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CASE-BASED UPDATE

Embryonal tumor with multilayered rosettes: illustrative case and review of the literature

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Abstract

Background Embryonal tumor with multilayered rosettes (ETMR) is a very rare entity and has seldom been reported. It has been newly defined tumor entity included in the latest update (revised fourth edition) of WHO 2016 Classification of Tumors of the Central Nervous System which portends a uniform dismal prognosis and survival even with the best of multimodality approaches.

Illustrative case This report documents the presentation of a 2-year-old girl with voluminous intracranial ETMR in the right parieto-occipital region. We describe clinical diagnosis, histological aspects, radiological features, and current management of this very aggressive tumor.

Conclusion Pediatric intracranial ETMR is a highly aggressive neoplasm, and it should be considered in the differential diagnosis of pediatric brain tumors.

Keywords Embryonal tumor with multilayered rosettes · C19MC · LIN28A · Surgery

Introduction

Embryonal tumor with multilayered rosettes (ETMR), C19MC-altered is a very rare and a highly aggressive, malignant tumor which has been newly defined tumor entity included in the latest update (revised fourth edition) of WHO Classification of Tumors of the Central Nervous System [1].

Fewer than 100 cases of the entity have been described till now [2].

They are most commonly diagnosed in children below the age of 4 years.

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Here, we present a case of brain ETMR in a 2-year-old girl. We discuss the clinical, radiological, and histopathological findings in this rare case and compare them with data in previously published cases in the literature.

Background

Historical background

ETMR was first described by Eberhart et al. in the year 2000 as a pediatric neuroblastic tumor with abundant neuropil and ependymoblastic rosettes [3]. ETMRs are highly malignant World Health Organization (WHO) grade IV [4].

It encompasses a group of three morphologically distinct embryonal tumors which were described as separate entities in the 2016 fourth edition of the WHO blue book [2] (Table 1). These include embryonal tumor with abundant neuropil and true rosettes (ETANTR), ependymoblastoma (EBL), and medulloepithelioma (MEPL).

Since this entity is known, specific molecular alterations have been identified, and authors showed amplifications at 19q13.42 using fluorescence in situ hybridization (FISH) analysis involving the C19MC; Korshunov et al. observed

Table 1 Comparison of CNS embryonal tumor category between 2007 and 2016 WHO classifications

CNS embryonal tumor, not otherwise specified**	Medulloblastoma	Desmoplastic/nodular medulloblastoma
		Medulloblastoma with extensive nodularity
		Anaplastic medulloblastoma Large cell medulloblastoma
	Atypical teratoid/rhabdoid tumor (AT/RT)	
	CNS primitive neuroectodermal tumor (PNET)*	CNS primitive neuroectodermal tumor (PNET)*
		Medulloepithelioma
		CNS neuroblastoma
		CNS neuroblastoma
2016 WHO classification	Medulloblastoma, genetically defined**	WNT-activated** SHH-activated and TP53-mutant**
		SHH-activated and TP53 wild-type**
		Non-WNT/non-SHH (group 3 and group 4)**
	Medulloblastoma, histologically defined	Classic
		Desmoplastic/nodular
		With extensive nodularity
		Large cell/anaplastic
	Medulloblastoma, not otherwise specified (NOS)	Atypical teratoid/rhabdoid tumor§
		Embryonal tumor with multilayered rosettes (ETMR), C19MC-altered**§
		Medulloepithelioma
		CNS neuroblastoma
		CNS ganglioneuroblastoma
		CNS embryonal tumor, not otherwise specified**

*Removed in 2016 WHO classification. **Added since 2007 WHO classification. § Both AT/RT and ETMR are now defined by genetic/molecular alteration of INI1 or C19MC, respectively. In the absence of that feature, the morphologic diagnoses CNS embryonal tumor with rhabdoid features or embryonal tumor with multilayered rosettes, NOS are also available, when based on histologic findings alone

ADC apparent diffusion coefficient, *AT/RT* atypical teratoid/rhabdoid tumor, *CNS* central nervous system, *CSF* cerebrospinal fluid, *ETMR* embryonal tumor with multilayered rosettes, *H-E* hematoxylineosin, *NOS* not otherwise specified, *PNET* primitive neuroectodermal tumor, *WHO* World Health Organization

amplification at 19q13.42, at a high frequency of 93% the ETMRs [1, 5]. This hallmark cytogenetic feature suggested that both these tumors are a single biological entity originating from a common precursor cell [5, 6].

