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Autopsy report and review of the 2016 WHO classification of congenital supratentorial embryonal tumors, not otherwise specified

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ABSTRACT

Purpose: Central nervous system embryonal tumors, not otherwise specified (ETNOS), comprise a group of rare, poorly differentiated embryonal neoplasms of neuroectodermal origin (WHO grade IV) that lack the specific histopathological features and molecular alterations that define other embryonal tumors, such as medulloblastoma and embryonal tumors with multilayered rosettes, C19MC altered. ETNOS accounts for less than 0.5% of all brain tumors and predominantly affects children aged 0–14 years.

Case report: The authors report an autopsy case of ETNOS in a female newborn of 22 weeks of gestational age. The brain weighed 68.0 g and measured 61.0 mm in occipitofrontal diameter. A white-gray, soft, infiltrative tumor measuring 0.9 cm in the largest dimension was found in the right lateral ventricle. Microscopic examination revealed a high-grade malignant neoplasm composed of small round blue cells, with marked atypia, solid pattern, and high mitotic index. Neoplastic cells showed positive immunostaining for synaptophysin, GFAP, NFP, CD99, INI1, vimentin, and EMA. The diagnosis of ETNOS was thus established. Differential diagnosis includes other embryonal tumors, such as medulloepithelioma, neuroblastoma, ganglioneuroblastoma, and atypical rhabdoid/teratoid tumor. Treatment is usually surgical resection combined with craniospinal irradiation and/or multimodality chemotherapy.

Conclusions: Congenital ETNOS are rare high-grade pediatric tumors, probably originated from primitive neuroepithelial cells. Overall, neoplastic cells are positive for synaptophysin, GFAP, INI1, and CD99. Immunohistochemistry panels are fundamental to establish the diagnosis.

1. Introduction

Central nervous system (CNS) embryonal tumors, not otherwise specified (ETNOS), comprise a group of rare, poorly differentiated embryonal neoplasms of neuroectodermal origin that lack the specific histopathological features and molecular alterations that define other embryonal tumors, such as medulloblastoma (MDB); medulloepithelioma (MEP); embryonal tumor with multilayered rosettes, C19MC-altered (ETMR); neuroblastoma (NBM); and atypical teratoid/rhabdoid tumor (AT/RT) [1–3]. The 2016 World Health Organization (WHO) classification of tumors defines embryonal tumors on the basis of histological and molecular signatures, avoiding the previous designation “CNS primitive neuroectodermal tumor” [1–4].

CNS embryonal tumors correspond to WHO grade IV and account for

Abbreviations: AT/RT, Atypical teratoid/rhabdoid tumor; CNS, Central nervous system; ETMR, Embryonal tumor with multilayered rosettes, C19MC-altered; ETNOS, Embryonal tumor, not otherwise specified; GNBM, Ganglioneuroblastoma; MDB, Medulloblastoma; MEP, Medulloepithelioma; NBM, Neuroblastoma; WHO, World Health Organization.

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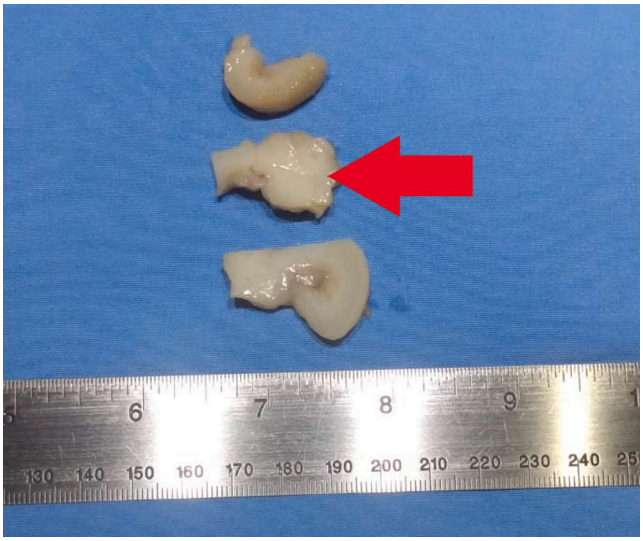

Fig. 1. Central nervous system embryonal tumor, not otherwise specified: Gross specimen showing a white-gray, infiltrative, periventricular tumor.

