

# Embryonal tumors in the WHO CNS5 classification: A Review

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## ABSTRACT

Embryonal tumors are a heterogeneous group of neoplasms mostly defined by recurrent genetic driver events. They have been, previously, broadly classified as either medulloblastoma or supratentorial primitive neuroectodermal tumors (PNETs). However, the application of DNA methylation/gene expression profiling in large series of neoplasms histologically defined as PNET, revealed tumors, which showed genetic events associated with glial tumors. These findings led to the definitive removal of the term “PNET” in the 2016 World Health Organization (WHO) classification of CNS tumors. Moreover, further studies on a large scale of methylation profiling have allowed the identification of new molecular-defined entities and have largely influenced the 5<sup>th</sup> edition of the WHO classification of CNS tumors (WHO CNS5) for both medulloblastomas and other CNS embryonal tumors. The importance of molecular characteristics in CNS embryonal tumors is well represented by the identification of different molecular groups and subgroups in medulloblastoma. So, in the CNS5, the emerged group 3 and group 4 belong to the classification, and the four molecular and morphologic types are now combined into a unique section. Among other embryonal tumors, two new recognized entities are introduced in CNS5: CNS neuroblastoma, *FOXR2*-activated, and CNS tumor with *BCOR* internal tandem duplication (ITD). Embryonal tumor with multilayered rosettes (ETMR), already present in the previous classification now has a revised nomenclature as a result of the new *DICER1* alteration, additional to the formerly known C19MC. Regarding atypical teratoid/rhabdoid tumor (AT/RT), three molecular subgroups are recognized in CNS5. The combination of histopathological and molecular features reflects the complexity of all these tumors and gives critical information in terms of prognosis and therapy. This encourages the use of a layered diagnostic report with the integrated diagnosis at the top, succeeded by layers including the histological, molecular, and other essential details.

**KEY WORDS:** Atypical teratoid/rhabdoid tumor, *BCOR*, central nervous system, embryonal tumor, embryonal tumor with multilayered rosettes, *FOXR2*, medulloblastoma, neuroblastoma, World Health Organization

## INTRODUCTION

Embryonal tumors were previously classified into two broad groups: medulloblastoma and PNET. The relevance of genome-wide studies over the years led to a reclassification of these entities.<sup>[1,2]</sup> The application on a large scale of DNA methylation/gene expression profiling led to the identification of new molecular defined entities<sup>[3]</sup> [Table 1]. Here, we describe the newest molecularly defined types/subtypes of medulloblastoma and other embryonal tumors that will be included in the CNS5.

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## Medulloblastoma

In WHO CNS5, medulloblastomas are classified according to a combination of molecular and histopathological features. The current molecular classification, which reflects the clinico-biological heterogeneity of these neoplasms, is the result of extensive transcriptome and DNA profiling analysis.<sup>[4-24]</sup> The new classification

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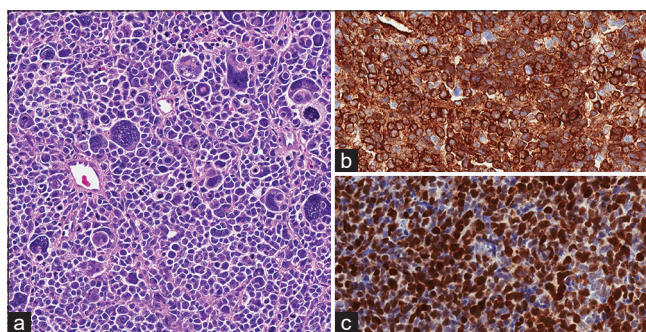
**Table 1: Embryonal Tumors: Comparison between 2016 and fifth WHO classification**

WHO Classification 2016	WHO Classification 2021 (CNS5)
<i>Medulloblastomas, genetically defined</i>	<i>Medulloblastomas</i>
Medulloblastoma, WNT-activated	Medulloblastoma, WNT-activated
Medulloblastoma, SHH-activated, and TP53-wildtype	Medulloblastoma, SHH-activated, and TP53-wildtype
Medulloblastoma, SHH-activated, and TP53-mutant	Medulloblastoma, SHH-activated, and TP53-mutant
Medulloblastoma, non-WNT/non-SHH	Medulloblastoma, non-WNT/non-SHH
<i>Medulloblastomas, histologically defined</i>	<i>Medulloblastomas, histologically defined</i>
Medulloblastoma, classic	<i>Other CNS embryonal tumors</i>
Desmoplastic/nodular medulloblastoma	Atypical teratoid/rhabdoid tumor
Medulloblastoma with extensive nodularity	Cribriform neuroepithelial tumor
Large cell/anaplastic medulloblastoma	Embryonal tumor with multilayered rosettes
<i>Embryonal tumor with multilayered rosettes C19MC-altered</i>	CNS neuroblastoma, FOXR2-activated
<i>Other CNS embryonal tumors</i>	CNS tumor with BCOR internal tandem duplication (ITD)
Medulloepithelioma	CNS embryonal tumor NOS
CNS neuroblastoma	
<i>Atypical teratoid/rhabdoid tumor</i>	
<i>CNS embryonal tumor with rhabdoid features</i>	

