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Embryonal tumor with multilayered rosettes; rare pediatric CNS tumor. A case report and review of literature

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ABSTRACT

Embryonal tumor with multilayered rosettes (ETMR), C19MC-altered is a newly designated entity of the embryonal tumors of the central nervous system (CNS) according to the 2016 WHO classification system of CNS. Characteristically, these tumors are newly defined based on their specific molecular genetic amplification in chromosome 19q13.42 found at locus C19MC. To the best of our knowledge, we present the first reported case of ETMR in Saudi Arabian pediatric population. A 2-year-old boy presented to the hospital with generalized tonic-colonic seizure, vomiting, irritability, and inability to walk. Computed tomography (CT) scan showed a large left thalamic supratentorial brain tumor. The tumor measured 6.1 × 5.6 × 5.6 cm and was characterized by cystic changes, prominent vasculature, and calcifications. Histopathology, immunohistochemistry examination, and fluorescence in situ hybridization (FISH) analysis confirmed the diagnosis of ETMR. In addition to reporting this rare case, we provide a brief literature review, treatment options, patient outcome, and disease prognosis.

1. Introduction

Embryonal tumor with multilayered rosettes (ETMR), C19MC-altered, is a newly classified, embryonal pediatric CNS neoplasm. It is categorized as a highly aggressive grade IV tumor. ETMR tends to affect children younger than 4 years of age, with rapid growth and aggressive clinical behavior. Their mean survival after combined therapies is 12 months. Previously, before the new CNS WHO 2016 classification, clinicians used to diagnose it as an embryonal tumor with abundant neuropil and true rosettes (ETANTR) [1,2]. Moreover, tumors with histopathologic features of rosette differentiation, such as ependymoblastoma (EBL) and medulloepithelioma (ME), were also included in this classification. The current grading of selected CNS tumors based on the latest 2016 CNS WHO classifies the embryonal tumors into medulloblastoma, ETMR C19MC-altered, medulloepithelioma, CNS embryonal tumors NOS, atypical teratoid rhabdoid tumor (AT/RT), and CNS embryonal tumor with rhabdoid features [1]. Molecular studies are crucial to confirm the diagnosis of ETMR. C19MC locus amplification at 19q13.42 chromosome was found in 93% of the diagnosed ETMR (37 out of 40 cases diagnosed morphologically as ETANTR or EBL) [3]. Previous studies have found amplification of 19q13.42 chromosomes in ETANTR, EBL, and ME [4]. This was linked to the RNA-binding protein known as LIN28A, which inhibits the pre-let-7 miRNA processing. LIN28A immunohistochemistry is considered highly specific for ETMR diagnosis [5]. ETMR is a rarely diagnosed aggressive tumor. We present a case of a 2-year-old boy who had a large left thalamic supratentorial tumor. We aimed to focus on the literature review and to widen the gaze for pathologists and clinicians for this rare and new entity. Moreover, we emphasized on the role of molecular and genetic studies of tumor pathophysiology, which may help to understand the tumor behavior and clinical outcome.

2. Case presentation

A previously healthy 2-year-old boy presented to the hospital with a generalized tonic-clonic seizure, vomiting, irritability, and inability to walk. Physical examination yielded a right-sided

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weakness and poor balance. Computed tomography (CT) scan showed a large left thalamic supratentorial brain tumor, measuring 6.1 × 5.6 × 5.6 cm characterized by cystic changes, prominent vasculature, and areas of calcifications. Magnetic resonance imaging (MRI) demonstrated a large intra-axial circumscribed tumor arising from the left thalamus (Fig. 1A), which measured 5.6 cm craniocaudally by 6.1 cm AP by 5.6 cm transverse, with a low level of contrast enhancement (Fig. 1B–D). Hydrocephalus identified at the level of Foramen of Monroe, causing midline shift secondary to a significant mass effect. The patient underwent a right ventriculoperitoneal shunt to reduce the midline shift. No evidence of drop lesions nor metastasis was found. Subsequently, surgical craniotomy with left middle temporal lobe corticotomy of the medial temporal lobe was performed under a microscope. The temporal horn of the lateral ventricle was opened, and CSF decompression was performed. The tumor was noted above the temporal horn. Frozen section was positive for a malignant process; however, the type of tumor could not be further specified. A maximum safe resection with debulking of the center of the tumor was done. The patient tolerated the surgery well and was shifted to the pediatric intensive care unit (PICU). Histopathological examination yielded biphasic architecture of both primitive and more differentiated components (Fig. 2A). The primitive, embryonal component comprised cells with very high nuclear-to-cytoplasmic ratio, nuclear molding, and numerous apoptotic cells. Multilayered true rosettes were identified in this primitive component (Fig. 2B). The more differential areas showed abundant neuropil. Immunostains demonstrated positive synaptophysin in the more differentiated tumor areas (Fig. 2C). Glial fibrillary acidic protein (GFAP) and S100 highlighted reactive astrocytes but were negative in the

