

Atypical teratoid rhabdoid tumor (AT/RT) in adults: review of four cases

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Abstract Atypical teratoid/rhabdoid (AT/RT) tumor is a rare, highly malignant tumor of the central nervous system (CNS) most commonly found in children less than 5 years of age. Although the vast majority of cases are diagnosed in young children, there have been isolated case reports in adults. Since its histological appearance can be confused with other tumors, especially in adults, separating AT/RT from other neoplasms may be difficult. In many instances, a reliable diagnosis is not possible without demonstrating the lack of nuclear INI1 protein expression by immunohistochemical methods. The patients (three males and one female) ranged in age from 23 to 42 years (mean age, 32 years). Radiographically, two tumors were localized in the right fronto-parietal region, one was frontal and the other was found in the left temporal lobe. Varying degrees of hydrocephalus and heterogeneous enhancement were present on MRI. In all cases, diagnosis during intraoperative consultation and preliminary diagnosis was different from the final diagnosis after immunohistochemical analysis. Immunohistochemical staining showed that the tumor cells were positive for vimentin and reacted variably for keratin, epithelial membrane antigen (EMA), synaptophysin, neurofilament protein, CD34, and smooth muscle

actin (SMA). All were negative for GFAP, S-100, desmin and CD99. Three of the four cases lacked nuclear expression of INI1. One patient is alive with no evidence of disease 17 years after the diagnosis. In adult examples of AT/RT, the diagnosis requires a high index of suspicion, with early tissue diagnosis and a low threshold for investigation with INI1 immunohistochemistry to differentiate this entity from other morphologically similar tumors. Although the prognosis is dismal in pediatric population, long term survival is possible in adult AT/RT cases after surgery and adjuvant radiotherapy and chemotherapy.

Keywords Adult · Atypical teratoid/rhabdoid · Immunohistochemistry · INI1 · hSNF5

Introduction

Described in 1978 by Beckwith and Palmer [1], rhabdoid tumor has become a well-accepted clinicopathological entity. Since the original description of an aggressive renal tumor in very young children [2], tumors with rhabdoid features have been reported in many extra-renal sites. In 1985, Rorke et al. [3] first recognized this tumor in the brain under the term AT/RT to emphasize the variable combination of rhabdoid cells, epithelial cells, primitive neuro-ectodermal as well as mesenchymal components. Most of these tumors are situated in the posterior fossa, or less commonly supratentorially, and in an exceptional instance in the spinal cord [4]. They show a propensity to spread through the subarachnoid space, which is often noted at the time of diagnosis. Although AT/RT is most often diagnosed in children less than 5 years, in rare instances, it may occur in adults [5–13]. The pathological characteristic to display multiple lines of differentiation in

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varying proportions can cause confusion of AT/RT with other neoplasms, especially in adults.

AT/RTs are associated with deletion of chromosome 22q and inactivation of INI1/hSNF5 (HIV-integrase interactor 1 (INI1)/human homolog of *Saccharomyces Cerevisiae* sucrose-nonfermenting 5 (hSNF5), referred for simplicity as INI1) tumor suppressor gene on chromosome 22q11.2 [12, 14, 15]. Mutation or deletion of both copies of the INI1/hSNF5/gene is observed in approximately 70% of primary tumors [16]. An additional 20–25% of tumors are estimated to have reduced expression at the RNA or protein level, indicative of a loss-of-function event. Recent development of the INI1 immunohistochemical stain has been helpful in identifying tumors with chromosome 22 deletions [17]. Therefore, the absence of INI1 nuclear expression by the tumor cells was used in this study as one of the hallmark criteria to identify AT/RT, although one of the cases retained the expression of this protein.

The aim of this study is to call attention to the occurrence of AT/RT in adult patients. Four additional adult cases are presented and the clinicopathologic features are discussed in relation to other cases described in the adult population.

Materials and methods

Clinical data

Two patients (Cases 1 and 2) diagnosed at Georgetown University Medical Center (GUMC) are included in this report. The other two cases (Cases 3 and 4) were received in consultation by one of the authors (EJR) at the Armed Forces Institute of Pathology (AFIP). When available, the clinical presentation, neuroradiologic appearance and operative findings were abstracted from the patient records or patient families. Preoperative computed tomographic (CT) and/or magnetic resonance imaging (MRI) scans was available for one case, Case 1.

Histology and immunohistochemistry

All four surgical specimens were formalin-fixed, routinely processed, sectioned at 5 μ m, and stained by the hematoxylin and eosin (H&E) method. The H&E slides of each case, including the two cases received in consultation, were reviewed and assessed for features including the general architecture, degree of cellularity, necrosis and mitoses.