maintains the original established four principal molecular groups as in 2016 WHO,<sup>[7,25-32]</sup> i.e., wingless-activated (WNT)-activated, sonic hedgehog (SHH)-activated, and non-WNT/non-SHH. SHH tumors are divided, as in WHO 2016, on the basis of *TP53* status (*TP53*-mutant and *TP53*-wildtype tumors) having very different clinico-pathological and biological characteristics.<sup>[26,33]</sup> However, DNA methylation profiling has led to the identification of 12 subgroups. There are four subgroups of SHH medulloblastoma<sup>[34]</sup> and eight subgroups of non-WNT/non-SHH (group 3 and group 4) medulloblastoma [Table 2].<sup>[35]</sup> Such further stratification of the molecular subgroups has critical biological and clinical implications regarding prognosis and therapeutic options.<sup>[36-43]</sup> This is demonstrated in the subgroup of medulloblastoma arising in very young children with poor prognosis; the standard treatment with chemotherapy is still too high for these young patients<sup>[13,38]</sup> and new trial evidence suggests promising targeted therapies.<sup>[44,45]</sup>

Immunohistochemistry can still be used to discriminate between WNT, SHH, and non-WNT/non-SHH medulloblastomas.<sup>[46]</sup> The WNT-activated group is identified by the nuclear immunoreactivity for beta-catenin, which is expressed in most neoplastic cells; however, some cases can show weak and variable expression. The SHH-activated group is defined by the cytoplasmic immunostaining for GAB1 and YAP1 proteins. Both WNT and SHH medulloblastoma groups show cytoplasmic immunoreactivity for Filamin A. Non-WNT/non-SHH tumors show a cytoplasmic expression for beta-catenin and are immunonegative for GAB1 and YAP1 [Table 2, Figure 1]. However, DNA methylation profiling is considered the standard method for determining medulloblastoma group or subgroup status.<sup>[27,47]</sup>

WHO CNS5 retains the four histological types listed in the 2016 WHO classification i.e., classic, desmoplastic/nodular, medulloblastoma with extensive nodularity, and large cell/anaplastic<sup>[20,36,48,49]</sup> [Figure 2], but compared to 2016 WHO, they have been combined into a single chapter named “medulloblastoma, histologically defined” in which the morphological variation as patterns of a single tumor type



**Figure 1: Anaplastic medulloblastoma, SHH subtype, p53 mutated. (a) H and E. Neoplastic cells show some pleomorphic enlarged bizarre nuclei (20 × magnification). (b) Filamin-A immunostain showing a diffuse cytoplasmic positivity (20 × magnification) (c) Diffuse nuclear expression of p53 (20 ×). (By courtesy of Dr. Cynthia Hawkins, SickKids Hospital, Toronto, Canada)**

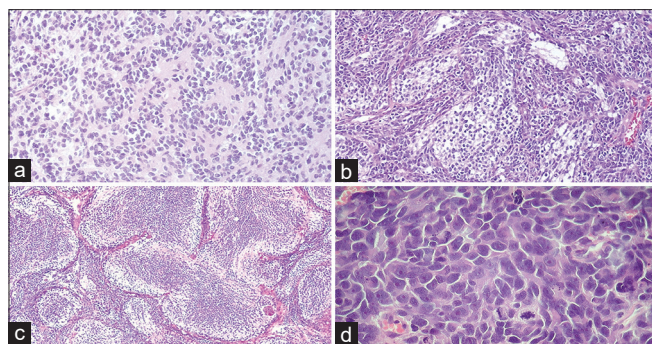
are described. However, it is acknowledged that there is a correlation between the histological patterns and the molecular subgroup i.e., 1) desmoplastic/nodular medulloblastomas and medulloblastomas with extensive nodularity belong to the SHH molecular group and most are in the SHH-1 and SHH-2 sub-groups; 2) WNT tumors have classic morphology, and 3) most large cell/anaplastic tumors are included in either to the SHH-3 subgroup or to the non-WNT/non-SHH (i.e. group 3/4) subgroup 2.<sup>[25,50]</sup> The twelve molecular subgroups are not included in the CNS5.

