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Case Report

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Pediatric Embryonal Tumors in True Rosettes (Etmrs) Presenting as a Low Grade Glioma– An Unusual Case Report

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Abstract

Pediatric Embryonal Tumors in Multilayered Rosettes (ETMR) are rare aggressive tumors with poor survival statistics, defined by the 2016 WHO classification of brain tumors. The tumors have a characteristic radiological appearance on MR imaging of the brain, which is easily decipherable. This combined with a clinical picture of raised intracranial pressure symptoms, seizures and rapidly progressive new onset neurological deficits make the diagnosis fairly obvious. The final confirmation of the diagnosis is done by immunehistochemical analysis of the C19Myc gene alteration.

Rarely certain radiological presentations are uncharacteristic and resemble other more benign pathologies with overlapping clinical presentations. This can be misleading, as ETMRs require aggressive surgery followed by adjuvant chemotherapy and radiation to ensure best possible survival. We present such a case report of what appeared to be a low-grade glioma in the frontal lobe. This tumor presented with 1 episode of generalized tonic clonic seizures not unusual as a presenting complaint in low grade gliomas per se. Surgical debulking under Ultrasonic guidance was done and the specimen sent to histopathological analysis. The histopathological analysis showed a surprise ETMR diagnosis which was sent for confirmation to 2 other centers.

This case report highlights the need to keep ETMRs as a rare differential diagnosis for even low-grade gliomas of the brain, thereby allowing accurate prognostication only after histopathological and immunohistochemical assessment. We present a brief literature review on unusual presentations of ETMRs reported in literature to further illustrate the chimeric nature of this rare disease.

Keywords: ETMR; PNET; Low grade glioma

Introduction

Embryonal tumor with multi-layered rosettes C19MC-altered (ETMR) is a WHO grade IV aggressive embryonal tumor, which is newly defined in the 2016 WHO Classification of Tumors of the Central Nervous System (CNS) [1]. ETMR mainly affects children aged < 4 years old and demonstrates a rapid growth and an aggressive clinical course (the mean survival is 12 months after combination therapies) [1]. Most paediatric CNS embryonal neoplasms were previously diagnosed as embryonal tumor with abundant neuropil and true rosettes (ETANTR), ependymoblastoma (EBL) and medulloepithelioma (ME), and any CNS embryonal tumor with C19MC amplification or fusion were included in this entity [1]. This definition distinguished ETMR from the previously defined CNS primitive neuroectodermal tumors (PNETs), in which ME and EBL are also included irrespective of the C19MC locus amplification status.

Amplification of the C19MC locus at 19q13.42 was observed in 37/40 (93%) of the tumors morphologically diagnosed as EBL or ETANTR [2]. Nobusawa et al. [3] found 19q13.42 amplification in ETANTR, EBL, and ME, but not in AT/ RT. Korshunov et al. [4] showed that LIN28A, an RNA-binding protein that inhibits the processing of pre-let-7 miRNAs, is a highly specific immunohistochemical diagnostic marker of ETMR [4].

ETMRs are aggressive tumors[4]. They therefore exhibit some characteristic features that are identifiable on MRI and CT scan of the brain [5]. Hence a clear diagnosis is usually made on radiology itself before subjecting he operative specimen to histopathological and immunohistochemical analysis. We present a rare case of what radiologically appeared to be a low-grade glioma, but histologically was seen to be an aggressive ETMR. We present a radiological review of ETMR presentations and discuss its impact on treatment and prognosis.

CASE REPORT

A 2-year-old child presented to our clinic with an episode of non-febrile, generalized Tonic Clonic Seizures. The seizure profile was as follows. Aura was absent. The ictus consisted of tonic-clonic movements of Bilateral upper and lower limbs, coupled with tongue bite and incontinence. The ictus lasted for 1-2 min. In the Post-ictal state, the child was confused & drowsy for 15 min before regaining normal consciousness. The child was immediately evaluated for the cause of this new onset seizure. The MRI of the child showed a left frontal lesion with minimal enhancement of contrast. The lesion was well demarcated with a uniform consistency. No cystic or hyperintense regions were seen. The surrounding brain appeared normal with no oedema. There was no mass effect on the surrounding brain seen. (Figure 1) The possible differential diagnoses considered were ganglioglioma, or Pleomorphic Xanthoastrocytoma. (PXA) Based on this, she was advised surgery. She was taken up for a left frontal craniotomy, and navigation and ultrasound guided excision of the lesion under general anesthesia.

