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Case Report

# Fatal outcome of intracranial embryonal tumor with multiple rosettes: Case report and review of the literature

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ABSTRACT

There are three known histological variant within the family of embryonal tumor with multiple rosettes. This family included embryonal tumor with abundant neuropil and true rosettes (ETANTR), ependymoblastoma (EBL), and medulloepithelioma (MEPL). Here we report a case and performed a comprehensive overview in terms of clinical, pathological, molecular and management outcomes of this rare entity of paediatric brain tumor. Clinically these variants found to have similar characteristics like age (<4 year) associated with highly aggressive nature with reported survival period of 2-3 years. In immunohistochemistry (IHC), most commonly applied markers were synaptophysin, neurofilament protein, Neu-N and glial fibrillary acidic protein (GFAP). Recent data on molecular subgroups of PNETs have led to new insights on diagnosis and treatment of these tumors. Subsequently, LIN28A immunoexpression was identified as a highly specific marker for ETMR. As these tumor having poor prognosis because of aggressiveness in nature, treated as high risk brain tumors. Here we want to report a highly aggressiveness nature of disease, a 6 year old child presented with fever, headache and vomiting. Radiological diagnosis suggestive of left parieto-occipital lesion in brain underwent two time surgery and IHC suggestive of embryonal tumors with multilayered rosettes -WHO grade-IV. He had not responded to treatment and died with overall survival of 2 months.



## 1. Introduction

Embryonal tumor of central nervous system (CNS) mostly occurs in paediatric group and account for 1-3% of all brain tumors. Embryonal tumor with abundant neuropil and true rosettes (ETANTR) was first described by Eberhart et al. in 2000.[1] According to 2007 World Health Organization (WHO) this tumor classified as undifferentiated or poorly differentiated neuroepithelial cells tumor unlike medulloepithelioma (MEPL) and ependymoblastoma (EBL) lacking specific feature of CNS PNET.[2] CNS PNETs are small cells, malignant embryonal tumor showing aberrant differentiation of variable degree along neuronal, glial or rarely mesenchymal lines. Some of case reports published in the literature used the term "embryonal" rather than "neuroblastic" and employed the term embryonal tumors with abundant neuropil and true rosettes (ETANTR).[1,3–5] So, embryonal tumor with multilayered rosettes family included ETANTR, EBL, and MEPL to describe subtype of CNS PNET.[6–8]. ETANTR is characterized by presence of undifferentiated neuroepithelial cells, broad zones of well differentiated neuropil, and ependymoblastic rosettes arising abruptly from paucicellular regions of neoplastic neuropil. The median age of presentation is 2.5 years (0.5-6), females are two time more prone to develop than male (F: M=2:1) and mostly in the supratentorial region.[9] Most of the patients present with partial convulsive

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seizure, altered general status and features of increased intra cranial pressure like headache, nausea vomiting, seizure, as per the location of tumor. Histopathological examination characterised by the presence of Homer Wright rosettes, foci of neurocyte, ganglionic cells maturation, intense synaptophysin expression and MYC/MYCN amplification.[10,11] immunohistochemistry showed staining with glial marker, Glial Fibrillary Acid Protein (GFAP), highlighted scattered cells with morphology consistent with reactive astrocytes. GFAP staining is mainly seen in neuropil like areas in stellate dispersed cells but not in undifferentiated areas. Synaptophysin stained neuropil areas and component with variable intensity.[12] Recently expression of LIN28A is a highly specific marker and has been found more prominent and intense in multilayered rosettes and poorly differentiated small cell tumors.[13,14]

Treatment of this rare tumor is still not standard, as this clinico-pathological entity is distinct from CNS PNET and considered as an aggressive paediatric brain tumors. Five-year Event free survival rates of 60% have been achieved in the last few years by different strategies, including high-dose chemotherapy (HDCT), hyperfractionated accelerated radiotherapy, or concomitant once per day administration of carboplatin during craniospinal irradiation (CSI) in combination with a variety of pre- and post-CSI chemotherapy regimens.[15–18] The most acceptable treatment of these aggressive tumors may be a multidrug chemotherapy based on HIT-SKK2000 protocol.[19,20] Pattern of disease progression were highly variable and mostly experienced local recurrence. However a small number of subset developed leptomeningeal dissemination and having progression free survival of 8 months.[21]