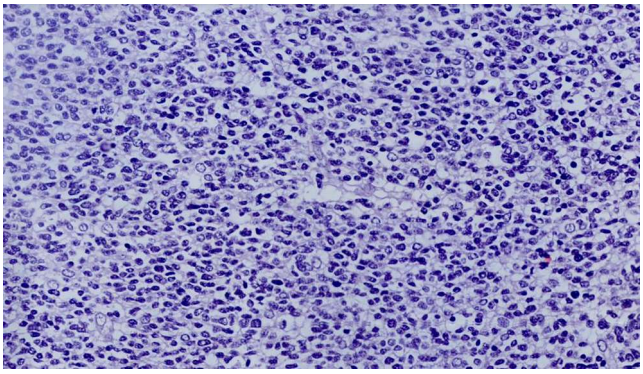

Fig. 2. Conventional histological findings of central nervous system embryonal tumors are the proliferation of small round blue cells disposed in a solid pattern (hematoxylin-eosin, ×400).

1% of all brain tumors. These neoplasms constitute about 13% of tumors arising in children aged 0–14 years, with no sex predominance [2,3,5,6]. Congenital ETNOS are even rarer [1,2,5,6]. Incidence of adult CNS embryonal tumors is difficult to determine because of their rarity and lack of signature biomarkers [2,4–6]. ETNOS are composed of poorly differentiated neuroepithelial cells that may exhibit neuronal, astrocytic, myogenic, or melanocytic differentiation [1,4,7–9], and are associated with aggressive clinical behavior and a very poor prognosis [5,6,10]. Here, the authors report an autopsy case of ETNOS in a female newborn infant, discuss the histogenetic features of this rare tumor, and emphasize the importance of ultrasound and magnetic resonance imaging in the prenatal period.

2. Case report

A 22-year-old pregnant woman was admitted to the hospital because of abnormal vaginal bleeding for the previous 3 h. Induced vaginal delivery was conducted 6 h after admission. Prenatal screening results included a positive Coombs test. No evidence of significant alterations, such as systemic arterial hypertension, diabetes mellitus, TORCH syndrome (with HIV screening), or urinary infection, were observed. The female newborn, weighing 515.0 g and measuring 19.7 cm in crown-rump length and 27.4 cm in crown-heel length, died shortly after birth. An autopsy was performed, and the gestational age was estimated

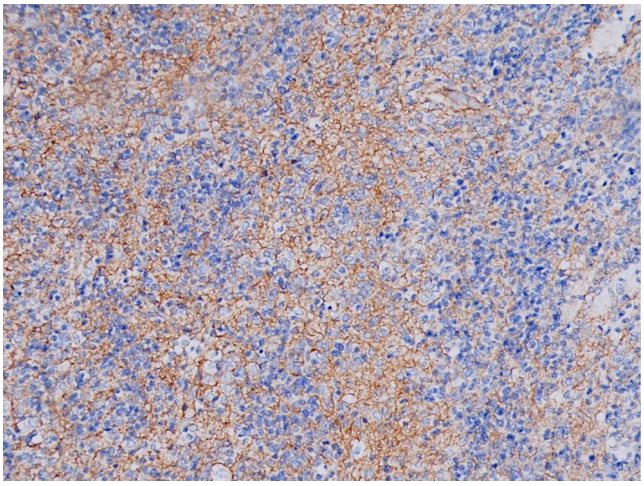

Fig. 3. Neoplastic cells showing positive immunostaining for synaptophysin are characteristic of central nervous system embryonal tumor, not otherwise specified (Ventana Systems, ×200).