Immunohistochemistry was performed on formalin-fixed, paraffin-embedded tissue sections using the Envision+ (Dako, Carpinteria, CA)—horseradish peroxidase system after the tissue was deparaffinized and rehydrated according to standard protocol. The following antibodies

were used: polyclonal antibodies against S-100, and synaptophysin (purchased from Dako, Carpinteria, CA), and monoclonal antibodies against epithelial membrane antigen (EMA), neurofilament proteins (Nf), MIB-1, glial fibrillary acidic protein (GFAP), vimentin, smooth muscle actin (SMA), muscle specific actin (MSA), desmin, CD34, CD31 and Factor 8 (from Dako, Carpinteria, CA), CD99 (O-13) (from Signet; Dedham, MA), BAF 47 (INI1) (from BD Biosciences Pharmingen, San Jose, CA) and keratin (a cocktail of AE1/AE3, CAM 5.2, and 35 β H11) (from Ventana Medical Systems, Tucson, AZ). In every case, formalin-fixed tissue was subjected to heat-induced antigen retrieval.

Case descriptions

Case 1

This 23-year-old-male presented with a history of two episodes of seizure activity occurring on the same day. In addition, he complained of a continuous headache for 2 weeks prior to the onset of seizures. On admission, MRI revealed a 3.6 \times 3.5 \times 3.2 cm heterogeneously enhancing mass with surrounding edema within the posterior left temporal lobe (Fig. 1). Craniotomy was performed and

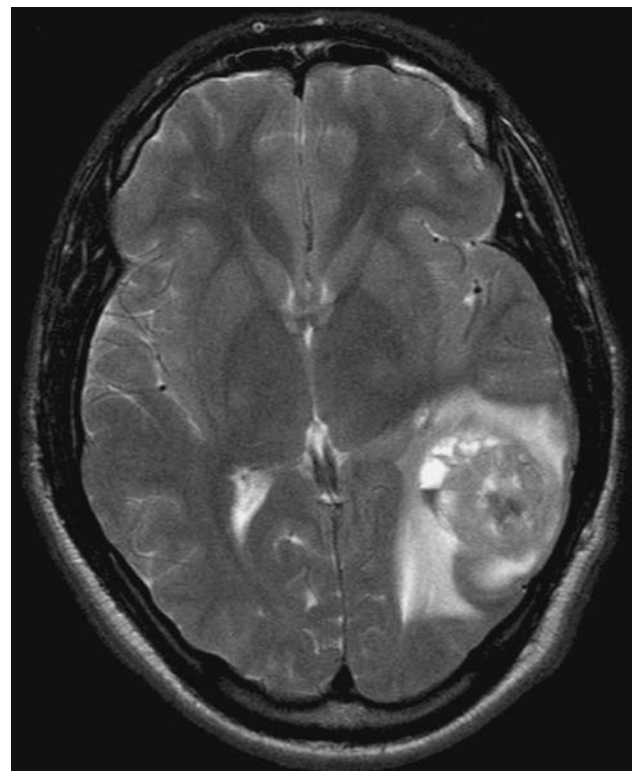


Fig. 1 T2 weighted axial MRI shows a left posterior temporal mass showing with heterogenous signal intensity and surrounding vasogenic edema

the mass was removed. The specimen was sent to surgical pathology, where a portion was used for frozen section diagnosis and the remaining tissue was submitted for permanent sections. The frozen section diagnosis was high grade malignant tumor with necrosis consistent with glioblastoma multiforme. However, a diagnosis of AT/RT was made after extensive immunohistochemical analysis. The patient had a stable post-operative course and was discharged after a week with a scheduled follow up appointment. Currently the patient is being followed at another institution, where he received adjuvant radiotherapy and chemotherapy after the surgery and is in remission 30 months after the diagnosis.

Case 2

Twenty-five-year old female with 1 year history of headaches and who was being treated for migraine presented with bilateral gaze palsy. A CT scan showed a 5 cm right frontal brain tumor. The patient underwent a craniotomy and the tumor was completely excised. A diagnosis of rhabdoid tumor was made. Because of the diagnosis, no adjuvant therapy was given initially. However, the tumor recurred 2 years later and she received gamma knife radiosurgery. Over the next 5 years, she experienced five more episodes of recurrence in the same tumor bed and additionally in the left frontal region in the last episode. The recurrent tumors were resected completely. In all these tumors the histology showed similar features. She received adjuvant radiotherapy and later chemotherapy after the last recurrence at another institution. No recurrence has occurred in the last 10 years and she is alive 17 years after the diagnosis.