## 2. Case History

A 6 years old male child presented with chief complaints of fever, headache and vomiting since 3 month. Contrast enhanced computed tomography (CECT) of brain was suggestive of large intra axial space occupying lesion involving left fronto-parietal lobe measuring approximately 6.5 × 4.5 × 5.5 cm in size, composed predominantly of large cystic component with patchy nodular calcific areas along its antero- lateral portion with minimal to non-enhancing hyper dense areas with compression over left lateral ventricle with midline shift of approximately 0.9 cm towards right side. Radiological diagnosis of these were suggested of neoplastic etiology like ganglioglioma/DNET/PNE (Figure 1). Fluid cytology from brain cystic fluid was suggested of cystic lesion with secondary haemorrhage. He underwent craniotomy and removal of cystic space occupying lesion under general anaesthesia. Post-operative histopathological examination was suggestive of astrocytoma grade III (WHO grading). After 2 week of asymptomatic period, symptoms reappeared and he had underwent re-aspiration of cystic component twice. He presented to us with complaints of headache, vomiting and irritant behaviour. On examination, he was well oriented to time, place or person. Higher functions, cranial nerve examination, sensory and motor functions were intact. On work up, haematological investigation were within normal limit. Chest-X- Ray PA view and Ultrasonography of abdomen were within normal limit. MRI of brain suggested of a large mixed intensity solid and cystic lesion measuring ~ 8.0 × 7.1 × 7.2 cm in size noted in left parieto-temporal region with mild perilesional edema. Adjacent sulci and gyri were effaced. Multiple areas of blooming were noted and suggested of intratumoral haemorrhage. No restriction was seen on diffusion weighed images. Solid part of lesion showed heterogeneous enhancement and cystic part showed peripheral enhancement. The mass was compressing ipsilateral lateral and $3^{rd}$ ventricle with midline shift of ~1.6 cm towards right side. Medially it was compressing body of corpus callosum. Inferiorly mass was compressing the midbrain with mild uncal herniation towards right side. Right lateral ventricle was prominent with mild periventricular oozeFigure 2. Slide and block reviewed at our institute revealed Embryonal Tumors with Multilayered Rosettes-NOS (WHO Grade-IV). On IHC, vimentin and CD99 was positive. Synaptophysin was positive in intervening neurophil and GFAP had framework positivity (negative in tumor cells) while Pan CK, S100, EMA, and Chromogranin were negative. Cerebrospinal spinal fluid cytology suggestive of absence of malignant cellsFigure 3 Magnetic resonance imaging for spinal screening was done and showed none metastatic deposits. We planned treatement with craniospinal irradiation (CSI) followed by boost to primary tumour. Meanwhile, he developed an episode of seizure and aspirated vomit's material. He admitted in intensive care unit for the same. After intensive care he came out from consequences of aspiration and became stable. We then started CSI 36 Gy with 1.8 Gy/# followed by boost to primary lesion up to 54 Gy. During the course of radiotherapy he developed recurrent seizures for which he was managed with antiepileptic drugs. He completed cranio-spinal irradiation and during boost phase, developed grade IV haematological toxicity. Radiation was then stopped and toxicity was managed with G-CSF and symptomatic treatement. Later, in course he stoped responding to medication and despite of all rigorous efforts he declared dead.

## 3. Discussion

Embryonal tumors of CNS in paediatric age group are rare and considered as a highly malignant tumor. Most of the studies strongly suggest incorporating in four molecular medulloblastoma subgroups classification as separate entities.[22] Most common site is supratentorial and predominantly in frontal lobe, it may be seen in the pineal

gland region, in posterior fossa.[7,23] Our case is also having origin from supratentorial region (parieto-occipital). Most of the patients appear under 4 years and predominantly are female.[24] In contrast our reported case is 6 year old male patient Andrey Korshunov et al.[9] also reported male female ratio of 1.1:1 with median age 2.3 year (0.5-6 years).

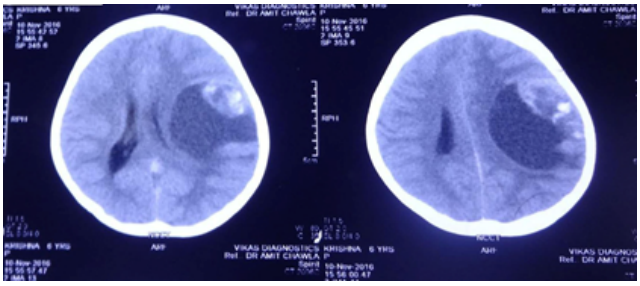

**Fig. 1:** A large space occupying lesion in fronto-parietal region, predominantly cystic component with patchy calcific nodular areas along the anterolateral wall and midline shift.