at 22 weeks on the basis of morphologic findings and neonatal screening. Malformations were not identified. Upper and lower limbs, abdominal and thoracic organs, and genital tract showed normal development for the gestational age. The brain weighed 68.0 g and measured 61.0 mm in occipitofrontal diameter. Meninges were translucent and pale, and hemispheres were predominantly smooth, with normal development of the Sylvian fissure and calcarine, parieto-occipital, central, and superior temporal sulci. A blood clot was found in the right lateral and third ventricles. Hydrocephalus and changes in the thickness of brain tissue adjacent to the lateral ventricles have not been identified. A white–gray, soft, infiltrative tumor, measuring 0.9 cm in the largest diameter, was identified in the right lateral ventricle (Fig. 1). Microscopic analysis revealed a high-grade malignant neoplasm composed of small round blue cells, with marked atypia, solid pattern, and high mitotic index (Fig. 2). Neoplastic cells showed positive immunostaining for synaptophysin (Fig. 3), GFAP, NFP, CD99, INI1, vimentin, and EMA. The Ki-67 proliferation index was estimated at 90%. Cells had negative immunostaining for H3K27M, Olig2, IDH1, p53, ATRX, NSE, NKX2.2, NB84, and β-catenin. The diagnosis of ETNOS was thus established. Other autopsy findings included lung, liver, renal, and adrenal hyperemia. The patient was referred to the obstetrics and medical genetics services for further clinical follow-up at the expense of the positive Coombs test and possible future chromosomal abnormalities identification. The present report (09-206-001) was approved by ethical committee of Hospital N. Sra. da Conceição, Porto Alegre, Rio Grande do Sul, Brazil.

3. Discussion

CNS ETNOS are typically located in the cerebral hemispheres, compromising predominantly the frontal and parietal lobes, with rare examples occurring in the brain stem and spinal cord. ETNOS are associated with tumor implants in 25–30% of cases (mostly in the subarachnoid space). [1,2,4,11]. On gross examination, ETNOS usually presents as solid, gray-pink masses with ill-defined borders in relation to normal brain tissue. Large lesions with cystic/necrotic zones are frequent. [2,3,6,8,10]. ETNOS are hypercellular lesions composed of poorly differentiated cells exhibiting round to oval crowded nuclei with stippled chromatin, high mitotic index, and frequent apoptotic bodies [1,4,12,13]. Overall, neoplastic cells are positive for synaptophysin, GFAP, INI1, CD99, and vimentin, and may also express NFP, EMA, p53, and CKM [1,2,4,9,14]. Little is known about the etiology of these tumors, although a small proportion are associated with genetic syndromes. The most common abnormalities in supratentorial ETNOS are

Table 1
Differential diagnosis of central nervous system embryonal tumor, not otherwise specified, from other high-grade brain tumors based on molecular data.

Histological type	Molecular findings
Medulloblastoma, WNT-activated/SHH-activated	c-MYC/N-MYC amplification, β-catenin (CTNNB1) mutation
Embryonal tumor with multilayered rosettes	C19MC amplification
Atypical rhabdoid/teratoid tumor	INI1 or BRG1 mutations
Neuroblastoma	Neoplastic neuron-like cells showing positive immunoexpression for synaptophysin
Pediatric glioblastoma	H3K27M mutations
Anaplastic gliomas	IDH1/IDH2 mutations
Embryonal tumor, not otherwise specified	CD99 immunoexpression

losses of 3p21, 3q26, and 8p23.6; and gains of 1q, 2p, and 19p. [1,2,4,9,14]. The authors describe a case of ETNOS along the internal surface of the lateral ventricle, suggesting that the neoplasm can originate from primitive neuroepithelial cells. The authors also emphasize that it is difficult to determine the incidence of congenital ETNOS since the current published data predominantly represent single case reports.

Clinical presentation is generally associated with mass effect and hydrocephalus [2,9,13]. On computed tomography, ETNOS usually appears as iso- to hyperdense lesions showing calcification areas and contrast enhancement. Magnetic resonance imaging reveals T1-hypointense lesions when compared with grey matter and T2-hyperintense lesions in necrotic zones [2,9,13]. Currently, indications for ultrasonography during pregnancy are diverse and include estimation of gestational age, estimation of fetal growth, bleeding from uterus, suspected multiple gestation, adjunct to an invasive procedure, suspected uterine abnormality, and malformations. In the context of congenital CNS tumors, malignant lesions are uncommon conditions that can be reliably detected by ultrasonography even in the first-trimester. Anencephaly, prominent hydrocephaly, severe neural tube defects, and brain tumors are rarely misdiagnosed by this method. Accuracy of diagnosis is variable and can be associated to experience of sonographer, gestational age at time of scanning, and used equipment. In addition, in low-risk or asymptomatic pregnant women in the first and second trimester, the authors emphasize that the most effective way to identify brain neoplastic processes is the use of ultrasound in prenatal exams.