Case 3

A previously healthy 42-year-old-male presented to a tertiary care provider with dysphasia and right sided weakness. On admission he was found to have a 1.5 × 1.0 × 1.0 cm mass within the right fronto-parietal region. Because of the location of the tumor, a complete resection was not

obtained. The specimen was sent to surgical pathology where the diagnosis of gemistocytic astrocytoma with the differential diagnosis of AT/RT was made. After surgery, the patient received adjunct radiotherapy and chemotherapy. The patient is alive 18 months after the diagnosis.

Case 4

This 37-year-old-male presented with a history of new-onset seizures that prompted referral to a tertiary care provider. Imaging studies revealed a right hemisphere mass. The contributor’s diagnosis (a recent case from abroad) was glioblastoma. AT/RT was considered as a differential diagnosis. There is no further clinical data available.

Results

Clinical features

Table 1 summarizes the clinical features of the four cases. The single female and three male patients ranged in age from 23 years to 42 years. All four tumors were located in the cerebrum. The cases presented with seizure (case 1 and 4), headache and gaze palsy (case 2) and dysphasia and right-sided weakness (case 3).

Pathological features

At low magnification, sections from the first case revealed a mixed population of cells comprising variable numbers of rhabdoid cells, primitive-appearing small blue cells, and spindle shaped cells having sarcomatoid appearance but on higher magnification the cells in all areas had rhabdoid features with eosinophilic cytoplasm (Fig. 2a–d). The second case had spindle cells without a discrete pattern or trabecular growth pattern with epithelioid cells with eosinophilic cytoplasm as well as typical rhabdoid morphology. The other two cases were relatively homogenous

Table 1 Clinical features of the four cases

Cases	Age sex	Clinical presentation	Location of tumor	Adjuvant therapy	Survival
Case 1	23 M	Two episodes of seizure in 1 day and headache over the last 2 weeks	Posterior left temporal lobe	Radiotherapy, Chemotherapy	30 Months + with no evidence of disease
Case 2	25 F	Headaches over the last 1 year and acute onset of bilateral gaze palsy	Right frontal lobe	Radiotherapy, Chemotherapy	17 Years + with no evidence of disease
Case 3	42 M	Dysphasia and right side body weakness	Right fronto-parietal region	Radiotherapy, Chemotherapy	18 Months + with no evidence of disease
Case 4	37 M	Seizures	Right fronto-parietal	Radiotherapy	Unknown

M, Male; F, Female; N/A, Not available

Fig. 2 Representative morphologic features from formalin fixed paraffin embedded sections (case 1). Lower magnification shows variegated appearance with small blue cell areas with geographic necrosis (arrow) or sarcomatous-looking and rhabdoid areas (a) and (b) (hematoxylin and eosin, $\times 40$, each). Higher magnification of the sarcomatous looking areas (c) and rhabdoid cells (arrow) (d) (hematoxylin and eosin $\times 400$, each)