The basis for merging these hitherto separate tumor entities is a unique molecular signature, that is, C19MC locus amplification which is common to these entities [4].

LIN28A, a RNA binding protein, high expression is noted in ETMRs. LIN28A may directly bind mRNAs to increase production of cell cycle regulators and maintains pluripotency [7]. LIN28A increase cellular proliferation, angiogenesis, metastasis, cell death resistance, and genomic instability of cancer cells [7].

Many authors state that LIN28A is a highly specific and sensitive marker for ETMR and recommend immunohistochemical for LIN28A as a rapid and reliable tool for the routine diagnosis of these tumors, whereas there is a paucity of literature regarding immunoreactivity of LIN28A across all embryonal CNS tumors [7, 8].

Although the sex ratio may fluctuate slightly around 0.4 reported by Horwitz et al. and 0.6 reported by Picard et al. [9, 10].

Clinical presentation and imaging

Presentation varies according to involved structures. In the literature, the localization of the majority of the primitive tumor is supratentorial, the cerebellum and brain stem are affected in 30% of cases [1]. Horwitz et al. reported one patient with an ETMR localized to the spinal cord [9].

Most ETMR are radiologically misdiagnosed and/or mistaken for medulloblastoma, ependymoma, atypical teratoid/rhabdoid tumor, pilocytic astrocytoma, or pilomyxoid astrocytoma [10, 11].

On imaging, the tumors are usually a large heterogeneous solid mass at MR imaging with or without a cystic component, accompanied by relatively little edema or enhancement. These tumors restrict diffusion, indicating high cellularity [12]. Many ETMR are reported to have dural attachment as the present one [11].

Diagnosis

Histopathologically, the hallmark of embryonal tumors includes biphasic histology with the presence of multilayered

true rosettes surrounded by primitive cells with high N/C ratio and abundant nuclear debris [1].

ETANTR were composed of a primitive cell component arranged in sheets and mature glial and/or neuronal component with easily appreciable background neuropil.

Scattered multilayered rosettes were also an integral component of this tumor type [13]. Ependymoblastoma (EBL) were composed of sheets of primitive cells, and frequent multilayered (ependymoblastic) rosettes and medulloepithelioma (MEPL) were composed of primitive cells arranged in papillae, tubules, and trabeculae with deposition of PAS-positive outer membrane at one of the surfaces, resembling primitive neural tube. Multilayered rosettes were also seen in these tumors [4, 13].

Immunohistochemically, the tumor cells are positive for vimentin, and the neuropil is positive for synaptophysin. MIB-1 labeling index will be very high as for all embryonal tumors [12].

Amplification of microRNA at chromosome 19q13.42 has emerged as the hallmark molecular signature for these tumors [13, 14].

Recent studies reiterate that LIN28A is a sensitive immunohistochemical marker for the diagnosis of ETMR. However, the authors also show that among CNS embryonal tumors, LIN28A is not specific to ETMRs and such immunoreactivity can also be seen in a proportion of AT/RTs. They observed that 100% of the ETMRs were LIN28A immunopositive compared to 12% of the AT/RTs [15]; it is 24.4% for Spence et al. [8] and it is 23% with Rao et al. [7].

Spence et al. highlight the fact that there are non-ETMR CNS tumors with LIN28A immunoreactivity, and the findings obtained in this study indicate that LIN28A immunopositivity with C19MC amplification does not always occur concurrently [8].