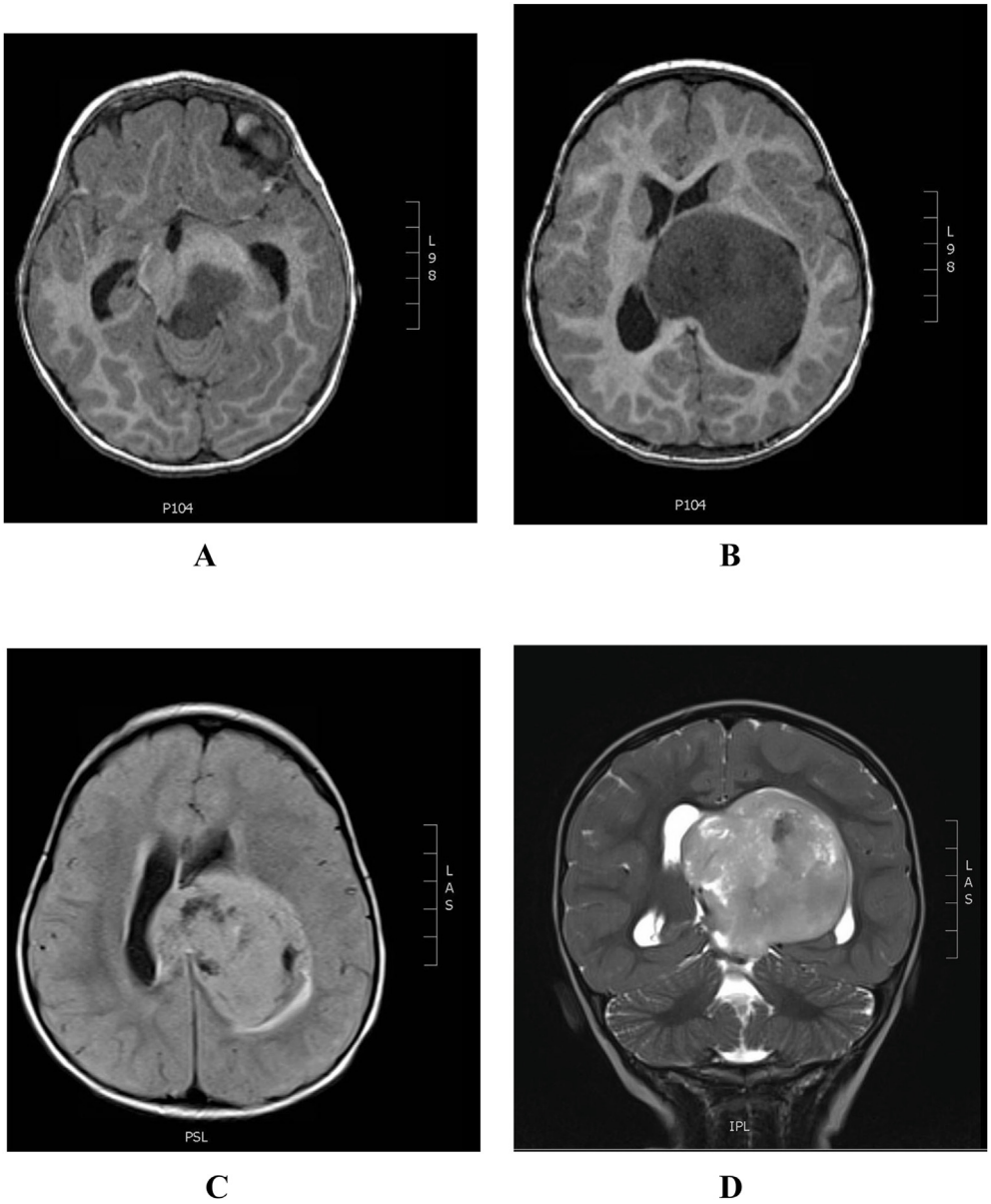

Fig. 1. Pre-operative planning MRI brain with and without contrast. (A–B): T1-weighted images with low levels of contrast show a large hypointense intra-axial mass arising from the left thalamus (yellow asterisk). (C): T2-weighted images revealed slightly hyperintense compared to the gray matter. The tumor exerts significant mass effect with rightward midline shift and obstruction associated with lateral ventricles entrapment and dilatation of the temporal horns. (D): Coronal T2-weighted images reveal regions of intratumoral cystic changes and prominent flow voids at its margins. A focal area of blooming is noted in its most central superior aspect, which might suggest calcification or blood