

RESEARCH ARTICLE

Atypical Teratoid/Rhabdoid Tumor of Brain: a Clinicopathologic Study of Eleven Patients and Review of Literature

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Abstract

Background: Atypical teratoid/ rhabdoid tumor (AT/RT) is a rare aggressive embryonal central nervous system (CNS) tumor of infancy and early childhood. Majority of the cases arise in the posterior fossa, and remaining in the cerebrum. **Aims:** To analyze the clinicopathologic features of AT/RT on a cohort of cases. **Materials and methods:** All reported cases of AT/RT at the Department of Pathology and Laboratory Medicine, Aga Khan University Hospital (AKUH) from 2007 to 2016 were reviewed for clinical and pathological features. Immunohistochemical stain for INI-1 was performed in all 11 cases. Follow up was obtained. **Results:** A total of 11 cases were identified. Seven patients were males and 4 were females. The ages ranged from 1 month to 48 months (mean 26.6 months). Six tumors were located in the cerebrum and 3 in the posterior fossa. Exact Location was not known in 2 cases. Histologically, rhabdoid cells were present in sheets in variable proportions in five cases, Medulloblastoma and PNET like areas were seen in 2 cases each. Immunohistochemical stains EMA (10/10), vimentin (7/7), CKAE1/AE3 (8/9), and CD99 (3/4), GFAP (6/10), ASMA (3/4) and synaptophysin (3/4) were positive in varying proportions while desmin was negative in all 6 cases in which it was performed. All 11 tumors lacked immunoreactivity for INI-1 protein. Four patients died of disease with a follow up ranging from 5 to 24 months. **Conclusions:** AT/RT is a rare highly aggressive embryonal tumor of CNS. A male predominance was noted in our series. We report the first and largest series from Pakistan.

Keywords: Atypical teratoid/rhabdoid tumor- posterior fossa- cerebrum- INI 1

Asian Pac J Cancer Prev, 18 (4), 949-954

Introduction

Atypical Teratoid/rhabdoid tumor (AT/RT) is defined as a malignant central nervous system (CNS) embryonal tumor composed predominantly of poorly differentiated elements frequently with rhabdoid cells and inactivation of SMARCB1(INI 1) or extremely rarely SMARCA4 (BAG1). (Judkins et al, 2016) Atypical Teratoid/Rhabdoid Tumor (AT/RT) is a rare, highly malignant and aggressive CNS neoplasm which mostly occurs in infants and young children under the age of 3 years (mean age approximately 2 years). It is very rare in children older than 6 years; however occasional cases occur in adults. It is more common in males (male to female ratio 1.6 to 2.0 :1.0). (Hilden et al., 2004; Raisanen et al., 2005; Judkins et al., 2007; Makuria et al., 2008) It mostly occurs in the cerebral and cerebellar hemispheres, cerebellopontine angle and brain stem; spinal examples are exceedingly rare. (Yang et al., 2007) Especially in infants, signs and symptoms are non-specific and include lethargy, vomiting and failure to thrive. (Judkins et al., 2007) AT/RT commonly seeds via the cerebrospinal fluid pathways. Findings on CT and MRI are similar to those seen in medulloblastoma and tumors previously designated as CNS PNETs. Almost all AT/RTs

are contrast enhancing, and leptomeningeal dissemination is seen in almost 25% cases at the time of presentation. (Meyers et al., 2006) Macroscopically, AT/RT is large in size, soft and fleshy in consistency, with necrotic areas. On histology, usually a complex histologic pattern is seen due to combination of rhabdoid, primitive neuroepithelial, epithelial and mesenchymal components. These divergent histologic patterns sometimes results in misdiagnosis of AT/RT as medulloblastoma, CNS PNET, choroid plexus carcinoma etc. In the past, it was mostly reported as medulloblastoma or PNET. Loss of immunohistochemical expression of INI-1 protein is sensitive and specific and a reliable diagnosis is not possible without demonstrating loss of INI-1 CNS protein expression. (Judkins et al., 2007; Makuria et al., 2008) AT/RT corresponds to WHO grade IV, and demonstrates a marked proliferative (Mib 1/Ki-67) index usually more than 50%. (Ho et al., 2000) Its genetic hallmark is mutation or loss of INI 1(hSNf5/SMARCB1) locus at 22q11.2. (Biegel et al., 2000) Prognosis is dismal, most patients die soon after diagnosis. Various studies have reported mean survival times ranging from 11 to 24 months. (Hilden et al., 2004; Chen et al., 2005; Burger et al., 1998) Prognosis is better in patients older than 3 years; and in the rare adults cases, long term survival

