliable than morphology alone to distinguish AT/RT from other poorly differentiated brain tumors.

Limitations

Potential limitations of the present analysis include: (i) the relatively small cohort of patients studied; (ii) the extraction of data from single case reports and small case series, as data distribution is often inhomogeneous from one case report/series to another; (iii) presence of confounding factors (i.e. health and/or functional status of patients might represent confounding factors for evaluating the impact of adjuvant therapy on survival); (iv) inappropriate histologic diagnosis, as some tumors with overlapping morphologic features, including rhabdoid meningiomas or dedifferentiated/poorly differentiated chordomas, may also exhibit INI-1 loss.

Conclusions

The present analysis revealed that AT/RTs are rare tumors in adult population, that predominantly arise in female patients and in supratentorial location. Midline structures, including the sellar region, are the most affected sites, especially among females aged > 40 years. Male gender is more prevalent between the age of 18 and 40 years and more frequently associated with non-midline tumors. Factors significantly associated with better prognosis are patient's age (< 40 years), combined radio-chemotherapy adjuvant approach and Ki-67 score < 40%. Although prognosis remains poor in adult patients, adult AT/RTs seem to have more variable prognosis than their pediatric counterparts, as some patients may reach long term survival without evidence of disease. From the present analysis, age, adjuvant therapy and Ki-67 score are the main factors that affect prognosis of adult patients.

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Data availability The data of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declare no conflict of interest.

Informed consent The study complied with the Ethical Principles for Medical Research Involving Human Subjects according to the World Medical Association Declaration of Helsinki; the non-interventional, retrospective nature of our study did not require any informed consent, even if a written informed consent had been obtained from each patient before surgical procedures. The clinical information had been retrieved from the patients' medical records and pathology reports. Patients' initials or other personal identifiers did not appear in any image. Finally, all samples were anonymized before histology and immunohistochemistry; therefore, no further ethical approval was necessary to perform the retrospective study.

References

1. Rorke LB, Packer RJ, Biegel JA (1996) Central nervous system atypical teratoid/rhabdoid tumors of infancy and childhood: definition of an entity. J Neurosurg 85:56–65. https://doi.org/10.3171/jns.1996.85.1.0056
2. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, Hawkins C, Ng HK, Pfister SM, Reifenberger G, Soffietti R, von Deimling A, Ellison DW (2021) The 2021 WHO classification of tumors of the central nervous system: a summary. Neuro Oncol 23:1231–1251. https://doi.org/10.1093/neuonc/noab106
3. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, Ohgaki H, Wiestler OD, Kleihues P, Ellison DW (2016) The 2016 World Health Organization classification of tumors of the central nervous system: a summary. Acta Neuropathol 131:803–820. https://doi.org/10.1007/s00401-016-1545-1