On the basis of such heterogeneity, medulloblastomas have to be classified in a layered and integrated format containing a combination of histopathological and molecular features. However, in the absence and impossibility to perform molecular analyses, the diagnostic pathologist is always given the option to report such tumors using the not otherwise specified (NOS) and not elsewhere classified (NEC) options.<sup>[51]</sup>

Medulloblastomas can originate in several inherited cancer syndromes<sup>[52,53]</sup> such as Gorlin (*SUFU* and *PTCH1* mutations),<sup>[54-59]</sup> Li-Fraumeni (*TP53* mutations),<sup>[60]</sup> familial adenomatous polyposis (*APC*

**Table 2: Clinico-pathological and genetic characteristics of medulloblastoma groups**

Molecular groups	WNT	SHH		G3	G4
		TP53 wild type	TP53 mutated		
Age	Childhood	Infancy/Adulthood	Childhood	Childhood	All age groups
Location	Central, frequently contiguous to brainstem		Hemispheric (rarely midline)	Midline (filling 4 <sup>th</sup> ventricle)	Midline (filling 4 <sup>th</sup> ventricle)
Histology	Mostly classic, rarely large cell anaplastic	Desmoplastic/Large cell/anaplastic	Nodular	Classic, Large cell anaplastic	Classic, Large cell anaplastic
Immunohistochemistry	Nuclear beta-catenin Filamin A positive YAP1 positive GAB1 negative	P53 negative	Cytoplasmic beta catenin Filamin A positive YAP1 positive GAB1 positive p53 positive	Cytoplasmic beta catenin Filamin A negative YAP1 negative GAB1 negative	
Subgroups	α, β		α, β, γ, δ	II, III, IV (Group 3)    I, V, VII (Group 3/4)	VI, VIII (Group 4)
Genetics	CTNNB1, DDX3X, SMARCA4 and TP53 mutations	PTCH1, SMO, SUFU, TP53 mutation	TERT promoter mutations	MYC, OTX2, SMARCA4, NOTCH, TGF-β mutations	MYCN, KDM6A, CDKNA, mutation, SNCAIP duplications
Chromosomal abnormalities	Monosomy of chromosome 6	9q deletion, 10q loss	MYCN amplification, GLI2 amplification, 17p loss	MYC amplification, isodicentric 17q, 1q gain, 5q and 10q loss	MYC amplification, isodicentric 17q, 8, 10 and 11 loss, 4, 7 17, and 18 gain
Outcome of subgroups (5 years survival)	97% (α), 100% (β)	69.8% (α), 67.3% (β), 88% (γ), 88.5% (δ)		50% (II)    77% (I) 43% (III)    59% (V) 80% (IV)    85% (VII)	81% (VI) 81% (VIII)
Metastasis (%)	12%	20%(α), 33%(β), 9% (γ), 9% (δ)		57% (II)    35% (I) 56% (III)    62% (V) 58% (IV)    45% (VII)	45% (VI) 50% (VIII)



**Figure 2: Different histological types of medulloblastoma (H&E). (a) Classic type (20 ×). (b) Desmoplastic/nodular medulloblastoma (20X). (c) Medulloblastoma with extensive nodularity (10X). (d) Largecell/anaplastic medulloblastoma (40 ×)**

mutations),<sup>[61]</sup> Rubinstein–Taybi (*CREBBP* mutations),<sup>[62]</sup> and Nijmegen (*NBN* mutations).<sup>[63]</sup> A new one has been recently identified, which is listed in WHO CNS5, i.e., *ELP1*-medulloblastoma syndrome. Germ-line mutations of *ELP1* gene can be present in 40% among pediatric patients with SHH medulloblastoma *TP53* wild-type.<sup>[64]</sup>

### Other CNS embryonal tumors

The other embryonal tumors listed in WHO CNS5 are AT/RT; Embryonal tumor with multilayered rosettes (ETMR); CNS neuroblastoma, *FOXR2*-activated, and CNS tumor with *BCOR* internal tandem duplication (ITD). Whereas AT/RT and ETMR were included in previous WHO classifications, CNS neuroblastoma, *FOXR2*-activated, and CNS tumor with *BCOR* ITD are new to CNS5. Moreover, cribriform neuroepithelial

tumor (CRINET) has been introduced as a provisional entity within this category. As for other CNS tumors, the broad designation CNS embryonal tumor NEC or NOS is included for embryonal tumors that lack molecular features for a more specific diagnosis.