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may be possible after surgery, adjuvant radiotherapy and chemotherapy.(Makuria et al., 2008;Takautz et al., 2005)

The Section of Histopathology at the Aga Khan University Hospital, Karachi is the largest center for histopathology in Pakistan. CNS tumors are common in practice (Ahmad et al., 2011; Ahmad et al., 2016). We diagnosed our first case of AT/RT in 2004. Here, we present a series of 11 cases of AT/RT that were reported by us.

Materials and Methods

Eleven cases reported as AT/RT between 2004 and 2016 were retrieved from the surgical pathology files of the Section of Histopathology, Aga Khan University (AKU). All 11 patients had been operated outside AKUH and tissue (or blocks in 2 cases) was sent to us for histopathological examination. All specimens had been fixed in 10% buffered formalin, embedded in paraffin wax and paraffin sections were cut at a thickness of 3µm on a routine microtome. The sections were routinely stained with Hematoxylin and Eosin (H and E). Formalin fixed, paraffin embedded tissue sections were cut at 3 µm for immunohistochemical studies. Sections were deparaffinized, rehydrated and moistened with running tap water. The sections were pretreated in a microwave oven at 800W for 20 minutes with target retrieval solution at high pH (heat induced epitope retrieval or HIER). The sections were incubated with primary antibodies on an automated immunostaining system for 30 minutes at room temperature (DAKO autostainer plus, Glostrup, Denmark). Immunohistochemical staining was performed with the ready to use (RTU) Envision system using the following antibodies: Desmin (Dako, Glostrup, Denmark, monoclonal, dilution 1:100); CD99 (Dako, monoclonal, 1:50); Cytokeratin(CK) AE1/AE3 (Dako,monoclonal,1:400); GFAP (Dako,monoclonal, 1:100); Smooth muscle actin (SMA, Dako, monoclonal,1:150); S100 protein (polyclonal, Dako,1:300), epithelial membrane antigen (EMA, Dako, monoclonal,1:100),synaptophysin (Dako, monoclonal, 1:50); Chromogranin A (Dako, monoclonal, 1:200); Vimentin (Dako, monoclonal,1:120); CD99 (Dako, monoclonal, 1:50); Neurofilament (Dako,monoclonal, 1:100). As INI 1 was previously not available in our section, paraffin blocks were sent to Hospital for Sick Children,Toronto, Canada, where INI 1 immunostaining (Santa Cruz; Santacruz, CA, USA,1:50) was performed. However, INI 1 antibody was acquired in late 2014, and in the last 2 cases (diagnosed in 2015 & 2016 respectively), INI 1 was performed in our section. Molecular tests for inactivation of SMARCB1 and SMARCA4 were not available and were not performed.

Epidemiological data such as age of patient, gender, site of tumor, clinical signs and symptoms, survival time following diagnosis etc was recorded.

The slides of all 11 cases were reviewed by the two principal authors (NU and ZA).

Results

Out of 11 patients, 7 were males and 4 were females, the age at presentation ranged from 1 month to 48 months (mean 26.6 months). Tumor location was posterior fossa in 3 cases; frontoparietal and temporoparietal lobes in 2 cases each; frontal and temporoparietal lobes in 1 case each. In 2 cases, exact location was not known. Radiology was available in 5 cases. Radiologically, CT and MRI showed bulky, slightly hyperintense and contrast enhancing lesions with cystic, necrotic and hemorrhagic areas. Gross size of resected tumor fragments ranged from 1 to 5 cms (mean 3.5cms) in maximum dimension. The clinical and morphological features(Figure 1A, B, Figure 2A-D) and follow up information (6 cases) of all 11 cases is shown in Table 1. Follow up was available in only 6 of 11 cases.