products. The mass extends inferior toward the left cerebral peduncle and the midbrain with an exophytic component within the supravermian cistern (favor displaced rather than invasion).

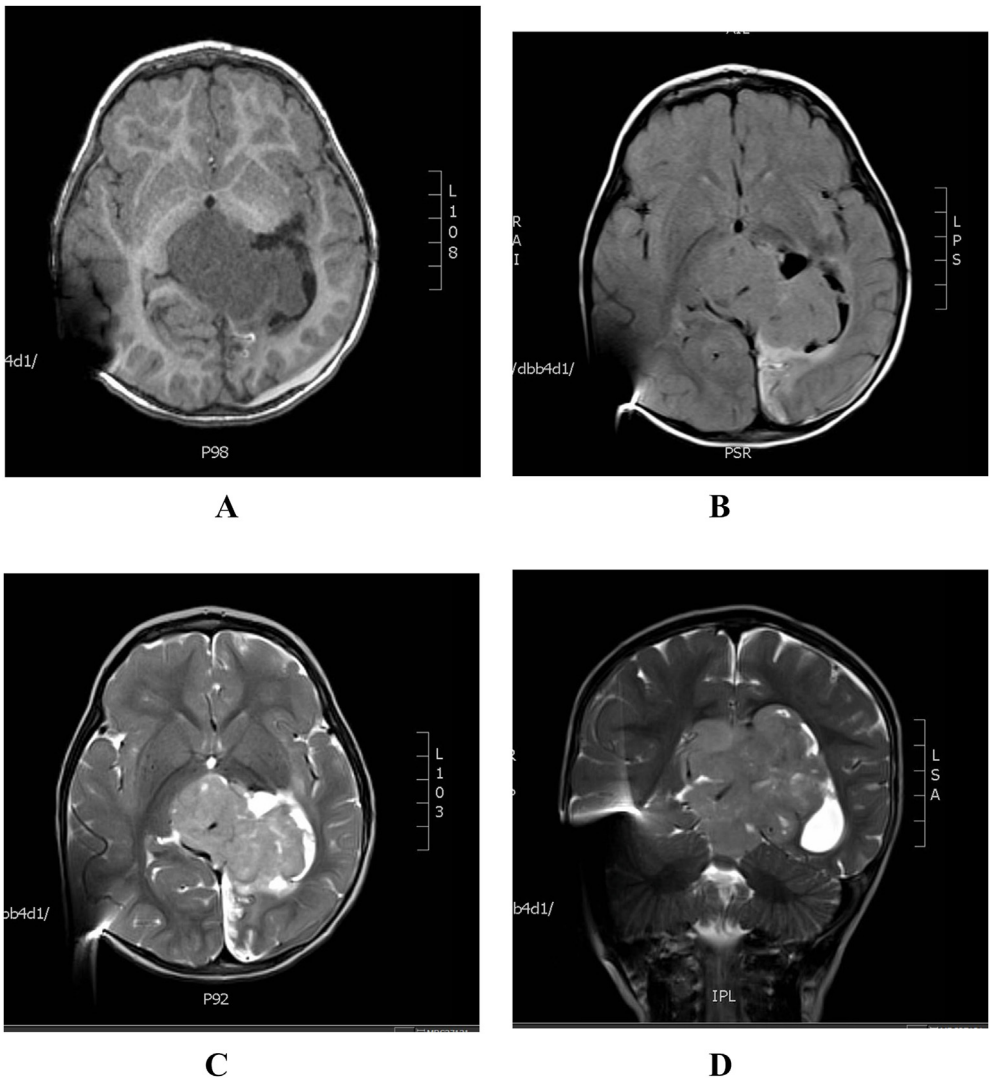

Fig. 2. Hematoxylin and eosin (H&E)-stained sections and immunohistochemistry studies. (A): A low-power view demonstrates a biphasic architecture of both primitive and more differentiated components (H&E; 10x). (B): Multilayered true rosettes are identified within primitive components containing numerous apoptotic cells (H&E; 20x). (C): Positive synaptophysin in the differentiated neuropil area (20x). (D): Ki-67 labeling index is expressed as approximately 70–80% of the primitive embryonal tumors (20x).

