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A Typical Teratoid / Rhabdoid Tumor (ATRT) in a 6 Year Male: A Rare Case Report

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Abstract: ***Atypical teratoid /rhabdoid tumor (ATRT) is an extremely rare and highly malignant CNS (central nervous system) embryonal tumormost commonly seen in children less than 3 years of age. The most common location of its occurrence is cerebral hemisphere in posterior fossa. Radiological and histopathalogical features are similar to those of medulloblastoma and other CNS primitive neuroectodermal tumors (PNET). The key differentiating feature between ATRT, meduloblastoma other PNET is the presence of characteristic rhabdoid cells and typical molecular finding of deletion of INI1 on chromosome 22. Due to rarity and aggressive nature of tumor, there are yet no consensus guidelines regarding the management of this tumor. Prognosis is poor despite of treatment with high tendency of early relapses. We hereby present a case report of a 6 years boy with ATRT in supratentorial location in parietal lobe treated at our centre by surgical excision followed by adjuvant radiotherapy to cranio - spinal axis and a boost dose to tumor bed.***

1. Introduction

Atypical teratoid /rhabdoid tumor (ATRT) is a rare and highly malignant embryonal tumor that accounts for 1 - 2% of all pediatric CNS tumors [(1).] It has peak incidence of 0 - 3 years of age [(2).] It is associated with high frequency of early relapses and carries a dismal prognosis with overall survival of 6 to 13 months after diagnosis [(3).] Although it can arise in any location within CNS including spine, but majority of tumors arise in the posterior fossa [(4).] Radiological and histopathalogical features are similar to those of medulloblastoma and other CNS primitive neuroectodermal tumors (PNET). The key differentiating feature between ATRT, meduloblastoma other PNET is the presence of characteristic rhabdoid cells and typical molecular finding of deletion of INI1 on chromosome 22.

There are currently no consensus treatment guidelines. Preferred approach is multimodality treatment in which surgeryis followed by adjuvant radiotherapy and chemotherapy. Role of early initiation of radiotherapy has been seen in some studies and includes craniospinal irradiation. Furthermore, treatment depends upon age, presence of metastasis, presence of leptomeningeal spread and location (supra/ infratentorial) of tumor. Here we report a case of ATRT in supratentorial location inparietal lobe in a 6year old male child.

2. Case Report

A previously well, developmentally normal 6 year old male child presented in neurosurgery OPD with complaint of right sided headache with vomiting since 4 days. There was no history of fever, trauma, seizures or any focal deficit. On examination child was lethargic, afebrile with features of some dehydration. On neurological examination GCS was 5/15 with signs of raised intracranial pressure. Pupils were unequal sized with right pupil fixed, dilated and non - reactive to light. All of the limbs were hypertonic and deep tendon reflexes were exaggerated. Bilateral plantar reflexes were upgoing. There were no signs of meningeal irritation. The child was euglycemic, serum electrolytes were normal and sepsis screen was negative. Based on above findings, clinical possibility of ICSOL (intracranial space occupying lesion) was kept.

CECT brain was done which was suggestive of welldefined heterogenous supratentorial mass of 5.5 X 6cm in right gangliocapsular region, corona radiata, centrum semiovale and external capsule (figure1, 2). Mass was causing compression of ipsilateral ventricle, effacement of cortical sulci, subfalcine herniation and midline shift of 10 mm towards left.

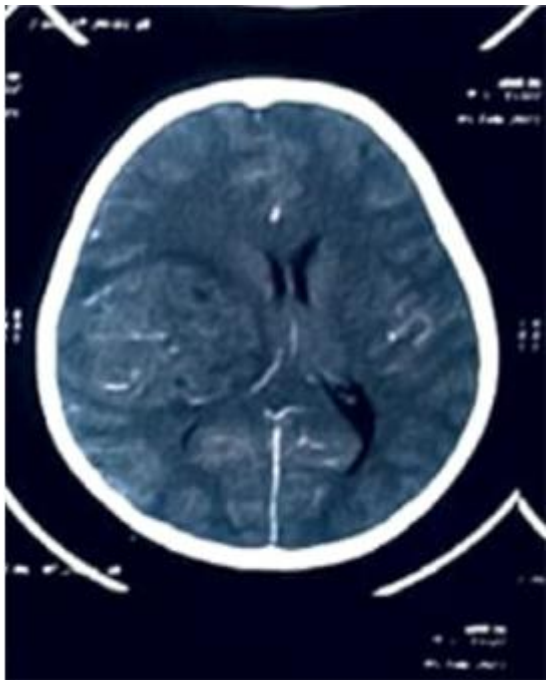

Figure 1: Axial view CECT brain showing heterogenous supratentorial mass of 5.5 X 6cm in right parietal lobe