Discussion

Clinical history in most of our cases was either not available or was vague and nonspecific. Radiological films were not available in majority of cases. We receive cases from all over Pakistan and even from neighboring Afghanistan. By an unfortunate coincidence, most of our 11 cases came from remote areas (including one from Afghanistan) and contact with surgeons was not possible or proved difficult. The clinicians themselves were

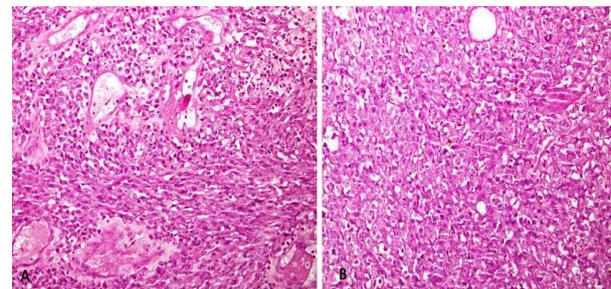


Figure 1: A) Mixture of Spindle and Epithelioid Tumor Cells and B) Sheets of Epithelioid Cells (H and E, 200x Magnification)

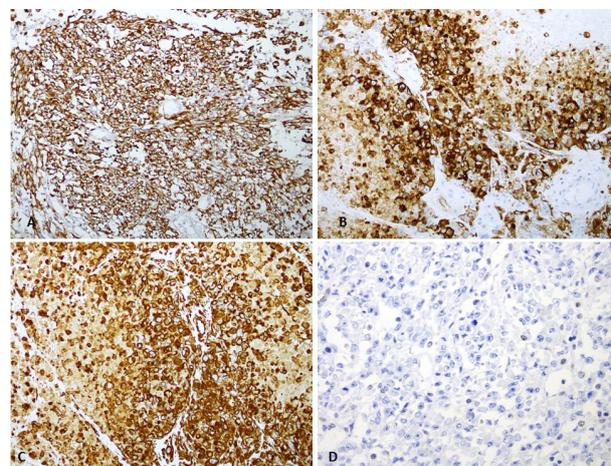


Figure 2. Immunohistochemical Expression of AT/RT. the Tumor Cells Showed Positivity for Cytokeratin AE1/AE3 (A), EMA (B) and Vimentin (C). There is Loss of Expression of INI 1 (D)

Table 1. Clinical and Morphologic Features and Follow Up Information of All Patients (n=11)