tumor cells. P53 expressed in a subset of tumor cells. Epithelial membrane antigen (EMA) and pancytokeratin were negative. Ki67 labeling index was very high in the primitive component (Fig. 2D). Chromosomal microarray testing revealed genomic alterations including a gain of chromosome 2, gain of chromosome 11, and gain/low-level amplification of 19q13.42 (disrupting the C19MC region and TTYH1and potentially generating a TTYH1-C19MC fusion). The final integrated diagnosis corresponding to the current 2016 WHO classification of CNS tumors was consistent with embryonal tumor with multilayered rosettes (ETMR), C19MC-altered. The patient started on chemotherapy and focused radiation. Three months after the surgery, new MRI showed interval growth of a large soft tissue mass occupying the left thalamic surgical bed extending across the midline measures 5.7 × 5.5 × 4.0 cm in maximum ML x CC x AP dimensions, respectively, occupying the posterior aspect of both lateral ventricles and supravermian cistern with complete effacement of the aqueduct of Sylvius (Fig. 3). The patient was recommended to undergo immediate chemo and radiotherapy. The patient was lost to follow-up to the hospital. His last follow-up was in August 2020.

3. Discussion

Embryonal tumors of the CNS are composed of a heterogeneous group of highly aggressive primitive neoplasms that contain disparate histological and distinct molecular features. ETMR used to be known as an embryonal tumor with abundant neuropil and true rosettes (ETANTR), which was first described by Eberhart et al., in 2000 [6]. Up to 80 case reports worldwide reported this rare pediatric tumor, with the largest series of cases reported by Gessi et al., in 2009, who reviewed 29 cases of the previously named ETANTR [7–9]. ETMR commonly occurred below the age of 4 years, and most of the cases are reported in the first 2 years of life. It tends to have a female predominance. Two-thirds of the cases occur in the supratentorial region, mainly in the cerebral cortex hemisphere, mostly frontal and parietotemporal lobe. They are rarely found in the cerebellum, brainstem, and spinal cord region. Presenting signs and symptoms are different depending on the affected area of the brain by the tumor. The most common symptom is hydrocephalus, signs of increased intracranial pressure, and focal neurological deficit. CT scan usually detects a large solid hyperattenuating mass, and MRI may reveal a well-defined mass