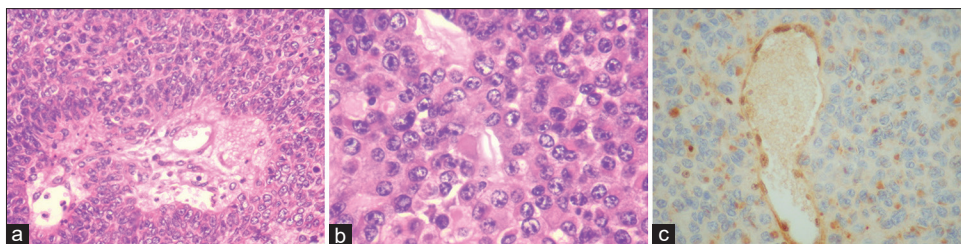
### Atypical teratoid/rhabdoid tumor and cribriform neuroepithelial tumor

The definition of AT/RT in WHO CNS5 practically overlaps that of the previous edition: *a highly malignant composed of poorly differentiated cells showing focal or diffuse rhabdoid features with polyphenotypic differentiation and genetically defined by biallelic inactivation of SMARCB1 (also known as hSNF5, INI1, or BAF47)<sup>[65–70]</sup> or rarely (in <5% of cases) of SMARCA4 (BRG1).[68,71]* In the majority of the cases, the diagnosis of these tumors still relies on the histology and immunohistochemistry showing the typical differentiation along neuroepithelial, epithelial, and mesenchymal lines and, most important, loss of expression of *SMARCB1* (INI1) [Figure 3] or *SMARCA4* (BRG1) in the rare cases with such mutation.

The most important change in CNS5 is the identification of three molecular sub-groups defined by DNA methylation and/or gene expression profiling. These three molecular subgroups are named AT/RT-TYR, AT/RT-SHH, and AT/RT-MYC. Each subgroup delineates different groups of patients in terms of age, site of origin, and *SMARCB1*/chromosome 22 alteration pattern [Table 3].<sup>[72,73]</sup>

AT/RT-SHH tumors (~44%) exhibit an overexpression of proteins involved in the pathways of SHH and Notch signaling.





**Figure 3: AT/RT. (a) H and E. Neoplastic rhabdoid cells display a perivascular arrangement (20 ×). (b) The tumor has medium-sized, round cells with distinct borders, eccentric nuclei, and prominent nucleoli (H and E) (40 ×). (c) INI1 immunostain showing positive endothelial and reactive cells. Tumor cells are negative for INI1 protein (20X)**

**Table 3: Clinico-pathological and genetic characteristics of AT/RT molecular subgroups**

Molecular subgroups	AT/RT-SHH	AT/RT-TYR	AT/RT-MYC
Incidence	44%	34%	22%
Age	2-5 years (median age: 20 months)	0-1 years (median age: 12 months)	>3 years (median age: 27 months)
Location	More frequently supratentorial	More frequently infratentorial	More frequently supratentorial (rarely spinal)
Copy Number Alteration of Chromosome 22	None	Complete loss (monosomy)/partial loss	None
SMARCB1 alterations	Point mutations/Focal deletions	Point mutations/Focal deletions	Extensive deletions
Involved pathway	SHH and NOTCH pathway	BMP and melanosomal pathway	Overexpression of MYC gene and HOX cluster genes

The median age of patients is 20 months and in 67% of cases, they arise in the supratentorial compartment. Compound heterozygous *SMARCB1* point mutations are frequently seen in this group.<sup>[74]</sup>

AT/RT-TYR tumors (~34%) are characterized by an upregulation of proteins involved in the melanosomal pathway (tyrosinase), the bone morphogenetic protein (BMP) pathway, and development-related transcription factors, including *OTX2*. These tumors occur in very young patients (median age: ~12 months) and are localized mainly in the infratentorial compartment. Loss of *SMARCB1* gene is mostly generated by the mutation in one allele and a complete or partial loss of chromosome 22, removes the second allele<sup>[74]</sup>

AT/RT-MYC tumors (~22%) are characterized by the expression of the *MYC* oncogene and *HOX* cluster genes. This group, compared to AT/RT-SHH or AT/RT-TYR groups, affects older patients (median age: ~27 months).<sup>[74]</sup> They are more commonly supratentorial, rarely they can occur in the spinal cord. The rare AT/RTs occurring in adults are confined in the sellar region and also belong to this group.<sup>[75]</sup> Potential immunohistochemical surrogate markers for identification of AT/RT-SHH and AT/RT-TYR subgroups are antibodies against ASCL1 and tyrosinase, respectively.<sup>[72,76]</sup> Moreover, a recent study has found a significant correlation between histological patterns and molecular subgroups.<sup>[77]</sup>

*SMARCB1*-deficient AT/RT can occur in the setting of the rhabdoid tumor predisposition syndrome 1 with a frequency between 26% and 41%, whereas the risk of rhabdoid tumor predisposition syndrome 2 in a patient with a *SMARCA4*-deficient tumor is substantially higher.