| No | Year of resection | Gender | Age(in months) | Site of tumor | Histologic features | Immunohistochemical profile | Radiology | Follow up |
|----|-------------------|--------|----------------|-------------------------|---|--|--|---|
| 1 | 2004 | Male | 12 | Posterior fossa | Cellular. Tumor cells in fascicles and sheets. Large cells with abundant pink cytoplasm. Pleomorphic, hyperchromatic nuclei, prominent nucleoli. Cells arranged around blood vessels (pseudorosettes) | Vimentin EMA GFAP Chromogranin Synaptophysin ASMA Desmin CKAE1/AE3 CD31 INI 1 | +ve +ve +ve +ve +ve -ve -ve -ve -ve | N.A. N.A. |
| 2 | 2007 | Male | 48 | Posterior fossa | Sheets of rhabdoid cells; distinct borders; large, vesicular nuclei with prominent nucleoli. Some cells with clear cytoplasm. Nests & sheets of small undifferentiated cells with dense, hyperchromatic nuclei. Spindle cells in fascicles. Arrangement of tumor cells around blood vessels (pseudorosettes). Cytoplasmic Glycogen (PAS positive) | Vimentin EMA CKAE1/AE3 ASMA CD99 CD56 Synaptophysin Desmin GFAP LCA INI 1 | +ve +ve +ve Focal Focal Focal Focal Few cells +ve +ve -ve -ve | N.A. N.A. |
| 3 | 2008 | Male | 1 | Lt frontoparietal lobe | Cellular. Medium to large, round to oval cells. Eccentric nuclei. Fine granular, pink cytoplasm. Also cells with vesicular nuclei and large nucleoli. Fascicles of spindle cells. Areas of fibrosis & necrosis. Cytoplasmic Glycogen (PAS positive) | Vimentin EMA CKAE1/AE3 CD99 GFAP Neurofilament INI 1 | +ve +ve +ve +ve -ve -ve -ve | N.A. N.A. |
| 4 | 2010 | Male | 6 | Rt frontoparietal lobe | Diffuse sheets of round to oval cells. Eccentric nuclei with prominent nucleoli. Abundant, pink, granular cytoplasm. Fascicles of spindle cells. Mitoses 15/10 HPFs approx. Cytoplasmic Glycogen (PAS positive) | Vimentin EMA CKAE1/AE3 GFAP ASMA Desmin INI 1 | +ve +ve +ve +ve -ve -ve -ve | N.A. Developed tumor recurrence 3 months after diagnosis, given radiotherapy and chemotherapy but died 2 months later. |
| 5 | 2010 | Female | 36 | Rt temporoparietal lobe | Cellular. Sheets, tubules, rosettes. Abundant, pink cytoplasm. Pleomorphic, hyperchromatic nuclei, inconspicuous nucleoli. Raised mitoses. Foci of necrosis | Vimentin EMA CKAE1/AE3 ASMA Synaptophysin CD56 GFAP INI 1 | +ve +ve +ve +ve Focal Focal -ve -ve | N.A. Died 5 months after diagnosis. Chemo and radiotherapy were offered but parents decided against any further treatment. |
| 6 | 2010 | Female | 29 | Lt frontal lobe | Sheets of round, oval and polygonal cells. Round to oval nuclei, coarse chromatin, prominent nucleoli. Moderate pink cytoplasm. Some cells with eccentric nuclei and abundant pink cytoplasm. Some fascicles of spindle cells with myxoid stroma. | EMA CKAE1/AE3 Synaptophysin CD99 GFAP INI 1 | +ve +ve -ve +ve Focal +ve -ve | Yes Died 5 months after diagnosis. Chemo and radiotherapy were offered but turned down. |