Since ETMRs are recognized as a distinct entity in the WHO 2016 classification, 63 cases have been published till now (Table 2). Immunohistochemical for LIN28A immunoreactivity was performed on 22 cases and was positive in 19 cases. We observed amplification at 19q13.42 in 90% from a total of 20 cases (Table 2).

In those cases in which molecular testing cannot be performed, the presence of multilayered rosettes is mandatory and such cases should be diagnosed as ETMR, not otherwise specified [1].

In our illustrative case, as well as in many other case reports cited here, neither LIN28 immunostaining nor C19MC amplification analysis was performed, as the facilities are not available at our center.

Management and outcomes

A standard effective and well-accepted treatment protocol for the optimal management of ETMR patients is yet to be defined. Many author recommend complete surgery resection which is critical to relieve intracranial hypertension followed by systemic chemotherapy and craniospinal radiation when appropriate [9].

Extended resection up to 1 cm in the surrounding brain, or including infiltrated tissue, is reported to improve patient outcome [19].

In this strategy, chemotherapy relies on high-dose chemotherapy which could compensate for the avoidance or dose reduction in prophylactic craniospinal irradiation. But, the effectiveness of high-dose chemotherapy on long-term survival is difficult to extrapolate from the literature due to small patient numbers [9, 23].

In more recent studies, conventional craniospinal radiotherapy, which is given after a complete surgery and high-dose chemotherapy, may contribute to improved outcomes. These findings are consistent with the experience of Horwitz et al. [9] who reported the 1-year event free survival (EFS), and overall survival (OS) rate were 36% CI 95% (23–55) and 45% CI 95% (31–64), respectively. The 2-year EFS and OS rate reported by Chi et al. were 53% and 70% [24].

In comparison, the 1-year EFS and OS rate reported by Korshunov et al. were 16% and 14%, respectively. Their treatment strategy relies only on chemotherapy and high-dose chemotherapy after surgery [25].

However, as children with ETMR are for the most of all less than 4 years old, radiotherapy potentially impairs neurocognitive function; some authors reported the feasibility and effectiveness of chemotherapy followed by conventional craniospinal radiotherapy but benefits and long-term toxicities have to be balanced [26, 27].

Exemplary case description

A 2-year-old girl presented with two episodes of seizure, multiple episodes of vomiting, and weakness of the left side of the body since 7 days.

There was no history of trauma. She was otherwise in good health and had no relevant past medical history. Salient findings on neurological examination were tightness of left limbs, ptosis, and limitation of upward gaze in the left eye. Both pupils measured 3 mm with a normal reaction to light and accommodation. Fundus examination was normal. There was no other cranial nerve deficit.

The rest of the head and neck examination was unremarkable.

Our patient's magnetic resonance imaging (MRI) scan findings are consistent with those in previous reports; it demonstrated a 7 × 6 × 5 cm heterogeneous solid mass lesion, mass effect, and mild midline shift in the right parieto-occipital region. The tumor was hypointense on T1-

Table 2 Summary of the most recent reported cases of intracranial embryonal tumor with multilayered rosettes