In WHO CNS5, cribriform neuroepithelial tumor is a provisional entity distinct from AT/RT and defined as “a nonrhabdoid neuroectodermal tumor characterized by cribriform strands and ribbons and showing loss of nuclear *SMARCB1* expression.” This is a remarkably rare neoplasm occurring mostly in the periventricular areas (lateral, third, and fourth ventricles) in infants (mean age 20 months). Histologically, these are composed of strands and ribbons conferring a cribriform pattern of nonrhabdoid cells with strong positivity for EMA and loss of *SMARCB1* expression. In terms of DNA methylation profiling, the tumor clusters within the AT/RT molecular subtype AT/RT-TYR. There are only a small number of reported cases which thus does not permit to delineate the biological behavior of this lesion. However, small retrospective series have shown significantly longer survival compared to standard AT/RT-TYR cases.

#### Embryonal tumor with multilayered rosettes

The term “embryonal tumor with multilayered rosettes (ETMR)” has been introduced as a unifying diagnosis for tumors with diverse histological designations such as ependymoblastoma, embryonal tumor with abundant neuropil and true rosettes (ETANTR), and medulloepithelioma all characterized by a molecular hallmark i.e., the amplification of the microRNA cluster on chromosome 19 (C19MC) present in ~90% of the ETMR cases.<sup>[78,79]</sup> For this reason, in WHO 2016, the entity was designated as “Embryonal tumor with multilayered rosettes C19MC-altered.” The discovery that tumors lacking the C19MC amplification frequently harbor biallelic *DICER1* mutations, of which the first hit is generally present in the germline of the patients, led to the removal of the term “C19MC-altered” in the nomenclature of this entity in WHO CNS5.

ETMRs more frequently occur in the cerebral hemispheres but they can also develop in the infratentorial compartment

involving the cerebellum and brainstem.<sup>[80-83]</sup> The histological feature of these tumors includes embryonal cells organized in a pseudostratified epithelium around a central area of neuropil containing a lumen to form multilayered mitotically active rosettes [Figure 4a]. The three main histological patterns comprise: embryonal tumor with abundant neuropil and true rosettes (ETANTR), ependyoblastoma, and medulloepithelioma. These three histological patterns, based on DNA methylation profile and gene expression, cluster in the same group, reflecting a different morphological range of the same tumor entity. ETMR with embryonal tumor with abundant neuropil and true rosettes (ETANTR) histology shows a biphasic architecture including more compact areas with hyperchromatic nuclei and scant eosinophilic cytoplasm arranged in a sheet-like pattern along with wide neuropil-like areas with scattered neoplastic neurocytic and ganglion cells. In dense areas, multilayered rosettes are more frequently found. ETMRs with ependyoblastoma histology show large sheets of poorly differentiated rosettes and low neuropil content. ETMR with medulloepithelioma pattern has different patterns including papillary, tubular, or trabecular structures appearing like the primitive neural tube, constituted by neoplastic pseudostratified neuroepithelium with an external [Periodic acid-Schiff (PAS)-positive] limiting membrane. Different differentiation patterns like epithelial, myeloid, osteoid, myoid, or other mesenchymal differentiation, including even melanin pigmented cells can be identified.