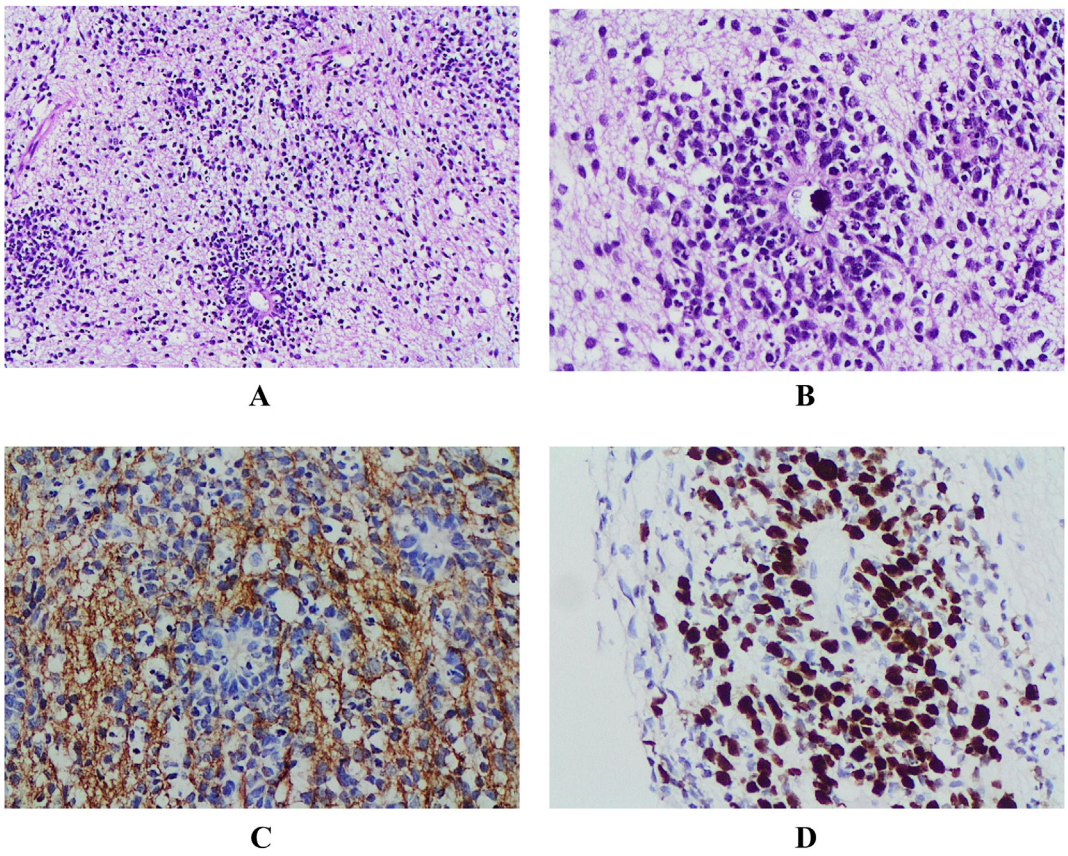

Fig. 3. Post-operative planning MRI brain with and without contrast. (A) T1 hypointense/(B–C) T2 hyperintense signal with evidence of diffusion restriction and variable internal enhancement, the mass occupying the lateral ventricles with entrapment of the temporal horn. (D) Coronal T2-weighted images reveal no significant mass effect, with associated patchy meningeal enhancement at the site of collections of the previous craniotomy site.

with minimal vasogenic edema, with or without cystic components often without contrast enhancement in higher grade tumors. However, there are no specific distinguishing radiological features for ETMR. Additionally, some cases were reported to have a dural attachment [7,10]. Histologically, ETMRs are composed of primitive cells, arranged in sheets of dark blue cells in a mature neural and glial background. Scattered characteristic multilayered rosettes are integrated as part of the tumor component. Tumor cells are positive for nestin and vimentin. Synaptophysin can be expressed in the neuropil component. MIB-1 (Ki-67) labeling index, as for all other primitive embryonal tumors, frequently is very high. C19MC gene amplification was discovered in unique primitive neuroectodermal tumors of the CNS by Li et al. These tumor subsets usually have aggressive behavior, dismal clinical outcome, and poor prognosis [11]. Korshunov et al. studied 97 cases and found 93% of the cases exhibit C19MC amplification on chromosome 19 [12]. The new WHO 2016 CNS classification systems reclassified and grouped a significant number of neoplasms with integrations of their molecular genetic profile. C19MC amplification is mandatory for the final diagnosis of ETMR, even if the multilayered rosettes are not detected histologically. Cases with no confirmation through molecular testing, along with the presence of multilayered rosettes should be named as embryonal tumors with multilayered rosettes, not otherwise specified (NOS) [13]. LIN28A was described as developed immunohistochemistry to diagnose tumors by genetic expression antibody profile testing and showed a specific expression of biomarkers [14]. The differential diagnosis includes other tumors with primitive cell morphology of the embryonal tumor family such as EBL, ME, AT/RT, and medulloblastoma. EBL and ETMR represent both ends of the morphological spectrum in which EBL represents the undifferentiated histologic morphology, while ETMR is the more differentiated histology. EBL is mostly composed of primitive cells arranged in sheets with frequent ependymoblastic multilayered rosettes. ME are composed of primitive cells aggregated in tubules, trabeculae, and papillary structures. Periodic acid–Schiff (PAS) positive staining on the outer epithelial surface membrane can be helpful for labeling primitive neural tube. Other unilayered rosettes primitive tumors such as AT/RT and medulloblastoma are distinguished by the absence of the multilayered rosettes, which is specific to the group of ETMR mentioned above. Loss of INI1 protein expression is very helpful in the diagnosis of AT/RT. Medulloblastoma is a primitive tumor that reacts strongly with synaptophysin and NeuN antibodies. However, ETMR is a very aggressive tumor with an estimated survival average rate of 12 months. They also tend to recur, with a potential for widely disseminated disease. Treatment options include surgery, tumor radiation, and high doses of chemotherapeutic agents. The better prognostic outcome might be associated with gross total resection along with radiation.