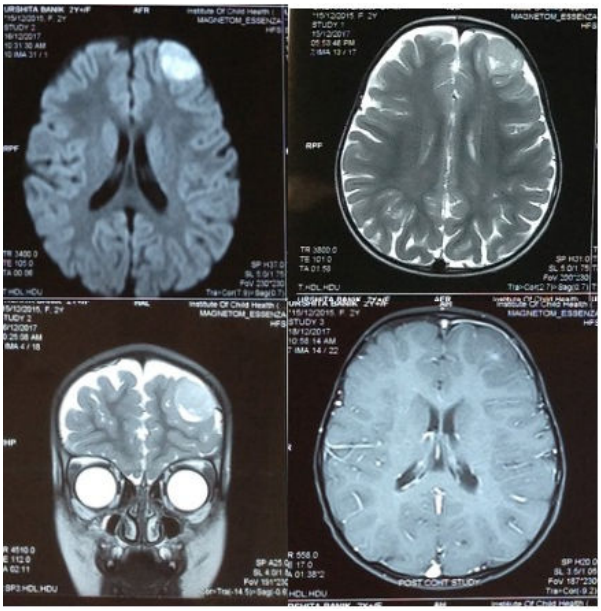

Figure 1: Showing MRI images pre-op, with Axial DWI in (A) demonstrating the altered density of the lesion, Axial T3nin (B), Coronal T2 in (C) both demonstrating the lack of water within the lesion hinting at a highly cellular tumor, and Axial contrast in (D) showing almost no enhancement.

Total excision of the affected lesion was confirmed by on-table neuro-ultrasound of the tumor bed. (Figure 2) Ultrasonic localization was essential as tumor tissue was indistinguishable from the normal brain parenchyma. No oedema, or increased vascularity was seen in comparison to the normal tissue. Post Excision the child was observed for 3 days in hospital, and then eventually discharged on antiepileptics to review after a week in order to obtain the histopathological diagnosis and thereby plan adjuvant therapy if required. No decongestants were added as there was absolutely no oedema and post-operative CT scans of the brain showed no such features.

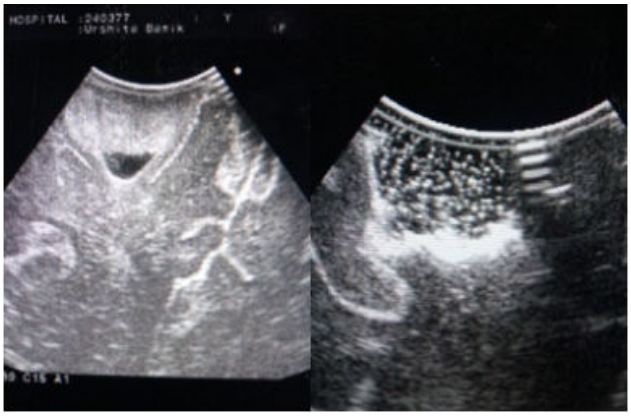

Figure 2: Ultrasound guided Tumor resection showing tumor present in (A) and completely excised in (B).

The Histopathological analysis showed a biphasic cellular tumor composed of monomorphic cells arranged in sheets and papillary pattern interspersed with foci of small embryonal cells with hyperchromatic nuclei, scant cytoplasm, brisk mitotic activity, apoptotic bodies and necrosis. The cells were seen on a background of fibrillary stroma, with ganglionic cells also were seen. The cells show focal perivascular resetting, occasional focus of palisading cells with papillary like configuration occasionally. The presence of multilayered rosettes is unequivocal. (Figure 3) Immunohistochemical stains done show INI-1 retained expression, Neu-N positive confirming the presence of embryonic component, Synaptophysin positive for the fibrillary stroma alone, GFAP-negative indicating no proliferative glial component and a MIB-1 index of80% indicating WHO grade 4 tumor. LIN28A was done as a surrogate marker for C19Myc detection. It was strongly positive indicating C19Myc amplification. (Figure 4)

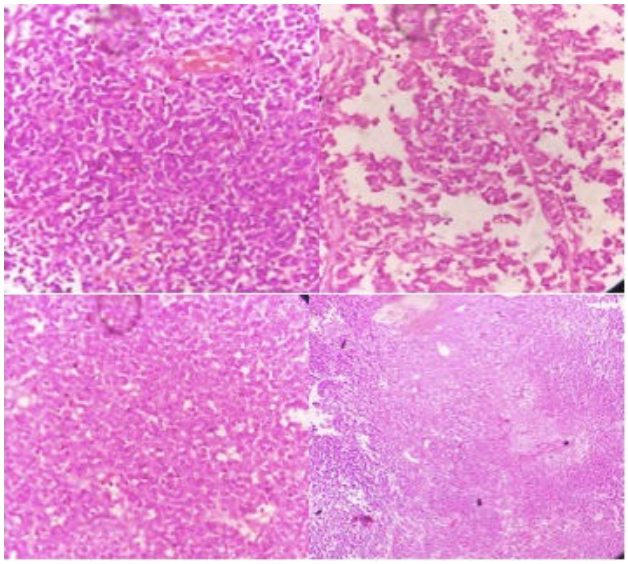

Figure 3: Showing histopathological assessment of the specimen showing sheets of small round cells with interspersed with embryonal cells (A), papillary patterns (B), Dense packing of cells with hyperchromatic nuclei and poor cytoplasm (C), with rosettes seen clearly in (D).