4. Biswas S, Wood M, Joshi A, Bown N, Strain L, Martinsson T, Campbell J, Ashworth A, Swain A (2015) Exome sequencing of an adult pituitary atypical teratoid rhabdoid tumor. Front Oncol 5:236. https://doi.org/10.3389/fonc.2015.00236
5. Ahmad M, Sekar V, Healy E, Rennie I, Cooke S (2019) Case report: the unusual case of a sellar/suprasellar extrarenal rhabdoid tumour in an adult. Interdiscip Neurosurg 17:36–39. https://doi.org/10.1016/j.inat.2019.01.014
6. Almalki MH, Alrogi A, Al-Rabie A, Al-Dandan S, Altwairgi A, Orz Y (2017) Atypical teratoid/rhabdoid tumor of the sellar region in an adult with long survival: case report and review of the literature. J Clin Med Res 9:216–220. https://doi.org/10.14740/jocmr2922w
7. Almalki MH, Altwairgi A, Orz Y (2020) Unusually long survival of an adult patient with atypical teratoid/rhabdoid tumor of the sellar region: a follow-up report. Ibnosina J Med Biomed Sci 12:53–56. https://doi.org/10.4103/ijmbs.ijmbs_88_19
8. Alzoubi H, Gianno F, Giangaspero F, Bartolini D, Riccioni L, Miele E, Antonelli M (2020) Dural-based atypical teratoid/rhabdoid tumor in an adult: DNA methylation profiling as a tool for the diagnosis. CNS Oncol 9:CNS54. https://doi.org/10.2217/cns-2020-0006
9. Arita K, Sugiyama K, Sano T, Oka H (2008) Atypical teratoid/rhabdoid tumour in sella turcica in an adult. Acta Neurochir (Wien) 150:491–495. https://doi.org/10.1007/s00701-008-1500-y
10. Asmaro K, Arshad M, Massie L, Griffith B, Lee I (2019) Sellar atypical teratoid/rhabdoid tumor presenting with subarachnoid and intraventricular hemorrhage. World Neurosurg 123:e31–e38. https://doi.org/10.1016/j.wneu.2018.10.198
11. Barresi V, Lionti S, Raso A, Esposito F, Cannavò S, Angileri FF (2018) Pituitary atypical teratoid rhabdoid tumor in a patient with prolactinoma: a unique description. Neuropathology 38:260–267. https://doi.org/10.1111/neup.12440
12. Bennett L, Yang M, Enikolopov G, Iacovitti L (2009) Circumventricular organs: a novel site of neural stem cells in the adult brain. Mol Cell Neurosci 41:337–347. https://doi.org/10.1016/j.mcn.2009.04.007
13. Biswas A, Kashyap L, Kakkar A, Sarkar C, Julka PK (2016) Atypical teratoid/rhabdoid tumors: challenges and search for solutions. Cancer Manag Res 8:115–125. https://doi.org/10.2147/CMAR.S83472
14. Bodi I, Giamouriadis A, Sibtain N, Laxton R, King A, Vergani F (2018) Primary intracerebral INI1-deficient rhabdoid tumor with CD34 immunopositivity in a young adult. Surg Neurol Int 9:45. https://doi.org/10.4103/sni.sni_334_17
15. Bokhari RA, Bafaqeeh M, Al-Obaysi S, Al-Aman A, Alshakweer W (2020) Atypical teratoid/rhabdoid tumor of the sellar region: a case report and review of the literature. J Neurol Res 10:13–16. https://doi.org/10.14740/jnr556
16. Bruch LA, Hill DA, Cai DX, Levy BK, Dehner LP, Perry A (2001) A role for fluorescence in situ hybridization detection of chromosome 22q dosage in distinguishing atypical teratoid/rhabdoid tumors from medulloblastoma/central primitive neuroectodermal tumors. Hum Pathol 32:156–162. https://doi.org/10.1053/hupa.2001.21572
17. Chacko G, Chacko AG, Dunham CP, Judkins AR, Biegel JA, Perry A (2007) Atypical teratoid/rhabdoid tumor arising in the setting of a pleomorphic xanthoastrocytoma. J Neurooncol 84:217–222. https://doi.org/10.1007/s11060-007-9361-z