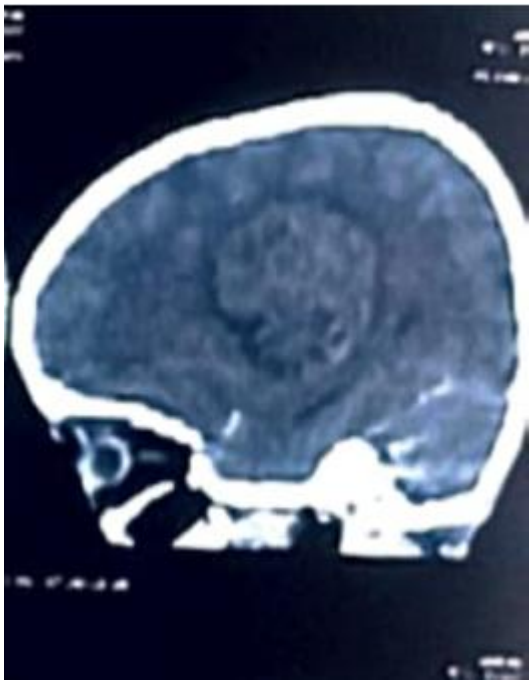

Figure 2: Sagittal section of CECT brain showing heterogenous mass in right parietal lobe

The patient underwent surgery and subtotal tumor excision was done from right parietal lobe. Operative findings were suggestive of tumor that was soft, friable, purplish and moderately vascular. Patient recovered well post operatively and was asymptomatic. CSF examination was done and was negative for malignant cells.

Histopathological examination revealed tumor composed of moderately pleomorphic cells with round to oval nuclei with minimal cytoplasm arranged in sheets suggestive of malignant round cell tumor. Immunohistochemical staining was positive for synaptophysin, vimentin, cyclin D1, GFAP, CD 56, CD 99 and BCOR (Figure 3, 4, 5, 6). There was loss of expression of INI - 1 gene. These features were consistent with ATRT (WHO grade 4).

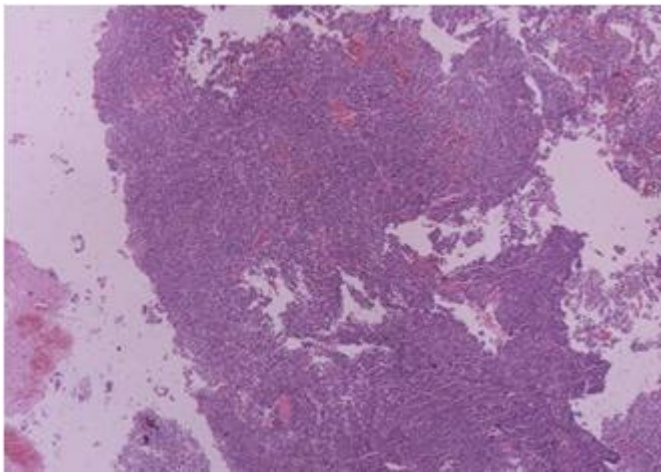

Figure 3: H&E staining s/o pleomorphic cells with round to oval nucliearranged in sheets.