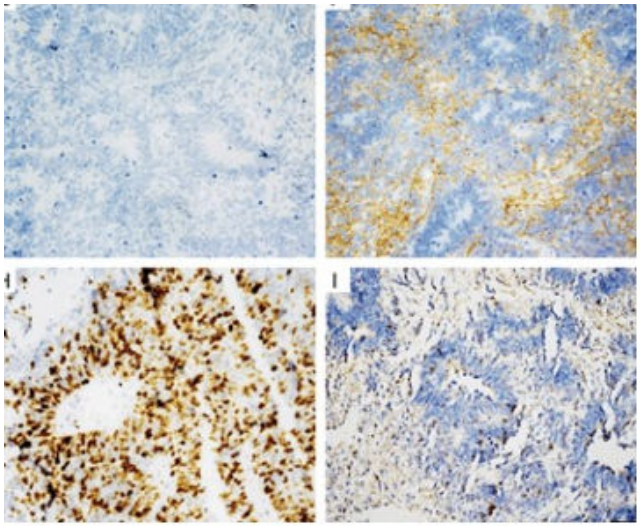

Figure 4: Showing special stains of the same sample, with (A) showing no Vimectin, (B) showing the stroma positive for synaptophysin, LIN28A positive as shown in (C), and MIB-1 showing approximately 70-80% in (D).

The child was reviewed, and her relatives were counselled about the negative turn of events. They were advised to go for adjuvant therapy but were lost to follow up.

Discussion

CNS embryonal tumors include several groups of paediatric brain tumors with typical multi-layered rosettes. These are supratentorial primitive neuroectodermal tumors (PNET), medulloblastoma (infratentorial location), medulloepithelioma, neuroblastoma, ependymoblastoma, and atypical teratoid/rhabdoid tumors (AT/RT) [7]. The 2016 WHO Classification proposed a new integrated diagnostic criterion for C19MC- altered ETMR [1]. If ETMR diagnosis is suggest- ed histologically, then 19q13.42 amplification should be assessed using FISH. If ETMR is diagnosed on the basis of histology alone, the tumors may be diagnosed as ETMR, NOS (not otherwise specified) [1].

Most C19MC-altered ETMRs have been reported as case reports (Table 1) [4-8]. ETMRs may develop in both the supratentorial and infratentorial compartments. The most common site is the cerebral hemisphere, with a frequent involvement of the frontal and parietotemporal

AGE	SEX	SYMPTOMS	LOCATION	RESECTION	IMMUNOHISTOCHEMISTRY	CHEMOTHERAPY	PROGNOSIS
2y		Personality changes and ataxia+ICP headache	Cerebellar Vermis	Subtotal	NeuN, Syn, INI1 positive MIB1 47%	Yes	>17months
2y9m	M	Increased Head circumference	Left Parieto-Occipital lobe	Near total	INI1, Syn, NF positive	Yes	10months
2y5m	M	Progressive visual loss	Bilateraal Parietal lobes	Subtotal	INI1, NeuN, NF, p53, Syn, Vim positive MIB1 70%	No	NA
4y	M	Left hemiplegia with ICP headache	Right Mid pons	Subtotal	INI1, Syn, LIN28A positive	No	NA
2y	M	Dysarthria, dysphagia and ataxia	Basilar Pns	Subtotal	INI1, Syn positive	Yes	7months
2y9m	M	Vomiting, Gait disturbances	Intramedullary mass	Subtotal	INI1, LIN28A, NeuN, NF, Syn positive MIB1 70%	Yes	6months
8m	F	Left eye ptosis with ICP headache	Left Cerebellar hemisphere	Subtotal	INI1, p53, NF, Syn, Vim, positive MIB1 80%	No	1week
2y	F	Seizures, left hemipariesis with ICP headache	Right Parieto-Occipital Lobe	Total	Syn, Vim positive	Yes	>6months

Table1: showing case reports in of paediatric ETMRs in the last 5 years.

Regions, as seen in our patient [6]. In addition to the supratentorial compartment, they can also originate in the cerebellum, brainstem, and spinal cord [7,8]. For the radiological features, the head computed tomographic (CT) image shows a hyper attenuating mass in the cerebral hemi-sphere. MRI is generally suggestive of an aggressive lesion well demarcated and enhancing with contrast along with significant surrounding oedema and mass effect. The lesion maybe variegated with cystic components as well. In our case, MRI showed well-defined margins, minimal vasogenic oedema, and subtle enhancement lesions [8]. There are no specific radiological features distinguishing ETMR andother brain tumors [8]. But the aggressive nature of the disease is well documented and can be discerned by indirect features such as surrounding brain oedema, contrast enhancement and rapid rate of growth. This was also not present here in our case.

In summary, C19MC-altered ETMR is a new entity that has a poor outcome in children. The incidence of ETMR remains unclear, because only single cases reports have become available so far. However, epidemiological data may be obtained in the future, as a new ICD-O code (9478/3) has been assigned to this new entity (2016 WHO Classification). The most common clinical manifestations are symptoms and signs of increased intracranial pressure and focal neurological signs. The radiological features are similar to other brain tumors. The integrated diagnosis should be based on histology (CNS embryonal tumor with multi-layered rosettes), immunoreactivity (synaptophysin, and the specific biomarker LIN28A), and genetics (amplification of C19MC locus at 19q13.42 by FISH wherever possible) to reliably diagnose this novel aggressive brain tumor.

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