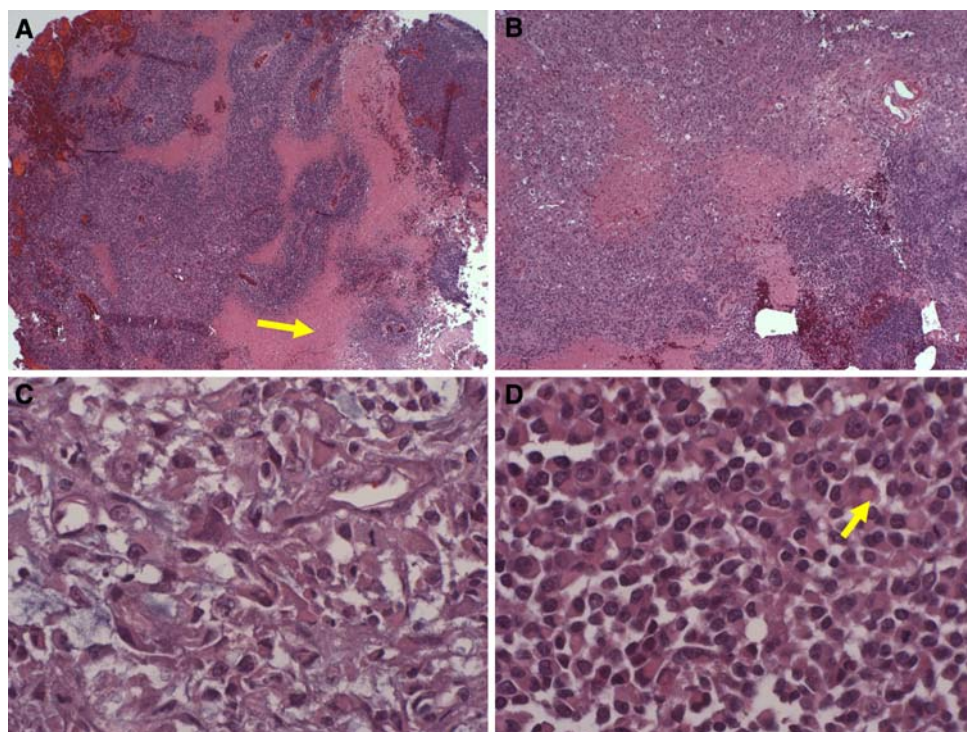
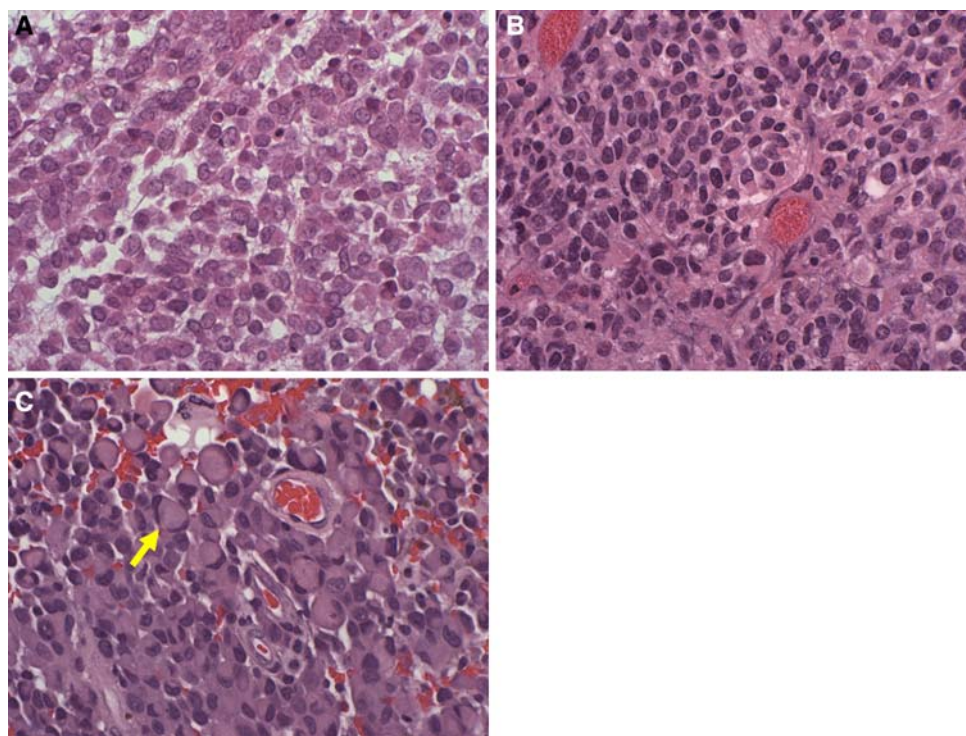


Fig. 3 Representative morphologic features from other cases. Higher magnification shows epithelioid cells with vague trabecular (case 2) (a), or nested growth pattern (case 3) (b), and rhabdoid cells with hyaline globular inclusions (arrow) (case 4) (c) (hematoxylin and eosin $\times 400$, each)



with rhabdoid cells and spindle cells and vague nested growth pattern (Fig. 3a–c). In none of the cases, a fascicular growth pattern was observed to consider a gliosarcoma. A common feature of these tumors, the rhabdoid cell, was characterized by discrete cell borders and eccentric reniform nuclei, often with prominent

nucleoli and eosinophilic cytoplasm. Some of these cells contained intracytoplasmic hyaline globular inclusions adjacent to the nucleus. In some cases, the neoplastic cells exhibited oligodendroglial-like features due to artifactual tumor cell vacuolation. Necrosis and mitotic figures were present in all cases.