18. Chan V, Marro A, Chainey J, Schmitt L, Das S (2019) Intraventricular atypical teratoid rhabdoid tumour in an adult: a case report and literature review. Folia Neuropathol 57:295–300. https://doi.org/10.5114/fn.2019.88460
19. Chan V, Marro A, Max Findlay J, Schmitt LM, Das S (2018) A systematic review of atypical teratoid rhabdoid tumor in adults. Front Oncol. https://doi.org/10.3389/fonc.2018.00567
20. Chen F, Mei W, Lu W, Zeng T, Kang D, Wu X, You H (2020) Atypical teratoid/rhabdoid tumor originated from the trigeminal nerve in a young male adult: case report and review of the literature. Front Neurol 11:265. https://doi.org/10.3389/fneur.2020.00265
21. Chi SN, Zimmerman MA, Yao X, Cohen KJ, Burger P, Biegel JA, Rorke-Adams LB, Fisher MJ, Janss A, Mazewski C, Goldman S, Manley PE, Bowers DC, Bendel A, Rubin J, Turner CD, Marcus KJ, Goumnerova L, Ullrich NJ, Kieran MW (2009) Intensive multimodality treatment for children with newly diagnosed CNS atypical teratoid rhabdoid tumor. J Clin Oncol 27:385–389. https://doi.org/10.1200/JCO.2008.18.7724
22. Chou SQH, Lo SSM, Wong HN, Lau PPL, Chan CM, Tang KW, Cheung YL (2013) Atypical teratoid/rhabdoid tumour in the sella turcica of a female adult. Hong Kong J Radiol 16:65–68. https://doi.org/10.12809/hkjr1311034

23. Dardis C, Yeo J, Milton K, Ashby LS, Smith KA, Mehta S, Youssef E, Eschbacher J, Tucker K, Dawes L, Lambie N, Algar E, Hovey E (2017) Atypical teratoid rhabdoid tumor: two case reports and an analysis of adult cases with implications for pathophysiology and treatment. Front Neurol 8:247. https://doi.org/10.3389/fneur.2017.00247
24. De Amorim Bernstein K, Sethi R, Trofimov A, Zeng C, Fullerton B, Yeap BY, Ebb D, Tarbell NJ, Yock TI, MacDonald SM (2013) Early clinical outcomes using proton radiation for children with central nervous system atypical teratoid rhabdoid tumors. Int J Radiat Oncol Biol Phys 86:114–120. https://doi.org/10.1016/j.ijrobp.2012.12.004
25. Dökmetaș HS, Çakır A, Cila A, Dökmetaș M, Kılıçlı F (2020) A rare tumor at the adult of the hypophysis: atipic teratoid rabdoid tumor. Endocr Abstr 70:EP329. https://doi.org/10.1530/endoabs.70.EP329
26. Geller JI, Roth JJ, Biegel JA (2015) Biology and treatment of rhabdoid tumor. Crit Rev Oncog 20:199–216. https://doi.org/10.1615/critrevoncog.2015013566
27. Gorayski P, Boros S, Ong B, Olson S, Foote M (2013) Radiation-induced primary cerebral atypical teratoid/rhabdoid tumour in an adult. J Clin Neurosci 20:1466–1468. https://doi.org/10.1016/j.jocn.2013.03.041
28. Gotti G, Biassoni V, Schiavello E, Spreafico F, Antonelli M, Calareso G, Pecori E, Gandola L, Massimino M (2015) A case of relapsing spinal atypical teratoid/rhabdoid tumor (AT/RT) responding to vinorelbine, cyclophosphamide, and celecoxib. Childs Nerv Syst 31:1621–1623. https://doi.org/10.1007/s00381-015-2755-x
29. Greeneway GP, Page PS, Patel V, Ahmed AS (2021) Atypical teratoid/rhabdoid tumor of the cerebellum in an adult: case report and literature review. World Neurosurg 145:57–63. https://doi.org/10.1016/j.wneu.2020.08.079