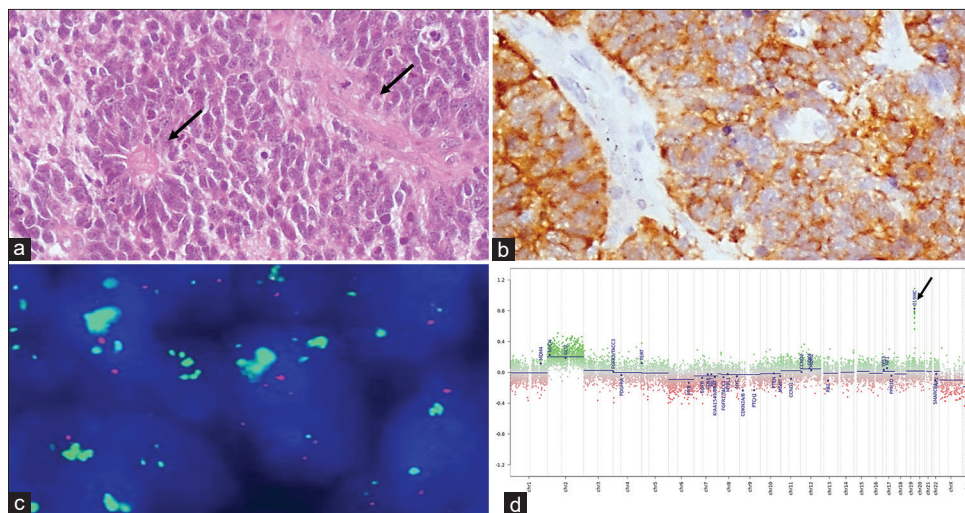
All three histological patterns show a strong and diffuse cytoplasmic immunoreactivity for LIN28A. Such expression can also be observed in some glial, neoplasms, atypical teratoid rhabdoid tumor (AT-RTs), germ cell tumors, and some non-CNS neoplasms.<sup>[84,85]</sup> However, within the appropriate histological setting, LIN28A is a very useful marker for the diagnosis of ETMR [Figure 4b] confirmatory diagnosis which requires the molecular detection of C19MC amplification or *DICER1* mutations.

C19MC microRNA cluster alteration at 19q13.42 has been found only in ETMRs and occurs in approximately 90% of cases<sup>[86,87]</sup> [Figure 4c]. These are usually focal amplifications, but fusions can also occur, generally with *TTYH1*. C19MC alterations can be easily detected by array-based copy-number profiling [Figure 4d] or interphase fluorescence *in situ* hybridization (FISH). The absence of C19MC alteration in ETMR suggests the presence of *DICER1* mutations. Such mutations are observed only in the 5% of C19MC negative ETMR and almost all of these cases are in the setting of a *DICER1* genetic tumor syndrome. Rare ETMRs without a C19MC alteration or *DICER1* mutation should be classified as ETMR NEC. Despite intensive multimodal treatment, the survival rates for ETMR remain very poor.

### CNS neuroblastoma, *FOXR2*-activated

CNS neuroblastoma, *FOXR2* activated (CNS NB-*FOXR2*), is a new entry in WHO CNS5. Its discovery originates from the re-evaluation by DNA methylation analysis of a previous CNS-PNET cohort in which many tumors could be included in specific entities. Additionally, four new entities were delineated based on specific DNA methylation profiles and genetic alterations.<sup>[1,88]</sup> One of these new entities showed morphological similarity with CNS neuroblastoma and harbored chromosomal rearrangements leading to an increased expression of the *forkhead box R2* (*FOXR2*) gene.

CNS NB-*FOXR2* histologically displays embryonal architecture composed of densely packed undifferentiated embryonal cells with hyperchromatic nuclei and inconspicuous cytoplasm arranged in a sheet-like pattern. Vascular pseudorosettes and Homer-Wright rosettes may be encountered. Mitotic Figures and apoptotic bodies are abundant/frequent. Areas of necrosis are commonly present. Some cases show focal neurocytic differentiation and a collection of mature ganglion cells ("ganglioneuroblastoma"). Most of these tumors disclose a strong immunopositivity for



**Figure 4: ETMR. (a) H and E. Neoplastic cells with hyperchromatic nuclei. Multilayered rosettes (arrows) are identified. (20x). (b) Immunohistochemistry for LIN28 showing strong cytoplasmic stain (20x). (c) FISH shows C19MC amplification at 19q13.42 (green signals). (d) Copy number variation analysis with C19MC amplification (arrow)**



OLIG2, whereas GFAP and vimentin are not expressed. Areas with neurocytic/ganglionic differentiation show positivity for synaptophysin [Figure 5a-c]. Overexpression of TTF-1 is also present in most tumors.

The detection of *FOXR2* rearrangements necessitates next-generation sequencing method, however alterations affecting the *FOXR2* locus on chromosome Xp11.21 may be visible by copy-number analysis [Figure 5d]. Nevertheless, the presence of a distinct cluster that includes CNS NB-*FOXR2* by DNA methylation profiling, highly facilitates the diagnosis of these tumors. In contrast to ETMR, patients with CNS NB-*FOXR2* present at an older age, have exclusively supratentorial tumors, and show higher response as well as superior survival rates.<sup>[89]</sup>

### CNS tumor with *BCOR* internal tandem duplication (ITD)

The inclusion in WHO CNS5 of CNS tumors with *BCOR* ITD as embryonal tumors, maybe provisional, in view of the fact that these neoplasms are not definitively neuroectodermal. Exon 15 *BCOR* ITDs have been reported in several histologically similar sarcomas, and therefore there is no consensus as to whether these tumors should be considered neuroepithelial or mesenchymal neoplasms.