Immunohistochemistry

Table 2 summarizes the immunohistochemical results. The rhabdoid cells consistently displayed immunoreactivity for vimentin (Fig. 4a). They stained variably for EMA, keratin, SMA (Fig. 4b), and less frequently for synaptophysin,

Table 2 Results of immunohistochemical analysis

Antibodies	Case 1	Case 2	Case 3	Case 4
Vimentin	3+	3+	3+	3+
EMA	2+	neg	2+	neg
SMA	3+	2+	neg	neg
NF	1+	1+	neg	neg
Synaptophysin	1+	2+	neg	neg
CD99	neg	neg	neg	neg
S-100	neg	neg	neg	neg
Keratin	3+	neg	2+	neg
Desmin	neg	neg	neg	neg
GFAP	neg	neg	neg	neg
INI1	neg	neg	neg	2+
CD34	neg	2+	n/a	neg
MSA	2+	none	neg	neg
Mib-1	2+	2+	2+	2+
Factor 8	neg	neg	n/a	neg
CD31	neg	neg	n/a	neg

3+ = Strongly positive; 2+ = Positive; 1+ = Weakly positive; neg = Negative; n/a = Not available

MSA and CD34. The primitive-appearing small blue cells and sarcomatous areas in the first case stained similar to rhabdoid cells. The rhabdoid component and all other tumor cells were negative for CD99, S-100, GFAP, and desmin. In all our cases, the tumors showed a high proliferation index, with MIB1 up-to 80% in one example (Fig. 4c). Three cases showed lack of nuclear staining for BAF 47 (INI1) antibody but showed normal nuclear positivity in adjacent control tissues (Figs. 4d, 5a–b). Case 4 was stained for INI1, but it was negative for other specific markers including Factor 8 (Fig. 5c–d). Additional cytogenetic, mRNA or protein analyses were not performed.

Discussion

In 1992, Horn et al. was the first to recognize AT/RT, as a malignant intracranial rhabdoid tumor in an adult patient [5]. Later, 16 additional cases were described in adults as malignant rhabdoid tumor of CNS or AT/RT in the English literature [4, 6–8, 11–13, 18–22]. Raisanen et al. described three adult cases where the diagnosis was supported by detection of 22q11.2 deletion, INI1/hSNF5 (INI1) mutation and/or loss of INI1 protein expression [12]. Of note, two patients were female, ages 20 and 31 and one was male, age 45 with two tumors occurring in the sella or sellar region and one in the cerebellum, respectively. More recently, Zarovnyaya described a 43-year old woman with AT/RT in the cervical spinal cord that recurred throughout

Fig. 4 By immunohistochemistry (case 1), the tumor cells are positive for keratin (a) and SMA (b). Mib-1 shows a high proliferative index (c). The tumor cells are negative for INI1 (arrow) (D) (×400, each)

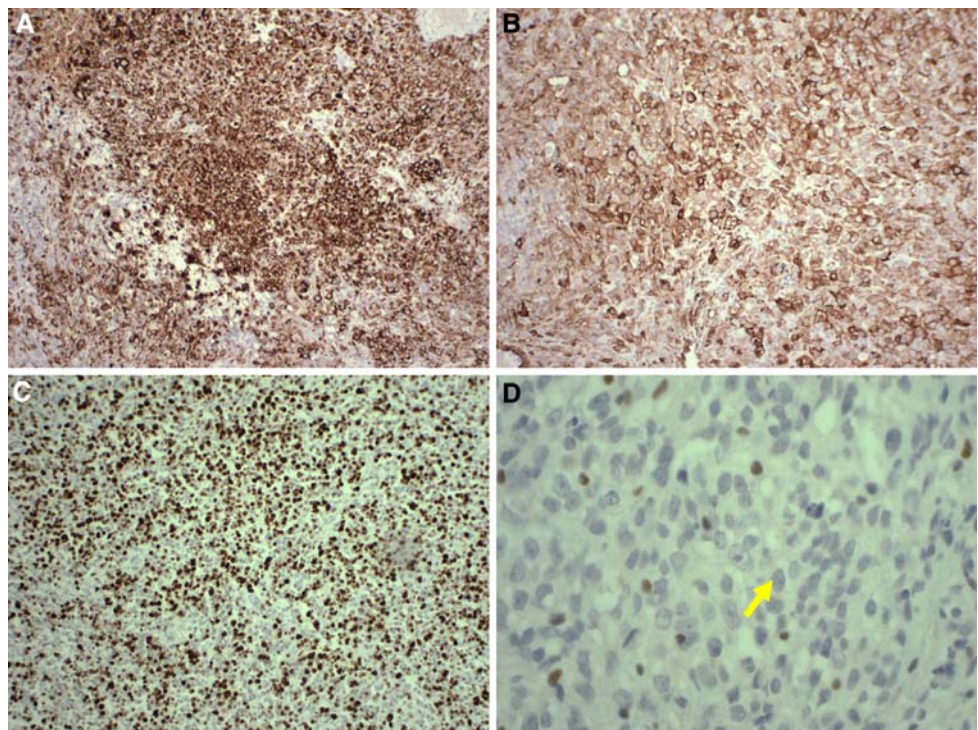
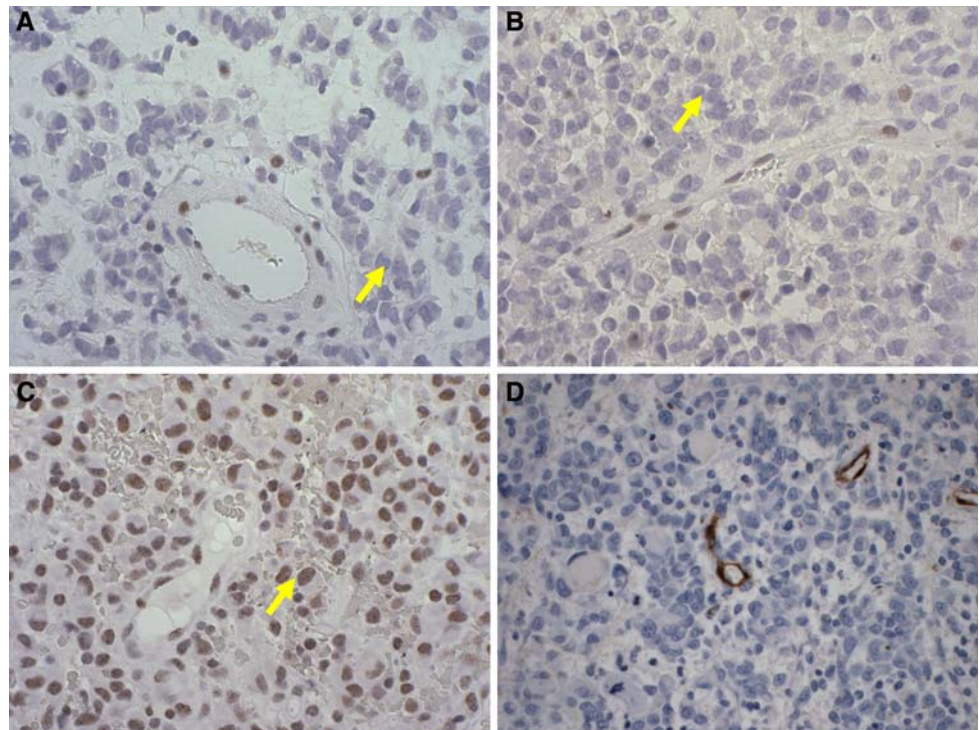