30. Ho B, Johann PD, Grabovska Y, De Dieu Andrianteranagna MJ, Yao F, Frühwald M, Hasselblatt M, Bourdeaut F, Williamson D, Huang A, Kool M (2020) Molecular subgrouping of atypical teratoid/rhabdoid tumors-a reinvestigation and current consensus. Neuro Oncol 22:613–624. https://doi.org/10.1093/neuonc/noz235
31. Hollmann TJ, Hornick JL (2011) INI1-deficient tumors: diagnostic features and molecular genetics. Am J Surg Pathol 35:47–63. https://doi.org/10.1097/PAS.0b013e31822b325b
32. Horiguchi H, Nakata S, Nobusawa S, Uyama S, Miyamoto T, Ueta H, Fujimoto N, Yokoo H (2017) Adult-onset atypical teratoid/rhabdoid tumor featuring long spindle cells with nuclear palisading and perivascular pseudorosettes. Neuropathology 37:52–57. https://doi.org/10.1111/neup.12317
33. Huq S, Honasoge M, Sulanc E (2018) Adult atypical sellar teratoid tumor presenting as diabetes insipidus. Endocr Pract 24:178–179
34. Ingold B, Moschopulos M, Hutter G, Seeger H, Röthlisberger B, Landolt H, Yonekawa Y, Jochum W, Heppner FL (2006) Abdominal seeding of an atypical teratoid/rhabdoid tumor of the pineal gland along a ventriculoperitoneal shunt catheter. Acta Neuropathol 111:56–59. https://doi.org/10.1007/s00401-005-1112-7
35. Johann PD, Bens S, Oyen F, Wagener R, Giannini C, Perry A, Raisanen JM, Reis GF, Nobusawa S, Arita K, Felsberg J, Reifenberger G, Agaimy A, Buslei R, Capper D, Pfister SM, Schneppenheim R, Siebert R, Frühwald MC, Paulus W, Kool M, Hasselblatt M (2018) Sellar region atypical teratoid/rhabdoid tumors (ATRT) in adults display DNA methylation profiles of the ATRT-MYC subgroup. Am J Surg Pathol 42:506–511. https://doi.org/10.1097/PAS.0000000000001023
36. Johann PD, Erkek S, Zapatka M, Kerl K, Buchhalter I, Hovestadt V, Jones DTW, Sturm D, Hermann C, Segura Wang M, Korshunov A, Rhyzova M, Gröbner S, Brabetz S, Chavez L, Bens S, Gröschel S, Kratochwil F, Wittmann A, Sieber L, Geörg C, Wolf S, Beck K, Oyen F, Capper D, van Sluis P, Volckmann R, Koster J, Versteeg R, von Deimling A, Milde T, Witt O, Kulozik AE, Ebinger M, Shalaby T, Grotzer M, Sumerauer D, Zamecnik J, Mora J, Jabado N, Taylor MD, Huang A, Aronica E, Bertoni A, Radlwimmer B, Pietsch T, Schüller U, Schneppenheim R, Northcott PA, Korbel JO, Siebert R, Frühwald MC, Lichter P, Eils R, Gajjar A, Hasselblatt M, Pfister SM, Kool M (2016) Atypical teratoid/rhabdoid tumors are comprised of three epigenetic subgroups with distinct enhancer landscapes. Cancer Cell 29:379–393. https://doi.org/10.1016/j.ccell.2016.02.001
37. Kanoto M, Toyoguchi Y, Hosoya T, Kuchiki M, Sugai Y (2015) Radiological image features of the atypical teratoid/rhabdoid tumor in adults: a systematic review. Clin Neuroradiol 25:55–60. https://doi.org/10.1007/s00062-013-0282-2
38. Krill MK, Fogarty AE, Jacob S (2020) A 71-year-old man with a rare rhabdoid brain tumour: using a multidisciplinary medical and rehabilitative model of care. BMJ Case Rep 13:1–5. https://doi.org/10.1136/bcr-2019-231924
39. Kuge A, Sato S, Sakurada K, Takemura S, Kayama T (2012) Atypical teratoid rhabdoid tumor located in the pineal region following prophylactic irradiation for acute lymphoblastic leukemia. Brain Tumor Pathol 29:177–181. https://doi.org/10.1007/s10014-011-0075-8
40. Lafay-Cousin L, Payne E, Strother D, Chernos J, Chan M, Bernier FP (2009) Goldenhar phenotype in a child with distal 22q11.2 deletion and intracranial atypical teratoid rhabdoid tumor. Am J Med Genet A 149:2855–2859. https://doi.org/10.1002/ajmg.a.33119
