Practical Molecular Pathology and Histopathology of Embryonal Tumors

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KEYWORDS

• Embryonal tumors • Molecular pathology • Histopathology • WHO classification

ABSTRACT

There have been significant improvements in understanding of embryonal tumors of the central nervous system (CNS) in recent years. These advances are most likely to influence the diagnostic algorithms and methodology currently proposed by the World Health Organization (WHO) classification scheme. Molecular evidence suggests that the tumors presumed to be specific entities within the CNS/primitive neuroectodermal tumors spectrum are likely to be reclassified. All these developments compel reassessing current status and expectations from the upcoming WHO classification efforts. This review provides a synopsis of current developments and a practical algorithm for the work-up of these tumors in practice.

EMBRYONAL TUMORS IN WORLD HEALTH ORGANIZATION CLASSIFICATION

The original works of Cushing and Bailey were the first systematic efforts in the classification of tumors of the central nervous system (CNS).[1,2] In these seminal attempts, these investigators provided a rational and clinically relevant classification of intracranial tumors. Both investigators, together and separately, have incorporated an embryonal cell of origin hypothesis and provided the first nomenclature of embryonal, or blastic, tumors that has prevailed until present day.[3,4] In neither of the initial classification attempts of this school did embryonal tumors constitute a distinct category but were distributed among various categories of the scheme. The subsequent attempts, including the first classification of the World Health Organization (WHO), began segregating tumors into the "poorly differentiated and embryonal tumors" category.[5,6] This version of the classification scheme included glioblastoma and medulloblastoma within the same category of tumors.[2,5] After the publication of the first edition of the WHO, ensuing efforts in 1988 and 1990 led to a second classification attempt in 1993, in which the tumor grouping included morphology codes of the *International Classification of Diseases for Oncology* and the Systematized Nomenclature of Medicine for the first time.[7] This classification attempt clearly distinguished the embryonal tumor category from the glial and neuronal tumors as well as pineal parenchymal tumors, including pineoblastoma.

The classifications in 2000 and 2007 further refined the paradigms adopted in the 1993 edition and presented data for additional distinct entities.[1,8] Atypical teratoid/rhabdoid tumor (AT/RT) and large cell/anaplastic medulloblastoma (LC/A) were added in 2000, and the CNS primitive neuroectodermal tumors (PNETs) group was added in 2007.[1,8] The latter category included a group of tumor types, such as ganglioneuroblastoma, neuroblastoma, medulloepithelioma, and ependymoblastoma, that were considered distinct entities in 2000. The 2007 classification also included the CNS prefix to the PNETs category to enable a

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clear distinction from the tumors with the same name that occur at extracerebral sites.

Much has evolved since the publication of the last WHO classification scheme, and the additional information and insight gained during this period have affected almost all the entities in the embryonal tumor category. This article briefly summarizes these advances and the probable changes in the upcoming revision of the classification scheme.

MEDULLOBLASTOMAS

Medulloblastoma is the most common pediatric malignant brain tumor. This embryonal neoplasm of the cerebellum can be subdivided into several histopathologic variants according to the 2007 WHO classification scheme.[1] These variants include

- Classic medulloblastoma
- Desmoplastic/nodular medulloblastoma
- Medulloblastoma with extensive nodularity (MBEN)
- Anaplastic medulloblastoma
- Large cell medulloblastoma

Although medulloblastoma is a highly malignant tumor, classified as WHO grade IV, LC/As tend to be associated with a significantly worse prognosis and have a higher frequency of metastatic disease than other medulloblastomas.[9–11] With current therapeutic management, including surgical resection, craniospinal radiation, and chemotherapy, a majority of patients can be cured of their tumor, even though most have long-term disabilities.[12–14] These disabilities can be attributed to both their underlying disease and to the treatment.

RISK STRATIFICATION AND PROGNOSTICATION FOR MEDULLOBLASTOMAS

Because therapy is not benign, risk stratification is essential. Currently, risk stratification is based on histologic subgroup and clinical variables. Tumors with leptomeningeal metastases and incomplete surgical resection confer a higher risk. In addition, specific molecular alterations have been associated with poor prognosis, including isochromosome 17q, loss of 17p, and amplification of *MYC* or *MYCN*.[11,15,16] Similarly, nuclear accumulation of β-catenin (indicative of canonical WNT pathway activation) and monosomy 6 have been associated with a better prognosis.[11,17] Despite these advances, accurate assessment of disease risk for individual patients can be difficult.

Several researchers have used molecular strategies, including transcriptional profiling, to improve disease prognostication and stratification into molecular subgroups. In 2010, a consensus conference was held in which 4 subgroups of medulloblastoma were defined with unique demographic, clinical, transcriptional, and genetic differences.[18] Later, in 2013, a meeting of the International Medulloblastoma Working Group[19] recommended that the WHO classification of medulloblastoma be revised to incorporate both histopathologic and molecular categorization.

Because the histopathologic variants fit within more than 1 molecular subgroup, this discussion begins with the characteristic features of the 4 well-known histopathologic variants.[1,20] Many studies have helped define characteristic demographic, clinical, and molecular features of these subtypes, refining their prognostic implications. Then, the molecular subgroups are focused on, summarizing their demographic and clinical differences and the histopathologic variants they encompass. The currently accepted variants within the entity of medulloblastoma are briefly defined.

CLASSIC MEDULLOBLASTOMA

The classic variant is the most common and is characterized by a highly cellular, typically patternless neoplasm composed of highly proliferative cells with small to medium-sized nuclei, relatively unapparent nucleoli, nuclear molding, and minimal cytoplasm (**Fig. 1**A). Necrosis and karyorrhexis are common. As with all medulloblastomas, neuronal differentiation may be observed and can be highlighted by immunohistochemistry.

VARIANT: DESMOPLASTIC/NODULAR MEDULLOBLASTOMA

The desmoplastic/nodular variant is defined by striking nodules of differentiation resulting in reticulin-poor intranodular foci surrounded by densely cellular, proliferative reticulin-rich internodular regions (see **Fig. 1**B). These tumors are most often located in the lateral cerebellar hemispheres in patients ages 3 to 16 years. They are often located laterally within the hemispheres (see **Fig. 1**C) unlike the WNT group (group 1) tumors that are located in the midline.

VARIANT: MEDULLOBLASTOMA WITH EXTENSIVE NODULARITY

MBEN is largely composed of the reticulin-free pale areas and is most common in infants. MBEN has typical radiologic features with multiple nodules, often referred to as a bunch of grapes appearance (see **Fig. 1**D).