Fig. 5 By immunohistochemistry, the tumor cells are negative for INI1 (cases 2 and 3) (**a** and **b**), whereas tumor cells in case 4 is positive for INI1 (arrows) (**c**) and negative for Factor 8 (**D**) ($\times 400$, each)



the neuraxis secondary to leptomeningeal spread [4]. Originally diagnosed as a rhabdoid meningioma, in retrospective review, the tumor cells were found to exhibit monosomy 22 with loss of expression of the INI1 gene in 22q11.2 by molecular studies and absence of INI1 gene expression by immunohistochemical methods. Table 3 summarizes the adult cases reported in the English literature with a diagnosis of AT/RT or rhabdoid tumor.

The pathogenesis of AT/RTs is not very well understood, but a pluripotent cell with the ability to diverge into epithelial and mesenchymal cells has been suggested. In earlier reports, rhabdoid tumors were described as rhabdomyosarcomatoid tumors due to their morphologic resemblance to rhabdomyoblasts [1]. However, ultrastructural studies did not reveal myoblast differentiation.

In all four patients described in this report, the tumors contained sheets of typical rhabdoid cells, and morphologically were consistent with AT/RT. As noted, the rhabdoid cells have abundant eosinophilic cytoplasm with discrete cell border and eccentric nuclei, prominent nucleoli and hyaline globular inclusion adjacent to the nuclei similar to the observation by other investigators (Fig. 2). The hyaline globular inclusions are known to be aggregates of intermediate filaments identified as vimentin by immunohistochemistry. Similar to our cases, variable mitotic activity, necrosis, hemorrhage and cystic changes have also been described [23, 24] as seen in our cases. Owing to the mixed population of cells or divergent differentiation, AT/RTs show polyphenotypic immunoreactivity with different

immunohistochemical markers. The rhabdoid cells usually express vimentin and EMA. Also, there is variable expression of GFAP, S-100 and cytokeratin. Myogenous differentiation, when present, is usually observed in the small cell component [19, 25]. In the present cases, the rhabdoid cells expressed vimentin consistently, whereas in some cases they showed variable expression of keratin, EMA, SMA, MSA, synaptophysin, and neurofilament. All four cases were negative for S-100, GFAP, desmin and CD99. The lack of expression of CD99 as well as S-100 and EMA excludes the possible differential diagnosis of primitive neuroectodermal tumor (PNET) and rhabdoid meningioma, respectively, which may morphologically resemble AT/RT.