4. Conclusion

ETMRs are highly aggressive primitive neoplasms of the CNS that carry a very poor prognosis. ETMR must be differentiated from other CNS embryonal tumors as they exhibit a variable clinical course with diverse survival rate and disease prognosis. The histological examination should carefully detect multilayered rosettes. Molecular and genetic testing is required to confirm the final

diagnosis.

Consent for publication

This is a single case report with no identifiable patient information/characteristics are included in the case report. Therefore, there is no need to obtain the patient consent.

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Patient consent statement

This is a single case report with no identifiable patient information/characteristics are included in the case report. Therefore, there is no need to obtain the patient consent.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Louis DN, Perry A, Reifenberger G, Von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. Acta Neuropathol 2016 Jun;131(6):803–20.
[2] Pei YC, Huang GH, Yao XH, Bian XW, Li F, Xiang Y, et al. Embryonal tumor with multilayered rosettes, C19MC-altered (ETMR): a newly defined pediatric brain tumor. Int J Clin Exp Pathol 2019;12(8):3156.
[3] Korshunov A, Remke M, Gessi M, Ryzhova M, Hielscher T, Witt H, et al. Focal genomic amplification at 19q13. 42 comprises a powerful diagnostic marker for embryonal tumors with ependymoblastic rosettes. Acta Neuropathol 2010 Aug;120(2):253–60.
[4] Nobusawa S, Yokoo H, Hirato J, Kakita A, Takahashi H, Sugino T, et al. Analysis of chromosome 19q13. 42 amplification in embryonal brain tumors with ependymoblastic multilayered rosettes. Brain Pathol 2012 Sep;22(5):689–97.
[5] Korshunov A, Ryzhova M, Jones DT, Northcott PA, Van Sluis P, Volckmann R, et al. LIN28A immunoreactivity is a potent diagnostic marker of embryonal tumor with multilayered rosettes (ETMR). Acta Neuropathol 2012 Dec;124(6):875–81.
[6] Eberhart CG, Brat DJ, Cohen KJ, Burger PC. Pediatric neuroblastic brain tumors containing abundant neuropil and true rosettes. Pediatr Dev Pathol 2000 Jul;3(4):346–52.
[7] Gessi M, Giangaspero F, Lauriola L, Gardiman M, Scheithauer BW, Halliday W, et al. Embryonal tumors with abundant neuropil and true rosettes: a distinctive CNS primitive neuroectodermal tumor. Am J Surg Pathol 2009 Feb;33(2):211.
[8] Adamek D, Sofowora KD, Cwiklinska M, Herman-Sucharska I, Kwiatkowski S. Embryonal tumor with abundant neuropil and true rosettes: an autopsy case-based update and review of the literature. Child's Nerv Syst 2013 May 1;29(5):849–54.
[9] Neelima R, Easwer HV, Kapilamoorthy TR, Hingwala DR, Radhakrishnan VV. Embryonal tumor with multilayered rosettes: two case reports with a review of the literature. Neurol India 2012 Jan 1;60(1):96.
[10] Horwitz M, Dufour C, Leblond P, Bourdeaut F, Faure-Conter C, Bertozzi AI, et al. Embryonal tumors with multilayered rosettes in children: the SFCE experience. Child's Nerv Syst 2016 Feb 1;32(2):299–305.
[11] Li M, Lee KF, Lu Y, Clarke I, Shih D, Eberhart C, et al. Frequent amplification of a chr19q13. 41 microRNA polycistron in aggressive primitive neuroectodermal brain tumors. Cancer Cell 2009 Dec 8;16(6):533–46.
[12] Korshunov A, Sturm D, Ryzhova M, Hovestadt V, Gessi M, Jones DT, et al. Embryonal tumor with abundant neuropil and true rosettes (ETANTR), ependymoblastoma, and medulloepithelioma share molecular similarity and comprise a single clinicopathological entity. Acta Neuropathol 2014 Aug;128(2):279–89.
[13] Tariq MU, Ahmad Z, Minhas MK, Memon A, Mushtaq N, Hawkins C. Embryonal tumor with multilayered rosettes, C19MC-altered: report of an extremely rare malignant pediatric central nervous system neoplasm. SAGE Open Med Case Rep 2017 Nov 30;5. 2050313X17745208.
[14] Edmonson CA, Weaver KJ, Kresak J, Pincus DW. Embryonal tumor with multilayered rosettes of the fourth ventricle: case report. J Neurosurg Pediatr 2015 Nov 1;16(5):579–83.