They occur mainly in young patients with an age ranging from 0 to 22 years and are usually located in the cerebral or cerebellar hemispheres. They are generally composed of uniform oval or spindle-shaped cells, with round or oval nuclei showing a delicate chromatin pattern. Glioma-like fibrillary areas can be present as well as others with compact fascicular patterns frequently associated with a branching capillary network. The formation of ependymomalike perivascular pseudorosettes is quite characteristic, and myxoid or microcystic areas are often

encountered. Palisading necrosis is commonly observed. Mitoses are frequent. For such protean histology, the differential diagnosis includes high-grade gliomas, ependymomas, and embryonal tumors. By immunohistochemistry, the constant expression of vimentin and CD56 associated with negativity or scarce expression of OLIG2, GFAP, or S100 support the diagnosis [Figure 6].<sup>[88]</sup> Widespread strong nuclear expression of *BCOR* is a sensitive marker, but it is not specific because it may also occur in other tumors, such as astroblastomas<sup>[90]</sup> or solitary fibrous tumors.<sup>[91]</sup>

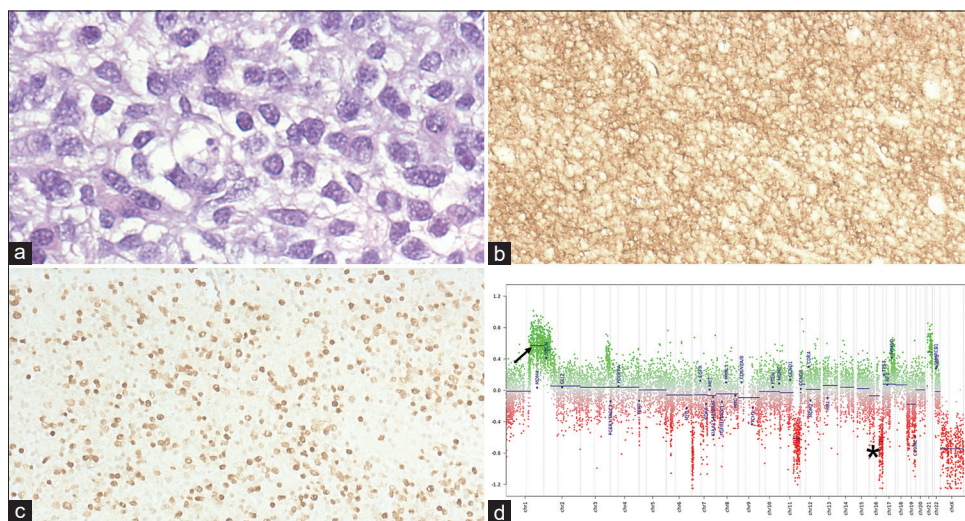
The definitive diagnosis relies on the molecular detection of a heterozygous ITD in exon 15 of the *BCOR* gene. As for other embryonal tumors, DNA methylation and gene expression profiles are reliable methods to identify CNS tumors with *BCOR* ITD from other CNS tumors.<sup>[1]</sup> Although the clinical data are limited due to the rarity, the overall survival of the patients harboring these tumors is poor.<sup>[90]</sup>

### CNS embryonal tumor NOS

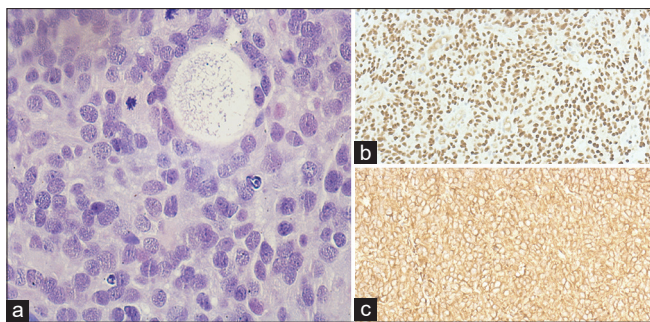
With this term, WHO CNS5 defines a *CNS tumor with embryonal histology and immunophenotype in which no alteration that would classify it as one of the molecularly defined CNS embryonal tumors can be detected or cases that, for any reason, are not susceptible to analysis.*

### CONCLUSIONS

All the classification systems have to be considered a work in progress, which provide both great opportunities in terms of research and therapeutic challenges. CNS5 exemplifies the concept that today the pathological diagnosis of CNS embryonal tumors is the result of a complex integration of histology, immunohistochemistry, and molecular features, and such diagnosis represents the basis for clinical decision making.