41. Laichuthai N, Snabboon T (2020) SUN-288 atypical teratoid rhabdoid tumor of the sellar region: an unusual cause of hypopituitarism. J Endocr Soc 4:SUN-288. https://doi.org/10.1210/jendso/bvaa046.004
42. Larrán-Escandón L, Mateo-Gavira I, Vilchez-López FJ, Gómez Cárdenas E, Aguilar Diosdado M (2016) Pituitary apoplexy as presentation of atypical teratoid/rhabdoid tumor in an adult | Apoplejía hipofisaria como forma de presentación de un tumor teratoide/rabdoide atípico en el adulto. Endocrinol Nutr 63:364–365. https://doi.org/10.1016/j.endonu.2016.05.004
43. Las Heras F, Pritzker KPH (2010) Adult variant of atypical teratoid/rhabdoid tumor: Immunohistochemical and ultrastructural confirmation of a rare tumor in the sella tursica. Pathol Res Pract 206:788–791. https://doi.org/10.1016/j.prp.2010.07.004
44. Lawler K, Robertson T (2019) A rare case of sellar region atypical teratoid/rhabdoid tumour in an adult female. Pathology 51:S89. https://doi.org/10.1016/j.pathol.2018.12.233
45. Lev I, Fan X, Yu R (2015) Sellar atypical teratoid/rhabdoid tumor: any preoperative diagnostic clues? AACE Clin Case Rep 1:e2–e7. https://doi.org/10.4158/ep14337.cr
46. Liu F, Fan S, Tang X, Fan S, Zhou L (2020) Adult sellar region atypical teratoid/rhabdoid tumor: a retrospective study and literature review. Front Neurol 11:1–11. https://doi.org/10.3389/fneur.2020.604612
47. Madhavan P, Schwartz P, Kantorovich V (2020) A rare case of atypical teratoid/rhabdoid tumor of sellar region in an adult, vol 4. JESOCI, Abstract Supplement
48. Makuria AT, Rushing EJ, McGrail KM, Hartmann DP, Azumi N, Ozdemirli M (2008) Atypical teratoid rhabdoid tumor (AT/RT) in adults: review of four cases. J Neurooncol 88:321–330. https://doi.org/10.1007/s11060-008-9571-z
49. Mathkour M, Carsky K, Chabot AB, Werner C, Berry JF, Carr C, Lockwood JD, Keen JR, Bui CJ, Biro EE (2020) Adult pineal region atypical teratoid rhabdoid tumor: a case for aggressive surgical and chemoradiation management with comprehensive literature review. World Neurosurg 142:117–127. https://doi.org/10.1016/j.wneu.2020.06.144

50. McGinity M, Siddiqui H, Singh G, Tio F, Shakir A (2017) Primary atypical teratoid rhabdoid tumor in the adult spine. Surg Neurol Int 8:34. https://doi.org/10.4103/2152-7806.202132
51. Monteiro J, Santiago B, Manilha R, Viegas C, Oliveira A, Cunha E, Sá M (2020) Adult atypical teratoid/rhabdoid tumor in the pineal region: case report and literature review. World Neurosurg 134:428–433. https://doi.org/10.1016/j.wneu.2019.11.075
52. Moretti C, Lupoi D, Spasaro F, Chioma L, Di Giacinto P, Colicchia M, Frajoli M, Mocini R, Ulisse S, Antonelli M, Giangaspero F, Gnessi L (2013) Sella turcica atypical teratoid/rhabdoid tumor complicated with lung metastasis in an adult female. Clin Med Insights Case Rep 6:177–182. https://doi.org/10.4137/CCRep.S12834
53. Moujahed R, Ghedira K, Zehani A, Charfi S, Nagi S (2020) Brain atypical teratoid rhabdoid tumor in an adult with long-term survival: case report and review of literature. J Cancer Res Ther 16:S243–S245. https://doi.org/10.4103/jcrt.JCRT_554_18