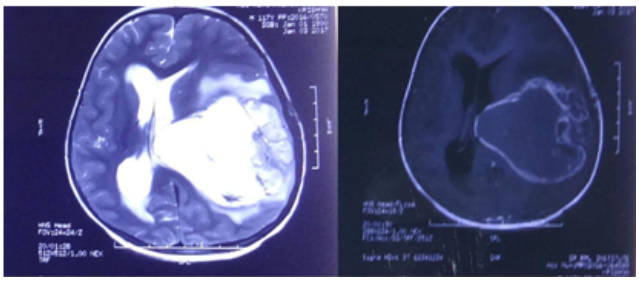

**Fig. 2:** T2 image showed a large hyper intense cystic component withperilesional oedema solid part of heterogeneous enhancement area. Multiple areas of blooming suggestive of intra-tumoral haemorrhage. On T1 weighed image cystic component is hypo-intense and solid part showed mixed intensity with peripheral enhancement.

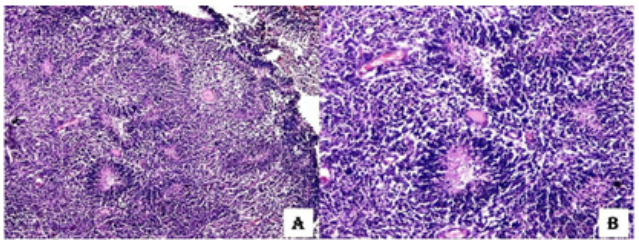


**Fig. 3:** A) Stained section oftumor tissue in sheets with complex rosettes formation and few perivascular rosettes. B). the complex rosettes are characterised by tumor cells arranged around central area filled with pail neuropil. Tumor cells are round with hyper chromatic nuclei and scant cytoplasm. (A=H&E × 100, B=H&E × 200).

Radiologically, ETANTR showed different features when compared with other embryonal tumors. The lesions are in most cases well demarcated and hyper intense on contrast enhanced T2 weighed images, in contrast to most CNS PNET, which are non enhancing or may enhance focally.[25] In our case MRI also suggested hyper intense lesion for both solid and cystic component. Judkins and Ellison[26] suggested withdrawing the diagnosis of EPBL from the classification of CNS tumors because ETANTR and EPBL are having single biological entity.

On immunohistochemistry, GFAP and synaptophysin stained neuropil like areas are seen in elongated or dispersed cells but not in undifferentiated areas while MIB1 index was high in undifferentiated areas.[12] In our case GFAP and synaptophysin are strongly positive for neuropil areas.

The prognosis of ETANTR is very poor. Gessi M et al. described the data of 25 patients and they had received postoperative chemotherapy alone or in combination with radiotherapy. Chemotherapy regimen was not consistent but most of the patients had received cisplatin, vincristin and cyclophosphamide. They reported 76% of mortality due to disease with a median survival of 9 months only. Other studies and case series also reported median overall survival of 9-16 months.[14,23,24] Further, aggressive treatment was also used for high risk embryonal tumor by Carsten Friedrich et al. called HIT 2000 protocol.[19] In which cisplatin, lomustin and vincristine chemotherapy regimen was used for 8 cycles as a maintenance therapy after post operative radiotherapy. They had also used sandwich protocol with SKK chemotherapy. They reported 3 year PFS and OS 66 % and 13 % respectively. We found that in our case, the disease was highly progressive in nature. Aspiration of cystic component was done thrice due to reappearance of symptoms within a period of 2 months. During radiotherapy he developed recurrent episode of seizures, may be due to disease progression, for which combination of four antiepileptic drugs was prescribed after consultation of neurology. At the end of CSI, patient developed grade IV haematological toxicity. This toxicity was may be due to synergistic effect of radiotherapy and antiepileptic drugs. Radiation was stopped and G-CSF and symptomatic treatment was given. He stopped responding to medication and even with all effort he declared dead.

## 4. Conclusion

On conclude, ETMR is a distinct entity of paediatric embryonic brain tumors that included ETANTR, EBL and MEPL. It may be considered as subtype of CNS PNET. This mostly occurs under 4 years of age preferably in females. These tumors may be presented with feature of increased intracranial pressure, seizure and symptoms according to location of tumor. On clinicopathological consideration, it is highly aggressive tumor and may be incorporated in future WHO classification under paediatric brain tumors. Recently developed biological markers are helpful for making a proper diagnosis especially expression of C19MC

and LIN28, GFAP, synaptophysin. It is useful to know the biological significance of prototype molecular knowledge of ETMR which may provide new targeted therapeutic approach for these type highly malignant tumors. Hopefully, the extensive molecular knowledge may be translated not only into a proper diagnosis, but also in improvement towards more efficacious management.

## 5. Source of Funding

None.

## 6. Conflict of Interest

The author declares that there is no conflict of interest.

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