References	Age at diagnosis	Sex	Initial symptoms	Location	Histological diagnosis	Imaging studies	Therapy
The present case	2 years	F	Headaches, vomiting, and progressive left hemiparesis	Right parieto-occipital	-ETMR -Positive expression for synaptophysin and vimentin -C19MC amplification LIN28A not performed	hypointense on T1-weighted images, hyperintense on T2-weighted images with minimal contrast enhancement	Surgical total resection
Leal Ferman et al. 2018 [16]	14 months	F	Intermittent ptosis of the right upper eyelid	The right ponto-mesencephalic junction	ETMR with C19MC amplification LIN28A positive	Non-enhancing hyperintense Lesion with restriction of diffusion	Subtotal resection
Gupta et al. 2018 [17]	7 years	M	Diplopia, facial deviation and difficulty in walking right sixth and seventh nerve palsy. Right sensorineural hearing loss with right-sided cerebellar signs	The right cerebellar peduncle with involvement of the pons	-ETMR with C19MC amplification LIN28Apositive-immunoreactivity forsynatophysin	CT: hypodense lesion MRI: hypointense on T1, hyperintense on T2 and on Fluid-attenuated inversion recovery, no diffusion restriction, and (E, F) mild heterogeneous contrast enhancement.	Total resection
Tanaka et al. 2018 [18]	23 years	M	Headache	Multiple lesions in the frontal horn of the bilateral lateral ventricles, third and fourth ventricles, and bilateral cerebello-medullary fissures	-ETMR with positivity for synaptophysin and chromogranin A -C19MC amplification LIN28A not performed	Contrast-enhancing tumor	Biopsy
Wang et al. 2018 [12]	− 2.9 years	F	-Worsening ataxia	-Brain stem	ETMR with	All tumors are solid: -Contrast enhancement is often heterogeneous and minimal or absent -No significant surrounding T2 FLAIR hyperintensity to suggest edema. -Restricted diffusion -High myoinositol -Lipid/lactate peak -Increased choline/creatine -Low NAA/Choline	Dose not mention
	− 4 years	M	-Cranial nerve VI, III, VII palsy and weakness	-Brain stem	-1 case: ependymoblastoma -1case: medulloepithelioma		
	− 3.5 years	M	-Abnormal eye movements, ataxia, and motor impairment	-Brain stem	-6 cases: synaptophysin expression		
	− 2.5 years	F	-Painless proptosis of the left eye	-Frontal lobe	-C19MC amplification		
	− 1.3 years	M	-Seizures and lip twitching	-Frontal lobe	LIN28A not performed in all cases		
	− 12 years	F	-Back pain, leg numbness, and weakness in her lower limbs, difficulty passing stools and urinary incontinence	-Spinal canal			
	− 4 years	M	-Low back pain and numbness in the legs, weakness in her lower extremities, difficulty passing stools, and urinary incontinence.	-Lumbar spinal canal			
Li et al. 2018 [19]	1 month	M	Routine ultrasonography 3 days before his birth had revealed an intracranial mass	The occipital horn of the right lateral ventricle	-Medulloepithelioma -Lin28A negative	Giant mass isointense on T1 and T2 showing heterogeneous enhancement	Surgical total resection

(continued)

References	Age at diagnosis	Sex	Initial symptoms	Location	Histological diagnosis	Imaging studies	Therapy
	11 months	F	Seizures, vomiting	Right cerebellopontine angle	Medulloepithelioma -Lin28A negative	Solid heterogeneous enhancing mass, hypointense on T1 and isointense on T2	Surgical total resection
Grassham et al. 2018 [20]	1 day	F	Macrocephaly, split sutures, and diminished spontaneous movement	Mass extending from the posterior fossa up the brain midline	Ependymoblastoma - Lin28A negative	Solid and cystic mass with heterogeneous enhancement Hydrocephalus	Subtotal removal
Tariq et al. 2018 [4]	8 months	F	Vomiting, drooping of left eyelid	Left cerebellar hemisphere	-ETANTR -C19MC amplification -LIN28A positive	Solid heterogeneous enhancing Mass Hydrocephalus	Gross total resection
Shah et al. 2018 [21]	2 years	M	Seizures	Right parietal lobe	-ETANTR -C19MC amplification LIN28A not performed	Non enhancing mass restricted diffusion	Gross total resection
	3 years	F	Vomiting	Right parietal lobe	-ETANTR -C19MC amplification LIN28A not performed	Peripheral contrast enhancement Increased choline/creatine	Gross total resection
	18 months	M	Seizures	Right frontal lobe	-ETANTR -C19MC amplification LIN28A not performed	Not described	Gross total resection
Govindan et al. 2017 [13]	3 years	F	Increased intracranial pressure	Right parieto-occipital region	-ETMR -Positive expression for synaptophysin and vimentin -C19MC amplification LIN28A not performed	Solid and cystic mass hypointense on T1 with mild contrast enhancement	Gross total resection
Chen et al. 2017 [22]	17 days	M	Macrocephaly	Cerebellar vermis	-ETMR -Positive expression for synaptophysin and vimentin -C19MC amplification LIN28A not performed	Solid and cystic mass, isointense on T1, hyperintense on T2	Partial surgical resection
Roa et al. 2017 [7]	2 years (1–-5 years)	3 M 2 F		Dose not mention	Supra and infratentorial	-ETANTR -C19MC amplification and LIN28A positive in all cases	Dose not mention
Dose not mention							
Mozes et al. 2016 [23]	2 years	F	Increased intracranial pressure and unsteady gait, and disturbances in coordination	Left cerebellum and left occipital lobe	-ETANTR -C19MC amplification LIN28A not performed	Contrast-enhancing lesion	Gross total resection
Horwitz et al. 2016 [9] 38 cases	Mean 40.8 (2.8–141) months	10 F 28 M		-Sided weakness: 13 cases. -Confusion: 10 cases -Increased IP: 17 cases -Seizures: 7 cases	-Supratentorial: 25 cases -Infratentorial:10 cases -Supra and infratentorial: 2cases -Spinal cord: 1 case	-ETMR: 8 cases -ETANTR: 17 cases -Medulloepithelioma: 13 cases −12 cases: C19MC amplification in 83%	Not described