54. Nakata S, Nobusawa S, Hirose T, Ito S, Inoshita N, Ichi S, Amatya VJ, Takeshima Y, Sugiyama K, Sonoda Y, Haga H, Hirato J, Nakazato Y, Yokoo H (2017) Sellar atypical teratoid/rhabdoid tumor (AT/RT): a clinicopathologically and genetically distinct variant of AT/RT. Am J Surg Pathol 41:932–940. https://doi.org/10.1097/PAS.0000000000000845
55. Neromyliotis E, Kalyvas AV, Drosos E, Komaitis S, Bartziotas D, Skandalakis GP, Stranjalis G, Koutsarnakis C (2019) Spinal atypical rhabdoid teratoid tumor in an adult woman: case report and review of the literature. World Neurosurg 128:196–199. https://doi.org/10.1016/j.wneu.2019.05.007
56. Nishikawa A, Ogiwara T, Nagm A, Sano K, Okada M, Chiba A, Agata M, Kaneko T, Tamada H, Uehara T, Hongo K (2018) Atypical teratoid/rhabdoid tumor of the sellar region in adult women: Is it a sex-related disease? J Clin Neurosci 49:16–21. https://doi.org/10.1016/j.jocn.2017.12.010
57. Nobusawa S, Hirato J, Sugai T, Okura N, Yamazaki T, Yamada S, Ikota H, Nakazato Y, Yokoo H (2016) Atypical teratoid/rhabdoid tumor (AT/RT) arising from ependymoma: a type of AT/RT secondarily developing from other primary central nervous system tumors. J Neuropathol Exp Neurol 75:167–174. https://doi.org/10.1093/jnen/nlv017
58. Nobusawa S, Nakata S, Hirato J, Kawashima T, Sato K, Fujimaki H, Okura N, Ikota H, Yokoo H (2016) Atypical teratoid/rhabdoid tumor in the sella turcica of an elderly female with a distinct vascular pattern and genetic alterations. Virchows Arch 469:711–715. https://doi.org/10.1007/s00428-016-2017-7
59. Nowak J, Nemes K, Hohm A, Vandergrift LA, Hasselblatt M, Johann PD, Kool M, Frühwald MC, Warmuth-Metz M (2018) Magnetic resonance imaging surrogates of molecular subgroups in atypical teratoid/rhabdoid tumor. Neuro Oncol 20:1672–1679. https://doi.org/10.1093/neuonc/noy111
60. Oliveira E, Lavrador JP, Roque L, Pimentel J, Miguéns J (2016) Atypical teratoid/rhabdoid tumour following craniopharyngioma radiotherapy during childhood. Child's Nerv Syst 32:1573–1575. https://doi.org/10.1007/s00381-016-3187-y
61. Oraibi O, Mau C, Daggubati L, Khormi Y, Manni A, Zacharia B (2020) MON-262 a case of the suprasellar atypical teratoid rhabdoid tumor (ATRT) presenting in an adult treated with intrathecal chemotherapy. J Endocr Soc 4:MON-262. https://doi.org/10.1210/jendso/bvaa046.1261
62. Ostrom QT, Chen Y, M de Blank P, Ondracek A, Farah P, Gittleman H, Wolinsky Y, Kruchko C, Cohen ML, Brat DJ, Barnholtz-Sloan JS (2014) The descriptive epidemiology of atypical teratoid/rhabdoid tumors in the United States, 2001-2010. Neuro Oncol 16:1392–1399. https://doi.org/10.1093/neuonc/nou090
63. Paolini MA, Kipp BR, Sukov WR, Jenkins SM, Barr Fritcher EG, Aranda D, SantaCruz KS, Al-Dandan S, Fisher P, McDonald WC, Bondurant CP, Van Dyke Darkow G, Giannini C, Parisi JE, Jentoft ME, Raghunathan A (2018) Sellar region atypical teratoid/rhabdoid tumors in adults: clinicopathological characterization of five cases and review of the literature. J Neuropathol Exp Neurol 77:1115–1121. https://doi.org/10.1093/jnen/nly091
64. Park HG, Yoon JH, Kim SH, Cho KH, Park HJ, Kim SH, Kim EH (2014) Adult-onset sellar and suprasellar atypical teratoid rhabdoid tumor treated with a multimodal approach: a case report. Brain Tumor Res Treat 2:108–113. https://doi.org/10.14791/btrt.2014.2.2.108