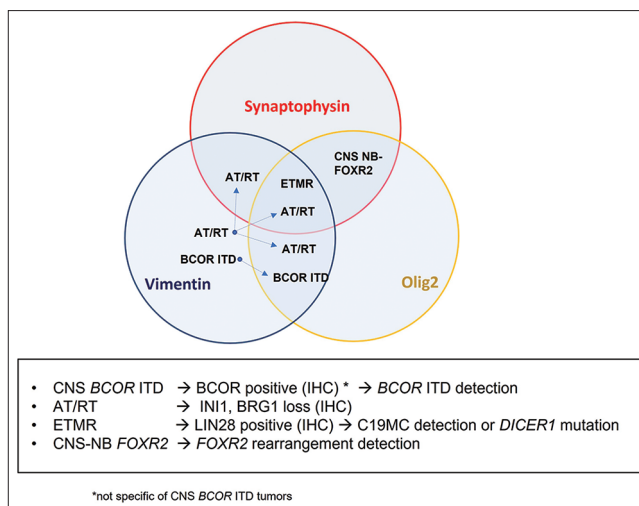
**Figure 5: CNS neuroblastoma, FOXR2-activated. (a) H and E. Neoplastic cells with small, round nuclei surrounded by a clear halo (40 ×). (b) Synaptophysin immunopositivity (10 ×). (c) Olig2 immunopositivity (10 ×). (d) Copy number variation. Gain of chromosome 1q (arrow) and focal or total loss of 16q (star)**



**Figure 6: CNS tumor with BCOR internal tandem duplication (ITD). (a) H and E. Tumor cells show an oligo-like aspect with monotonous round to oval nuclei, fine chromatin, and indistinct nucleoli. Evident some microcystic formation (40 ×). (b) Nuclear BCOR immunostaining (10 ×). (c) Diffuse immunopositivity for vimentin (10 ×)**

For nonmedulloblastoma tumors, a useful approach could be to start using three simple antibodies (synaptophysin, vimentin, and Olig2). They can give initial information and subsequent suggestions for the next more appropriate testing. So, for example, in the context of a morphologic embryonal neoplasm, the expression of Olig2 and synaptophysin should lead to the suspicion of a CNS NB-*FOXR2*. In this case, the next step should be the molecular documentation of the *FOXR2* rearrangement. Tumors presenting with undifferentiated small neoplastic cells and multilayered rosettes showing immunopositivity for synaptophysin, Olig2 and vimentin are suggestive of ETMR. In this case, the immunohistochemical analysis for LIN28 should be performed; in the case of positive expression, the molecular test (sequencing or FISH test) is mandatory to confirm the presence of C19MC alteration. In the case of positivity for vimentin, a combination of vimentin and Olig2 in the context of a poorly differentiated neoplasm, immunostaining for BCOR can be useful, even though this antibody is not specific and can be expressed by other nonembryonal tumors. Furthermore, in this case, molecular analysis for the detection of *BCOR* ITD is required. In the case of a neoplasm with rhabdoid morphology and a polyphenotypic differentiation, the expression of vimentin alone or in combination with synaptophysin and Olig2 can suggest a diagnosis of AT/RT. In this last case, the loss of INI1 or BRG1 protein supports the diagnosis of AT/RT [Figure 7].

For medulloblastoma, WHO CNS5 highlights the clinical and biological heterogeneity of this neoplasm. The integration of molecular information is an essential component of the classification although it raises some controversies and challenges. On one hand, the discovery of numerous molecular subgroups opens the possibility to the development of more specific target therapies, however, clinical trials on a small group of patients would not provide significant results. Also treating uniformly tumors harboring different molecular alterations would lead to the loss of critical therapeutic implications. So far, treatment for non medulloblastoma embryonal tumors remains the removal surgery followed by further additional treatments when required like craniospinal radiation as well as chemotherapy and eventually



**Figure 7: Diagnostic algorithm for approaching diagnosis of non-medulloblastoma embryonal tumors, including the integration of immunohistochemical and molecular analysis**

most effective molecular-targeted therapies<sup>[92]</sup> However, the increasing number of molecularly defined tumors included in a specific entity represents the basis to develop precise treatments for these children.

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### Conflicts of interest

There are no conflicts of interest.

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