Differential diagnosis of ETNOS includes other embryonal tumors. MDB is the most common CNS embryonal tumor of childhood (around 25% of cases). It originates from cerebellar/fourth ventricle tissue and is genetically defined as WNT-activated/group 1, SHH-activated/group 2, or non-WNT/non-SHH tumors/groups 3–4. MDBs are histologically classified as classic, desmoplastic/nodular, with extensive nodularity, or large cell/anaplastic. The genetic groups of MDB can be characterized according to the immunoexpression pattern of β-catenin/p53 [1,4,15,16]. ETMR is an aggressive tumor that can develop in the cerebrum (70% of cases), and is genetically characterized by a high-level amplicon at 19q13.42 named C19MC, which has not been identified in other pediatric brain tumors. It presents histologically as numerous rosettes formed by multilayered structures constituted by pseudostratified neuroepithelium, with a central, round, or slit-like lumen, showing positive immunoexpression for vimentin, INI1, LIN28A, nestin, and synaptophysin. [2,4,17–19]. Ependymoblastoma shows clusters of poorly differentiated cells admixed with numerous rosettes but without ganglion cell elements or a neuropil-like matrix [1,4,16]. MEP is constituted by large sheets of poorly differentiated cells and zones of neoplastic pseudostratified epithelium forming papillary, trabecular, and tubular structures, with an external membrane delimiting the neoplastic epithelium. In MEPs, the neuroepithelium exhibits positive immunoexpression for synaptophysin and NFP, whereas LIN28A immunoreactivity is found in C19MC-non-amplified MEP [1,2]. NBM is composed of poorly differentiated neuroepithelial cells, a variable amount of neutrophil-rich stroma, and areas of neurocytic cells [1,4,5,11,20,21]. GNBM shows neurocytic and ganglion cells intermingled with poorly differentiated cells [1,4,5,11,20,21]. AT/RT is constituted by poorly differentiated cells and rhabdoid cells showing inactivation of INI1 (SMARCB1) and BRG1 (SMARCA4) [2,4,22–24]. Table 1 presents important molecular features of different histological types of high-grade pediatric tumors [1,2,4,11,15,17,20–22,24,25].

Table 2
Some prior autopsy reports of supratentorial embrionary tumors, not otherwise specified, found in the international literature. All cases of neuroblastoma, ependymoblastoma, and medulloblastoma have been excluded.

Author	Gestational age	Gender	Topography	Associated brain lesions
Yamada et al. [28]	32 weeks	Male	Right cerebral hemisphere	Hydrochephalus
Kaczala et al. [29]	39 weeks	Male	Right frontal lobe	Hydrochephalus
Kir Sahin et al [30]	24 weeks	Female	Occipital lobe	Hydrochephalus
Kapoor et al [31]	24 weeks	Unavailable	Left thalamic and temporal regions	Enlarged right ventricle
Present report	22 weeks	Female	Right lateral ventricle	Blood clot in the right lateral and third ventricles

Treatment is usually surgical resection combined with craniospinal irradiation and/or multimodality chemotherapy. Currently, no definitive guidelines for the treatment of congenital ETNOS cases have been determined. [1,4,15,17,20–22,24,26]. Complications related to prematurity may determine more significant morbidity that the tumor itself. Hydrochephalus may worsen the outcome if delivery is delayed until term. Even cared by an expert neurosurgeon, the morbidity and mortality of ETNOS is greater in newborns and infants than in older children. It also be considered the inadvisability of radiotherapy to infants of two years or less in age. Targeted radioimmunotherapy is a possible therapy in the future. [1,4,15,17,20–22,24,27,28]. Table 2 presents important similar cases found in the international literature.

Common causes of spontaneous abortion include chromosomal abnormalities, increased maternal age, failure of implantation, maternal alcohol intake, poorly-controlled type 1 diabetes mellitus, and chorioamnionitis. [10,25–31] Herein, the authors described an autopsy in a second trimester female newborn due to CNS ETNOS, and discussed current diagnostic criteria for this rare tumor. Spontaneous abortion related to congenital brain tumors is an uncommon event, in special if compared to severe encephalic malformations. Prenatal screening is the only way to establish early diagnosis of ETNOS and to favor a possible surgical resection in some patients.

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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.

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