65. Peng AJ, Fan SC, Chen YX, Huang JH, Cao Y, Zhou LX, Chen N (2021) Atypical teratoid/rhabdoid tumor in adult: case series and an integrated survival analysis. Br J Neurosurg 17:1–16. https://doi.org/10.1080/02688697.2021.1885620
66. Pittman PD, Harrison WT, Buckley AF (2021) Adult atypical teratoid/ rhabdoid tumor (AT/RT): a case of mistaken identity. Clin Neuropathol 40:62–63. https://doi.org/10.5414/NP301306
67. Raisanen J, Biegel JA, Hatanpaa KJ, Judkins A, White CL, Perry A (2005) Chromosome 22q deletions in atypical teratoid/rhabdoid tumors in adults. Brain Pathol 15:23–28. https://doi.org/10.1111/j.1750-3639.2005.tb00096.x
68. Raisanen J, Hatanpaa KJ, Mickey BE, White CL (2004) Atypical teratoid/rhabdoid tumor: cytology and differential diagnosis in adults. Diagn Cytopathol 31:60–63. https://doi.org/10.1002/dc.20064
69. Regan J, Tehrani M, Rodriguez F, Watson J (2015) Adult At/Rt: predilection for the pituitary? J Neurol Neurosurg 2:110. https://doi.org/10.19104/jnn.2015.110
70. Renner C (2017) Atypical teratoid/rhabdoid tumor of the pineal region in a young adult male patient: case report and review of the literature. J Neurol Surg A Cent Eur Neurosurg 78:92–98. https://doi.org/10.1055/s-0036-1583180
71. Roy S, Mallik C, Maiti S, Chaudhuri T (2013) Temporal lobe atypical teratoid/ rhabdoid tumor in a 24-year old adult female. South Asian J Cancer 2:210. https://doi.org/10.4103/2278-330X.119909
72. Salhotra N, Laiq S, Livingston C, Al Hattali M, Al Kindi H, Al Hajri Z (2020) Atypical teratoid/rhabdoid tumor in adults an uncommon entity: a case report. Clin Case Rep Open Access 3:171. https://doi.org/10.46527/2582-5038.171
73. Samaras V, Stamatelli A, Samaras E, Stergiou I, Konstantopoulou P, Varsos V, Judkins AR, Biegel JA, Barbatis C (2009) Atypical teratoid/rhabdoid tumor of the central nervous system in an 18-year-old patient. Clin Neuropathol 28:1–10. https://doi.org/10.5414/npp28001
74. Schneiderhan TM, Beseoglu K, Bergmann M, Neubauer U, Macht S, Hänggi D, Reifenberger G, Riemenschneider MJ (2011) Sellar atypical teratoid/rhabdoid tumours in adults. Neuropathol Appl Neurobiol 37:326–329. https://doi.org/10.1111/j.1365-2990.2010.01111.x
75. Schweizer Y, Meszaros Z, Jones DTW, Koelsche C, Boudalil M, Fiesel P, Schrimpf D, Piro RM, Brehmer S, von Deimling A, Kerl U, Seiz-Rosenhagen M, Capper D (2017) Molecular transition of an adult low-grade brain tumor to an atypical teratoid/rhabdoid tumor over a time-course of 14 years. J Neuropathol Exp Neurol 76:655–664. https://doi.org/10.1093/jnen/nlx044
76. Shitara S, Akiyama Y (2014) Atypical teratoid/rhabdoid tumor in sellar turcica in an adult: a case report and review of the literature. Surg Neurol Int 5:75. https://doi.org/10.4103/2152-7806.133105
77. Shonka NA, Armstrong TS, Prabhu SS, Childress A, Choi S, Langford LA, Gilbert MR (2011) Atypical teratoid/rhabdoid tumors in adults: a case report and treatment-focused review. J Clin Med Res 3:85–92. https://doi.org/10.4021/jocmr535w
78. Siddiqui M, Thoms D, Samples D, Caron J (2019) Atypical teratoid/rhabdoid tumor presenting with subarachnoid and intraventricular hemorrhage. Surg Neurol Int 10:139. https://doi.org/10.25259/SNI-59-2019

79. Sinha P, Ahmad M, Varghese A, Parekh T, Ismail A, Chakrabarty A, Tyagi A, Chumas P (2015) Atypical teratoid rhabdoid tumour of the spine: report of a case and literature review. Eur Spine J 24(Suppl 4):S472–S484. https://doi.org/10.1007/s00586-014-3445-1