(continued)

References	Age at diagnosis	Sex	Initial symptoms	Location	Histological diagnosis	Imaging studies	Therapy
				-Cerebellar syndrome: 7 cases -Torticolis: 3 cases -Visual impairment: 4 cases		−11 cases: LIN28A positive in 100%	
7 cases							

References	Radiotherapy	Chemotherapy	Follow-up	Outcome	Leptomeningeal failure
The present case	No	Yes	6 months	Stable disease	No
Leal Ferman et al. 2018 [16]	No	Intrathecal cytarabine, vorinostat, isotretinoid, vincristine, etoposide, Cisplatin and cyclo-phosphamide	5 months	Death	Leptomeningeal spread to spine and brainstem
Gupta et al. 2018 [17]	Dose not mention	Dose not mention	Dose not mention	Dose not mention	Dose not mention
Tanaka et al. 2018 [18]	-Whole brain: 45 Gy -Spine: 36 Gy f	Ifosfamide, cisplatin, and etoposide	2 years	Stable disease	Widespread leptomeningeal tumor dissemination
Wang et al. 2018 [12]	Dose not mention	Dose not mention	Dose not mention	Dose not mention	Dose not mention
Li et al. 2018 [19]	No	Cyclophosphamide, vincristine, followed by carboplatin and etoposide	3 months	Complete remission	No
	No	Yes Protocol not mention	6 months	Death	No
Grassham et al. 2018 [20]	No	No	6 days	Death	Widespread leptomeningeal tumor dissemination
Tariq et al. 2018 [4]	No	No	7 days	Death	No
Shah et al. 2018 [21]	Proton beam radiation	Yes Protocol not mention	3.5 years	Death	Extracranial metastases
	Proton beam radiation	Yes Protocol not mention	3 years	Death	Extracranial metastases
	Proton beam radiation	Yes Protocol not mention	2 years	Death	Widespread leptomeningeal tumor dissemination
Govindan et al. 2017 [13]	No	No	1 day	Death	No
Chen et al. 2017 [22]	Dose not mention	Dose not mention	Dose not mention	Dose not mention	Dose not mention
Roa et al. 2017 [7]	Dose not mention	Dose not mention	Dose not mention	Dose not mention	Dose not mention
Mozes et al. 2016 [23]	Craniospinal irradiation 32 Gy	Vincristine cyclophosphamide etoposide carboplatin cisplatin	4 years	Stable disease	No
Horwitz et al. 2016 [9] 38 cases	16 cases	All cases	Mean 0.9 years (range 0.1 to 15.3 years)	71% mortality	7 cases