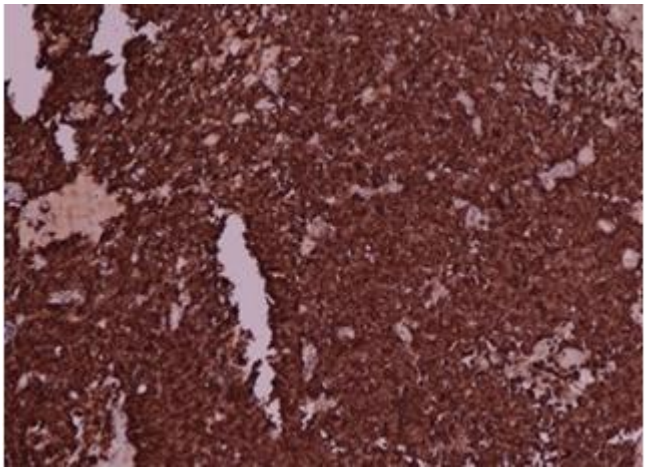

Figure 4: Cells staining positive for CD56

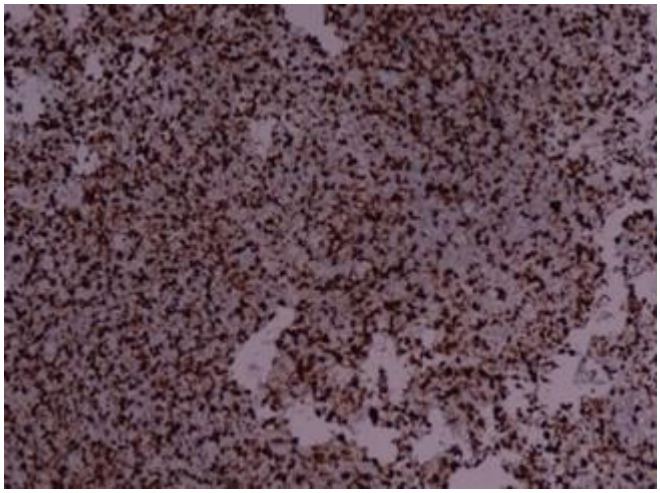

Figure 5: Cells showing Ki 67 immunoreactivity in 70 - 75% of cells

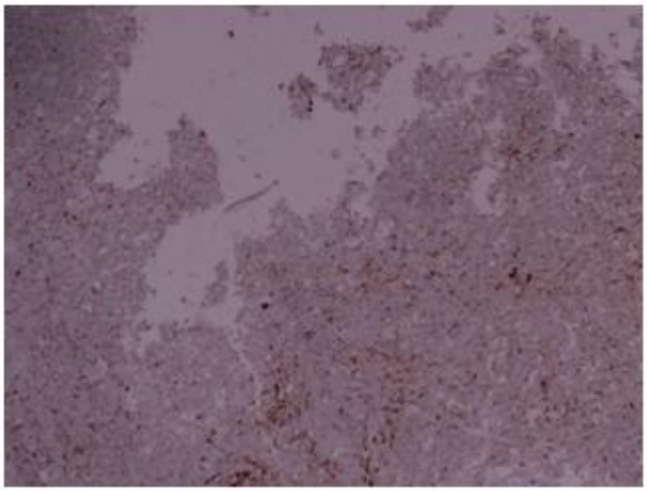

Figure 6: Cells staining positive for synaptophysin

Post operative radiotherapy was started 3 weeks after surgery in the form of cranio spinal irradiation. A dose of 36Gy/20# at the rate of 1.8Gy per fraction was delivered to craniospinal axis by 3D - CRT technique followed by boost of 18Gy/10# to the tumor bed. Patient tolerated the radiotherapy well and developed only grade I hematological, skin and pharyngeal toxicities.

3. Discussion

AT/RTs tumors are rare and highly malignant embryonal CNS neoplasms. They have been predominantly observed in very young children usually less than 3 years of age with male predominance. Up to one - third of patients have CSF dissemination at diagnosis [5]. It mostly occurs in the cerebral and cerebellar hemispheres, cerebellopontine angle and brain stem; spinal examples are exceedingly rare. In our case, the age of presentation is 6 years in a male child in supratentorial location at parietal lobe without CSF dissemination. Signs and symptoms are usually of raised intracranial pressure whereas in infants signs and symptoms are non - specificincluding lethargy, vomiting and failure to thrive. In our case, child presented with an acute onset of right sided headache with episodes of vomiting and clinical signs of raised ICP.

Findings on CT and MRI are similar to those seen in medulloblastoma and tumors previously designated as CNS PNETs. On CT scan, the tumor shows an iso - or hyper - dense solid part altering with cystic and necrotic hypodense areas with occasional hyperdensity due to calcification or hemorrhage. After contrast administration, the solid part shows marked enhancement. On histology, usually a complex histologic pattern is seen due to combination of rhabdoid, primitive neuroepithelial, epithelial and mesenchymal components, mimicking medulloblastoma and PNET tumors. Rhabdoid cells that are described as large, pale cells with oval, polygonal or elongated nuclei, and eosinophilic or pale cytoplasm are considered as the histological hallmark of AT/RT. However in our case, histopathological features showed tumor composed of malignant round cells.