Table 1. Continued

| No | Year of resection | Gender | Age(in months) | Site of tumor | Histologic features | Immunohistochemical profile | Radiology | Follow up |
|----|-------------------|--------|----------------|------------------------------|--|--|--|---|
| 7 | 2012 | Male | 2 | Posterior fossa (cerebellum) | Cellular. Loose aggregates and sheets of cells. Arranged around blood vessels (pseudorosettes). Moderate pink to clear cytoplasm, round to irregular nuclei, deeply hyperchromatic, coarse chromatin. Fibromyxoid stroma. Increased mitotic activity. Areas of necrosis. | EMA CK AE1/AE3 CK Cam5,2 CD56 Synaptophysin GFAP CD99 INI 1 +ve +ve +ve Focal +ve Focal +ve -ve -ve | Yes. Hydrocephalus. Space occupying lesion right cerebellar hemisphere. | Chemo and radiation therapy was planned but patient died before these could be given. |
| 8 | 2013 | Male | 48 | Right cerebellar hemisphere | Cellular. Polygonal to spindle cells. Perivascular arrangement (pseudorosettes). Pleomorphic nuclei. In some areas, rhabdoid cells with eccentric nuclei and pink cytoplasm. Increased mitoses, abnormal mitoses. Areas of necrosis and hemorrhage. | EMA CKAE1/AE3 Vimentin Synaptophysin Desmin GFAP INI 1 +ve +ve +ve -ve +ve +ve -ve | Yes. Diffuse glioma (astrocytoma). Right cerebral hemisphere on CT scan | N.A. |
| 9 | 2014 | Female | 28 | Not known | Polygonal, plasmacytoid cells. Pleomorphic vesicular nuclei, prominent nucleoli. Abundant dense, pink granular cytoplasm. Increased mitotic activity. Cytoplasmic Glycogen (PAS positive) | GFAP CKAE1/AE3 EMA Synaptophysin Chromogranin A Desmin INI 1 Focal +ve Focal +ve -ve -ve -ve | N.A. | N.A. |
| 10 | 2015 | Female | 24 | Rt temporo-parietal lobe | Sheets of cells with abundant pink cytoplasm. Pleomorphic nuclei, prominent nucleoli. Some cells have eccentric (plasmacytoid) nuclei. In areas, loose, reticular pattern of arrangement. | Vimentin EMA CKAE1/AE3 GFAP CD30 PL/AP S100 Melan A Desmin ASMA INI 1 +ve +ve +ve -ve -ve -ve -ve -ve -ve | Yes. Lesion, Rt temporo-parietal lobe | Died 2 months after diagnosis. Chemo and radiotherapy was planned but patient died before the treatment could be started. |
| 11 | 2015 | Male | 48 | Lt temporal lobe | Cellular. Nests and sheets of epithelioid and polygonal cells. Eccentric (plasmacytoid) hyperchromatic nuclei. Abundant pink to clear cytoplasm. Atypical mitoses. Myxoid stroma. | GFAP ASMA CK AE1/AE3 EMA CD56 Synaptophysin INI 1 Pachy +ve +ve -ve -ve -ve -ve | Yes. Lesion in Lt temporal lobe, involving lateral ventricle. Midline shift and edema. | One cycle of anthracycline based Chemotherapy and radiotherapy given. Patient died 6 months after surgery |

mostly unaware of this tumor entity. In all probability, all 11 patients underwent subtotal resection. Out of 6 patients in whom follow up was available, parents refused chemotherapy (a common scenario in remote, less developed areas of the country) and radiotherapy in 2 cases (patients 5 and 6). Other cases (patients 7 and 10), chemotherapy and radiotherapy were planned but patients died before these could be started. In 1 case (patient 4), chemo and radiotherapy were given after patient developed recurrence three months after surgery. In the remaining 1 case (patient 11), 1 cycle of chemotherapy (anthracycline based) and radiation were given but patient died about 6 months after surgery. Mean age of patients at diagnosis was 26.6 months in our series. Hilden et al. (Hilden et al., 2004) reported mean age at diagnosis of 24 months. Seven of our 11 patients were males. Schittenhelm et al. (Schittenhelm et al., 2011) also reported preponderance in males under 3 years of age. Even in adults affected by AT/RT, males were predominantly affected. (Makuria et al., 2008) We have, to date not reported any case in adults. Erickson et al. reported a case in a pregnant female. (Erickson et al., 2005) To our knowledge, these 11 cases are the first reported cases of AT/RT from Pakistan, although there are three studies from neighboring India. (Bansal and Goel, 2007; Biswas et al., 2009; Biswas et al., 2015) All 5 patients in Biswas et al's original study (Biswas et al., 2009) were males; 3 out of 5 cases were infratentorial (in posterior fossa) and 2 were supratentorial (in frontoparietal and frontotemporal lobes). In their recent study (Biswas et al., 2015), male to female ratio was 4:1, median age at presentation was 5 years while tumor location was supratentorial and infratentorial in 60% and 40% cases respectively. In this study, Biswas et al demonstrated that maximal safe resection followed by craniospinal irradiation and systemic chemotherapy with ICE (ifosfamide, carboplatin, etoposide) and VAC (vincristine, dactinomycin, cyclophosphamide) is an effective treatment strategy for these aggressive tumors. In our study, 3 cases were infratentorial (posterior fossa) and 6 cases were supratentorial (see results).