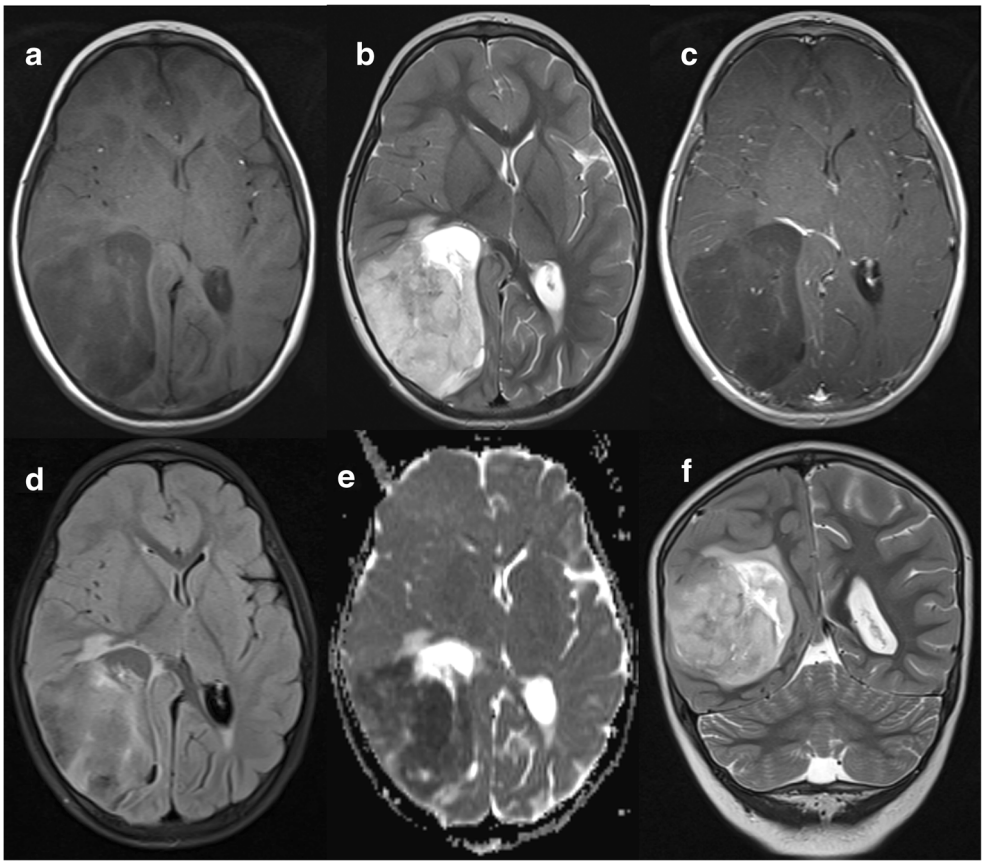

Fig. 1 Preoperative magnetic resonance imaging (MRI). Axial precontrast T1-weighted images show a huge and well-circumscribed mass in the right parieto-occipital region, which is hypointense to adjacent brain in most parts (**a**). The cerebral falx clearly shifts to the left. Axial (**b**) and coronal (**f**) T2-weighted image shows mass with mixed signal intensity, including iso- and hyperintense signal. Apparent vascular edema is present in surrounding area. Axial postcontrast T1-weighted images show the mass with minimal inhomogeneous contrast enhancement (**c**). Fluid-attenuated inversion recovery sequence reveals mild hyperintensity (**d**) and lesion shows no diffusion restriction (**e**)

weighted images, hyperintense on T2-weighted images with minimal contrast enhancement. (Fig. 1).

The imaging features were suggestive of a PNET. She underwent right parieto-occipital craniotomy with total resection. The tumor was seen gray-white, soft, friable and moderately vascular and had a poor plane of cleavage from the adjacent brain parenchyma with adherence to the dura.