Immunohistochemical examination is essential for distinguishing AT/RT from PNET/medulloblastoma. Vimentin, epithelial membrane antigen, cytokeratin, smooth muscle actin, glial fibrillary acid protein, S100, and synaptophysin are positive in varying proportions, whereas desmin and INI - 1 are usually negative. In our case, Immunohistochemical staining was positive for synaptophysin, vimentin, cyclin D1, GFAP, CD 56, CD 99 and BCOR with loss of expression of INI - 1 gene. AT/RT are almost always associated with a mutation in the tumor suppressor gene RSNFS/INI - 1 (known as SMARCB1) on chromosome 22q11.2 locus which are absent in medulloblastoma and PNET tumors but may be present in other tumors such as choroid plexus carcinoma.

Treatment of ATRT is radical surgery followed by aggressive chemotherapy and radiotherapy. Maximal safe surgical resection should be attempted. However in our case, only subtotal resection of tumor was possible. In case of children less than 3 years, surgery is followed by chemotherapy whereas in children >3 years of age surgery is followed by early initiation of radiotherapy. Radiotherapy is classically delayed for young children under 3 years due to its neurotoxicity such as cognitive, motor, visual, and hearing impairment. In our case, radiotherapy was started 3 weeks after surgery. High dose of chemotherapy is active against AT/RT but must be approached with caution due to its potential toxicity. Various chemotherapy protocols have been used in the management.

In CCG - 9921 induction chemotherapy regimen, a four drug combination, consisting of either vincristine, cisplatin, cyclophosphamide, and etoposide or vincristine, carboplatin, ifosfamide and etoposide were used. This induction regimen was found to be active in pediatric brain tumors with overall response rate 42% [6].

In IRS III Regimen 36, originally designed to treat parameningeal rhabdomyosarcoma, has been used in treatment of patients with AT/RT which consists of vincristine, cisplatin, doxorubicin, cyclophosphamide, dacarbazine, etoposide, actinomycin - D, and triple intrathecal chemotherapy with methotrexate, hydrocortisone, and cytarabine [7].

Gardner et al evaluated the role of postoperative intensive chemotherapy with stem cell rescue. The induction chemotherapy regimen consisted of vincristine, cisplatin, etoposide, and cyclophosphamide and consolidation chemotherapy consisted of carboplatin, thiotepa, and etoposide [8]. The estimated event - free survival (EFS) and OS rates at 3 years among the 13 children were 23%. Biswas et al evaluated the role of ifosfamide, carboplatin, and etoposide or vincristine, actinomycin - D, and cyclophosphamideas adjuvant chemotherapy in a retrospective series of 15 patients with AT/RT [9]. The median OS was 10 months, and the actuarial rate of OS at 2 years was 24.1%.

Radiotherapy is an important component of treatment in patients with AT/RT. CSI (craniospinal irradiation) has been used in older children >3 years due to highpropensity of leptomeningeal dissemination (15%–30%) of the tumor. The dose of RT required in patients with AT/RT has not been standardized perhaps due to rarity of the tumor and limited use of RT in many case series. Radiotherapy dose to tumor bed ranges from 50 Gy to 56 Gy, while dose to neuro axis ranges from 23Gy to 36Gy in conventional fractionation. In a retrospective series of 15 patients with AT/RT by Biswas et al [9], postoperative RT (CSI followed by boost to tumor bed) was started in six patients and completed in five. Use of CSI was a significant predictor of OS on univariate analysis (P= 0.0087).

In another retrospective series of 17 patients with CNS AT/RT by Chen et al, 52 total radiotherapy dose of 50 Gy was associated with significantly improved failure - free survival but not OS on multivariate analysis [10].

A meta - analysis by Athale et al, showed significant benefit of addition of RT to the treatment protocol in patients with AT/RT [11]. The mean survival of patients who received RT in addition to chemotherapy was 18.4 months as comparedwith 8.5 months in those who did not receive RT (P<0.097). In our case we delivered 36Gy of radiation at the rate of 1.8 Gy per fraction in 18 fractions to cranio - spinal axis followed by boost to tumor bed of 18Gy/10# by 3D - CRT.

Recently, proton beam therapy is being used in the management of patients with AT/RT due to the advantage of Bragg's peak, which adequately covers the target volume without exit dose. De Amorim Bernstein et al evaluated early clinical outcomes using postoperative proton radiation in ten children with CNS AT/RT with a median dose of 50.4 Gy [(12).] Nine out of ten patients were alive and disease free at a median follow - up of 27.3 months, and none of the patients had major radiotherapy - related toxicity.

Despite aggressive treatment, the outcome is very poor especially in very young children. Most patients succumb to their disease within 1 year of local recurrence. Hence more advances are required regarding the role of adjuvant therapy in management of this tumor.

Conflict of interest: none declared.

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