Although AT/RT has been shown to comprise 1-2% of childhood brain tumors (Wong et al., 2005; Rickert and Paulus, 2001), and is now increasingly recognized, most published data about this entity still remains based on case reports and case series. A number of case reports have been published on AT/RT from Asia especially the Far East. (Lee et al., 2004; Yang et al., 2007; Rehmat et al., 2008) Other case reports have described AT/RT arising in unusual sites such as spine (Yang et al., 2007), pineal region (Taki et al., 2010) and the third cranial nerve. (Wykoff et al., 2008) Reports of AT/RT in adults continue to be published. (Erickson et al., 2005; Makuria et al., 2008; Taki et al., 2010; Samaras et al., 2009) In the early years of the new century, several studies were published on the clinicopathological and radiological features of AT/RT (Bambakidis et al., 2002; Lee et al., 2002; Packer et al., 2002), which described these features and highlighted that diagnosis of AT/RT was based on distinctive light microscopic and immunohistochemical findings together with molecular genetic analysis especially chromosome

22q deletions and alterations of INI 1/hSNF5 gene. Other studies focused more on the chromosomal and genetic alterations which are seen not only in AT/RT in children. (Lee et al., 2002) but also in adults (Raisanen et al., 2005) However, these studies also emphasized that chromosome 22 alterations, although useful diagnostic markers of AT/RT, were not present in all cases. (Wharton et al., 2003; Biegel, 2006) Other studies at the time and later studied the prognostic and therapeutic factors and showed that aggressive therapy (chemotherapy, intrathecal chemotherapy, radiotherapy, stem cell rescue) prolong the natural history. (Hilden et al., 2004)

A study by Athale et al., (2009) demonstrated that craniospinal spread was the major cause of death in AT/RT and that intrathecal chemotherapy resulted in a significantly higher two year overall survival (OS) and lower prevalence of distant CNS metastasis, and they argued in favour of multimodal therapy and especially intrathecal chemotherapy. A recent study by Dufour et al., (2012) looked at the clinicopathologic prognostic factors in childhood AT/RT and concluded that the prognosis was dismal. They identified age less than 2 year, metastasis at diagnosis, and strong diffuse immunopositivities for claudin 6 as independent prognostic factors for increased risk of death. Most recent studies have also demonstrated the importance of SMARCB1/INI 1 genetic alterations on chromosome 22 in AT/RT which lead to loss of SMARCB1/INI 1 protein expression. However, occasionally such loss may not occur and conversely such losses may also be occasionally seen in choroid plexus carcinoma. (Schittenhelm et al., 2011; Hasselblatt et al., 2012; Hasselblatt et al., 2012) Indeed, distinguishing AT/RT with predominant epithelial differentiation from choroid plexus carcinomas can be difficult since both occur in the same age group and have similar histopathological features. (Schittenhelm et al., 2011). In the majority of cases, even the clinical details were sketchy at best. In our addition, by an unfortunate coincidence, most of our 11 cases came from remote areas, where the clinicians were mostly unaware of AT/RT and the therapeutic tools (limited in even major cities) were unavailable. Indeed, only 2 out of our 11 patients received chemotherapy and that too only when the tumor recurred. In all probability, the tumor had not been completely excised in any of the 11 unfortunate patients. We acquired the INI 1 immunohistochemical stain in 2014. However, we still do not have the molecular tests for AT/RT (the extreme rarity of the tumor makes this financially unfeasible in a general histopathology center and a specialized neuropathology center in Pakistan may still be years away. According to the 2016 CNS WHO update, in tumors corresponding to morphology of AT/RT but in which the expression of SMARCB1 (INI 1) and SMARCA4 (BRG1) could not be confirmed should be diagnosed as "CNS embryonal tumors with rhabdoid features". (Judkins, et al., 2016) We believe that this present series of 11 cases will raise awareness about AT/RT in Pakistan among histopathologists, neurosurgeons, medical and radiation oncologists and lead to better recognition, early diagnosis and more optimum treatment in the near future.

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