80. Slemp SN, Martin SE, Zhang S, Ulbright TM, Cheng L, Hattab EM (2014) Atypical teratoid/rhabdoid tumour in an adult with disseminated mediastinal germ cell tumour. Neuropathol Appl Neurobiol 40:789–793. https://doi.org/10.1111/nan.12081
81. Souki C, Abdel-Rhaman M, Qasem A, Al-Hussaini M (2014) Atypical teratoid rhabdoid tumor in adulthood. Clin Neuropathol 33:245–250. https://doi.org/10.5414/NP300683
82. Takahashi-Fujigasaki J, Matumoto M, Kan I, Oka H, Yasue M (2012) Atypical teratoid/rhabdoid tumor with 26-year overall survival: case report. J Neurosurg Pediatr 9:400–405. https://doi.org/10.3171/2012.1.PEDS11350
83. Takei H, Adesina AM, Mehta V, Powell SZ, Langford LA (2010) Atypical teratoid/rhabdoid tumor of the pineal region in an adult. J Neurosurg 113:374–379. https://doi.org/10.3171/2009.10.JNS09964
84. Uner M, Saglam A, Meydan BC, Aslan K, Soylemezoglu F (2017) Atypical teratoid rhabdoid tumor arising in a pleomorphic xanthoastrocytoma: a rare entity. Clin Neuropathol 36:227–232. https://doi.org/10.5414/NP301017
85. Voisin MR, Ovenden C, Tsang DS, Gupta AA, Huang A, Gao AF, Diamandis P, Almeida JP, Gentili F (2019) Atypical teratoid/rhabdoid sellar tumor in an adult with a familial history of a germline SMARCB1 mutation: case report and review of the literature. World Neurosurg 127:336–345. https://doi.org/10.1016/j.wneu.2019.04.083
86. Wang Z, Fan QH, Yu MN, Zhang WM (2006) Clinicopathologic and immunohistochemical study of atypical teratoid/rhabdoid tumor of central nervous system. Zhonghua Bing Li Xue Za Zhi 35:458–461
87. Wu WW, Bi WL, Kang YJ, Ramkissoon SH, Prasad S, Shih HA, Reardon DA, Dunn IF (2016) Adult atypical teratoid/rhabdoid tumors. World Neurosurg 85:197–204. https://doi.org/10.1016/j.wneu.2015.08.076
88. Yamamoto J, Takahashi M, Nakano Y, Soejima Y, Saito T, Akiba D, Hirato J, Nakazato Y, Nishizawa S (2012) Rapid progression of rhabdoid components of a composite high-grade glioma and rhabdoid tumor in the occipital lobe of an adult. Brain Tumor Pathol 29:113–120. https://doi.org/10.1007/s10014-011-0069-6
89. Yu F, Chiang F, Bazan C (2016) Atypical teratoid/rhabdoid tumor arising from the trigeminal nerve in an adult. Neuroradiol J 29:447–449. https://doi.org/10.1177/1971400916654319
90. Zarovnaya EL, Pallatroni HF, Hug EB, Ball PA, Cromwell LD, Pipas JM, Fadul CE, Meyer LP, Park JP, Biegel JA, Perry A, Rhodes CH (2007) Atypical teratoid/rhabdoid tumor of the spine in an adult: case report and review of the literature. J Neurooncol 84:49–55. https://doi.org/10.1007/s11060-007-9339-x
91. Zhao RJ, Wu KY, Zhang JG, Ma YH, Kong LF (2015) Primary intracranial atypical teratoid/rhabdoid tumors: a clinicopathologic and neuroradiologic study. J Child Neurol 30:1017–1023. https://doi.org/10.1177/0883073814551795
92. Zin F, Cotter JA, Haberler C, Dottermusch M, Neumann J, Schüller U, Schweizer L, Thomas C, Nemes K, Johann PD, Kool M, Frühwald MC, Paulus W, Judkins A, Hasselblatt M (2021) Histopathological patterns in atypical teratoid/rhabdoid tumors are related to molecular subgroup. Brain Pathol 31:e12967. https://doi.org/10.1111/bpa.12967

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