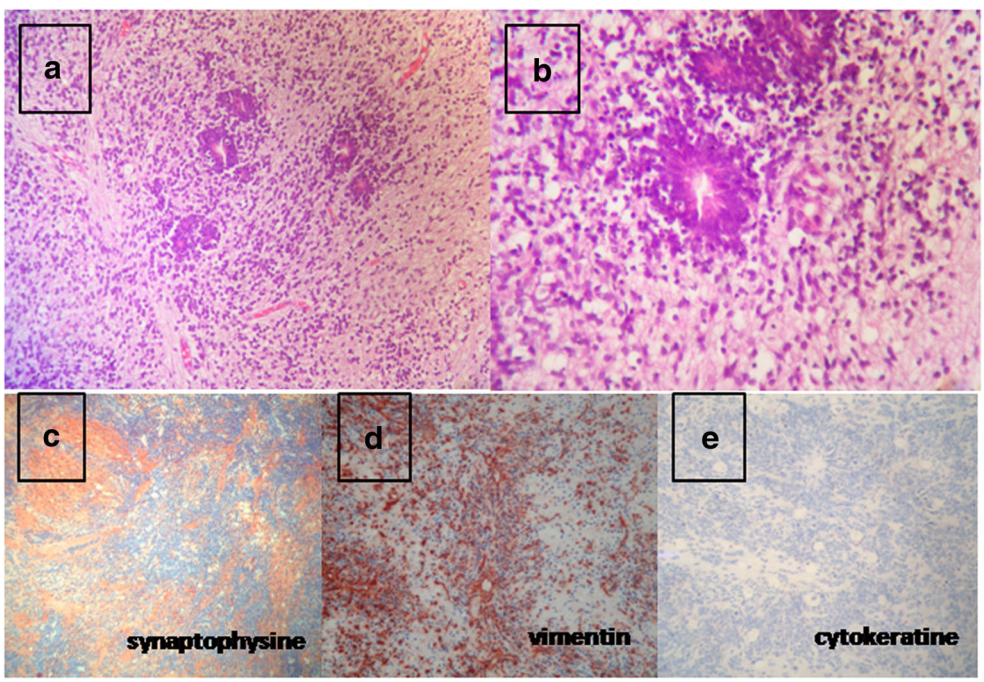

Fig. 2 Histopathology showed **a** H&E × 10: biphasic histologic pattern: areas of small embryonal cells with multilayered rosettes and paucicellular fibrillar areas. **b** H&E × 40: multilayered rosettes consisting of pseudostratified neuroepithelium with a central round lumen. Immunohistochemistry × 40: the neuropil-like areas show positive expression for synaptophysin (**c**) and vimentin (**d**). Tumor cells are negative for cytokeratin (**e**)

Histopathological examination found a tumor with a biphasic, histological architecture characterized by a combination of hypercellular areas of small blue cells with minimal cytoplasm admixed with paucicellular neuropil areas, and numerous multilayered rosettes were found in both regions of the tumor. Immunohistochemistry showed the cells to be positive for synaptophysin, vimentin, and they are negative for cytokeratin (Fig. 2); a diagnosis of embryonal tumor with multilayered rosettes was made.

She had an uncomplicated postoperative course with spontaneous recovery of the left oculomotor palsy 1 week after surgery that we do not have an explanation. She was sent for adjuvant chemotherapy. The girl was treated according to the medulloblastoma 2008 high-risk protocol (vincristine, cyclophosphamide, and etoposide). She has been under follow-up for the past 6 months with no evidence of recurrence.

Conclusion

Pediatric intracranial ETMR is a highly aggressive neoplasm and it should be considered in the differential diagnosis of pediatric brain tumors. In the absence of such guidelines, the role of adjuvant therapy remains unclear. Despite some case reports show long-term disease-free survival, the survival rate of patients with ETMR has been overall poor due to its highly malignant course.

Future studies should analyze clinical, radiological, biological, and prognostic results to try to better define therapeutic modalities.

Compliance with ethical standards

Conflict of interest None of the authors has any potential conflict of interest.

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