Molecular genetic studies have shown that majority of AT/RTs show deletion and/or mutation involving the INI1/hSNF5 tumor suppressor gene on chromosome 22q11 [12, 14, 15]. Loss of INI1/hSNF5 gene has been shown to affect the actin cytoskeleton which may explain the rhabdoid morphology seen in AT/RTs [26]. The recently developed INI1 antibody has been introduced as a useful marker to show the lack of expression of INI1 protein in tumor cells of AT/RT [17, 27]. The deletion can also be detected by fluorescent in-situ hybridization (FISH) although, 20–30% of tumors maintain a normal dosage of chromosome 22q suggesting that the absence of deletion should not exclude the consideration of AT/RT. This could explain the positive INI1 reactivity observed in one of our cases (Case 4), where the diagnosis of AT/RT was strongly

Table 3 Literature review of adult cases with diagnosis of AT/RT or rhabdoid tumor

Authors (year)	Age (years), Gender and history (if available)	Tumor location	Diagnosis confirmed by	Adjuvant therapy	Survival
Horn et al. (1992) [5]	21 M, presented with rapidly developing hypacusis and left face paresthesia	Left temporal	Immunohistochemistry. No INI1 analysis done	Radiation, Chemotherapy	6 Years
Fisher et al. (1996) [6]	32 M, presented with sudden onset of bifrontal headache, nausea and vomiting	Left periventricular caudate	Immunohistochemistry. No INI1 analysis done	None	1 Month
Ashraf et al. (1997) [7]	34 M, 1 month history of tingling sensation in right arm, slurred speech	Left parietal	Immunohistochemistry. No INI1 analysis done	Radiation	6 Months
Byram et al. (1999) [18]	35 M, 2 year history of facial numbness	Left temporal	Immunohistochemistry. No INI1 analysis done	Radiation	5 Years
Sugita et al. (1999) [19]	27 M, nausea, vomiting, papilledema	Pineal region	Immunohistochemistry. No INI1 analysis done	Radiation, Chemotherapy	2 Years
Arrazola et al. (2000) [8]	20 M, presented with seizure and 3 month history of episodes of sudden localised right hand dysaesthesiae	Left parietal	Immunohistochemistry. No INI1 analysis done	Radiation	7 years+
Lutterbach et al. (2001) [10]	30 F, pregnant with headache and vomiting followed by somnolence and ataxia	Cerebellum	Immunohistochemistry. No INI1 analysis done	Radiation, Chemotherapy	Delivered a healthy baby and died 11 months after diagnosis
Bruch et al. (2001) [20]	21 F	Spinal cord	Chromosome 22q loss by FISH	N/A	6 Months
Pimentel et al. (2003) [11]	31 F, 2 week history of partial motor seizures on her left limbs	Right parieto-rolandic	Immunohistochemistry No INI1 analysis done	Radiation, Chemotherapy	6 Months
Kawaguchi et al. (2004) [9]	22 M, 2 week-history of headache and nausea, mild left facial paresis and trunkal ataxia	Left cerebellum	Immunohistochemistry No INI1 analysis done	Radiation, Chemotherapy	24 Months + No recurrence
Kachara et al. (2003) [21]	35 M, 2 month history of bifrontal headache, numbness in left half of the body	Thalamus	Immunohistochemistry No INI1 analysis done	Radiation	N/A
Raisanen et al. (2005) [12]	20 F with loss of right eye vision	Sellar mass impinging on optic nerve	Chromosome 22q loss by FISH and immunohistochemistry	Radiation, Chemotherapy	28 months+
Raisanen et al. (2005) [12]	31 F	Sellar mass with suprasellar extension	Chromosome 22q loss by FISH and immunohistochemistry	Radiation	9 Months
Raisanen et al. (2005) [12]	45 F	Right cerebellar mass	Chromosome 22q loss by FISH and immunohistochemistry	Chemotherapy followed by radiation	15 Months+
Erickson et al. (2005) [22]	20 F, pregnant presented with headache, nausea and blurry vision	Right occipital	Immunohistochemistry, FISH was negative for chromosome 22 abnormality	N/A	N/A

Table 3 Literature review of adult cases with diagnosis of AT/RT or rhabdoid tumor

Authors (year)	Age (years), Gender and history (if available)	Tumor location	Diagnosis confirmed by	Adjuvant therapy	Survival
Rezanko et al. (2006) [13]	27 M, 30-day history of headache	Right frontal	Immunohistochemistry No INI1 analysis done	Radiation	4 Months
Zarovnaya et al. (2007) [4]	43 F, one week of neck and left upper extremity pain	Partial intra- and extra-medullary spinal mass (C4-C6)	Immunohistochemistry, FISH	Radiation, Chemotherapy	2½ Years

M, Male; F, Female; N/A, Not available; +Alive

considered by the morphologic features and also other possible differential diagnoses were excluded by immunohistochemistry. In the workshop on childhood AT/RT reviewed by Biegel et al. [28], the molecular and cytogenetic findings in a series of 76 rhabdoid tumors were detailed. The authors reported that AT/RTs demonstrate monosomy 22 at a higher frequency than renal or extrarenal rhabdoid tumors and that extrarenal rhabdoid tumors had a very high rate of homozygous deletions of the entire INI1 gene. The loss of one allele with concomitant mutation in the remaining copy of INI1 gene was reported in 42 of 76 rhabdoid tumors and compound heterozygous mutations or splicing mutations in 4 cases. Approximately 10% of the cases had no coding sequence mutations but had decreased expression levels of INI1 by RT-PCR or Western blot analysis. Approximately 15% of tumors had no alteration of the INI1 gene at the DNA, RNA or protein levels. Therefore, it is possible that patients with monosomy 22 at an early age may not develop AT/RT until mutation occurs in the remaining allele later in life.

INI1/hSNF5 is a component of SWI/SNF chromatin remodeling complex functioning as a tumor suppressor by positively regulating transcription of a particular set of eukaryotic genes including c-myc involved in differentiation and apoptosis [28–31]. Kalpana et al. [32] first isolated INI1 protein, in-vitro, using the yeast two-hybrid system by its interaction with HIV-1 integrase and named it *Integrase interactor 1*. INI1 protein (also called BAF47) forms functional core of SWI/SNF complex along with BRM (Brahma) or BRG-1 (Brahma-related gene 1) and BAF(BRG-1-Associated Factor)155 and BAF170. These other components may also show mutation in association with INI1 protein loss. Wong et al. [33] have identified mutation in the core ATPase subunit of BRG-1, along with INI1 protein loss, in approximately 10% of cell lines studied. The impact of lack of BRG-1 in tumorigenesis such as retinoblastoma has previously been described. Knudsen et al. [34] have shown that, retinoblastoma tumor suppressor protein inactivation is required for tumor progression and that BRG-1 is required for RB to exert antimitogenic activity [35].

The localization and behavior in adults appears to differ somewhat from childhood cases. The most common site for this tumor in children is posterior fossa and the overall prognosis of AT/RTs is rather bleak [36]. In adults, the tumor is seen mostly in cerebrum and survival based on the current cases and literature review averaged 38.7 months (Tables 1 and 3). Of the 21 adult patients, 11 patients survived more than 12 months and one patient is still alive 17 years after the diagnosis after complete resection of tumors and adjuvant multimodal treatment. These results suggest that depending on localization, AT/RT may be less aggressive in adults. Recent advances using aggressive

therapy might have also contributed to a better outcome [37]. One of the major concerns, leptomeningeal spread, which can be seen very early in the disease, appears to respond to intensive adjunctive chemo-and/or radiation therapy and this may change the natural history. The presence of necrosis and high proliferation index (Mib1) correlates with the aggressiveness of the tumor. The Mib 1 index in one of our cases was 80%. Allen et al. [38] in their case report have suggested that transformation to an aggressive tumor in the clinical course of a stable brain tumor may be associated to acquisition of INI1 gene mutation with corresponding rhabdoid morphologic change. Of note, Litman et al. [39] have reported the appearance of rhabdoid tumor in the lung and ileum 20 years after radiation treatment for Wilms' tumor. Based on the location of the tumor within the radiation field, the authors suggested that, in some cases, AT/RT may be radiation induced.

Conclusions

It is important to consider ATRT in the differential diagnosis of aggressive intracranial neoplasms with ambiguous morphology. The IN1 antibody can be a useful tumor marker in such cases. The association of INI1 protein loss with other proteins in the SWI/SNF chromatin remodeling complex, such as BRG-1, is important to better understand the pathogenesis and aid the search for therapy. Identifying the triggering factors that lead to mutation or deletion of INI1/hSNF5 tumor suppressor gene later in life is also crucial to our understanding of this entity. Further investigations that address the prevalence of the lack of expression of INI1 protein in adult AT/RT and other primary and metastatic brain tumors are needed to assess the specificity and reliability of this technique. Finally, the identification of a specific genetic abnormality is beneficial in searching for gene directed therapy and improving the prognosis of these aggressive and fatal tumors.

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