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Primitive Neuroectodermal Tumor

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Introduction

In 2016, the World Health Organization (WHO) published a revised classification of central nervous system (CNS) tumors using molecular parameters.[1] In this classification, some tumors previously recognized in the 2007 classification had been renamed or eliminated. The primitive neuroectodermal tumor (PNET) is no longer recognized. CNS embryonal tumors are now classified using specific genetic/molecular characteristics. Using molecular analysis, many tumors that were previously reported as PNET are now reclassified into know tumors with specific genetic characteristics.

Medulloblastomas are the most common embryonal tumors and have their own genetic/molecular defined groups (SHH-activated TP53-mutant, SHH-activated TP53-wildtype, WNT-activated, non-SHH/WNT group three, and non-SHH/WNT group four) in addition to their histologically defined groups (classic, desmoplastic/nodular, medulloblastoma with extensive nodularity, and large cell/anaplastic). A combination of the genetic profile and the histology determines the prognosis of these tumors.[1] The sonic hedgehog protein, important in cell specialization and growth, is encoded in the SHH gene at chromosome 7. The WNT gene family in the chromosome 12q13 region encode for signaling proteins that regulate cell proliferation, cell fate, and embryogenesis.

All other embryonal tumors are classified depending if they have an amplification of the C19MC region (19q13.42) on chromosome 19. If they have the amplification, they are called embryonal tumor with multilayered rosettes, C19MC-altered (WHO 9478/3*). If they do not have the amplification, they are called embryonal tumor with multilayered rosettes, NOS (WHO 9478/3). The other embryonal tumors are classified as medulloepithelioma (9501/3), CNS neuroblastoma (9500/3), CNS ganglioneuroblastoma (9490/3), and atypical teratoid/rhabdoid tumor (ATRT) with alterations of INI1 or in rare occasions BRG1.

Immunohistochemical staining for INI1 or BRG1 expression is used to distinguish them. Those tumors that do not have alterations of either INI1 or BRG1 are classified as embryonal tumors with rhabdoid features (WHO 9508/3). Those embryonal tumors without amplification of the C19MC, no alterations of INI1 or BRG1, and no rosettes, are called embryonal tumor, NOS (WHO 9473/3). This last group is a wastebasket category for the tumors previously called PNET, which can not be classified under a genetic/molecular group.[1] In tumors with the “NOS” designation (not otherwise specified), there is insufficient information for classification. Some of these tumors were previously named embryonal tumor with abundant neuropil and true rosettes.

Concurrent with the publication of the WHO 2016 classification, a group recognized four new categories for PNET.[2] They reviewed their previously classified PNET database and found that based on molecular analysis of the tumor samples, most of them were indistinguishable from known CNS supratentorial tumors and were classified into those known CNS supratentorial tumors. The small group of other tumors which can not be attributed to known CNS supratentorial tumors were classified into the four new categories. The new categories include CNS neuroblastoma with Forkhead Box R2 (FOXR2) activation, CNS Ewing sarcoma family tumor with CIC alteration, CNS high-grade

neuroepithelial tumor with meningioma 1 gene (MN1) alteration, and CNS high-grade neuroepithelial tumor with BCL6 Corepressor (BCOR) alteration. The small number of tumors that did not show any molecular specificity to be included in a specific category were called CNS embryonal tumors, NOS. This group is similar to the wastebasket category of the WHO 2016 classification. The significance of these results have yet to be analyzed and incorporated in a future WHO classification. These four new groups had also been confirmed by a Polish study in 2020.[3]

Etiology

The PNET terminology has been removed from the CNS tumors with the new 2016 WHO revised classification. They were aggressive tumors from poorly differentiated embryonic cells in young children, but on rare occasions affecting adolescents and adults.

Tumors are now classified according to their molecular characteristics. Embryonal tumors are primarily classified depending if they have on chromosome 19 an amplification of the C19MC region (19q13.42). Atypical teratoid/rhabdoid tumor tumors have an alteration of INI1 or, on rare occasions, BRG1. Other embryonal tumors have FOXR2 activation, CIC alteration, MN1 alteration, and BCOR alteration. The SMARCB1 (also known as INI1, BAF47, hSNF5,) located on chromosome 22 at locus 22q11.2 is important for the SWI/SNF chromatin-remodeling complex.[4] The ATPase subunit SMARCA4 (BRG1) located on chromosome 19p13.2 is another SWI/SNF chromatin-remodeling complex member.[5]

Those embryonal tumors that no amplification of the C19MC, no alterations of INI1 or BRG1, or no rosettes are identified, are called embryonal tumor, NOS (WHO 9473/3). At present, there are no molecular or genetic alterations associated with them. These embryonal tumors have to be well investigated. This is an exclusion diagnosis. They have to be differentiated from supratentorial ependymoma, high-grade glioma, embryonal tumor with multilayered rosettes, and ATRT based on their specific genetic alterations.[6]

Epidemiology

Primary CNS tumors are the second most common tumor in children and adolescents after leukemia.[7] Approximately 20% of pediatric brain tumors are CNS embryonal tumors. This number includes all the medulloblastomas and all other embryonal tumors.[7][8] Embryonal tumors are the most common CNS tumor in children aged 0–4 years (13.1%), and the fifth most common in children and adolescents age 0 to 19 years (10.1%).[9] The CNS embryonal tumors have a preference for children below the age of 4 and are more common in females.[10][11][12] Supratentorial embryonal tumors are found in older children with a mean age of 8.4 years, with a 2.3:1 female to male predominance.[11][12]

Using the data available for CNS tumors diagnosed in the United States in the years 2012-2016, and excluding medulloblastoma, the incidence of PNET is 0.15 per 100,000 children age 0 to 4, 0.05 per 100,000 children age 5 to 9, 0.04 per 100,000 children age 10 to 14, and 0.03 per 100,000 adolescents age 15 to 19 years.[9] The 10-year survival estimates for PNET is 30%.

The incidence of ATRT is 0.32 per 100,000 children ages 0 and 4 and 0.03 per 100,000 children ages 5 to 9 years. Very few cases are diagnosed after nine years of age. The 10-year survival estimates for ATRT is 37%.[9] There is no significant difference between males and females for the incidence of ATRT in children age 0 to 14.[9]

The high-grade neuroepithelial tumor with BCOR alteration is an extremely rare tumor, with only 24 cases reported. The four-year survival is 50%.[13] They are treated similarly to other embryonal tumors.

A study investigating previously histological supratentorial PNET, which reanalyzed them using molecular parameters, found that the diagnosis changed in 71%.[12] A supratentorial lesion has an increased probability of being a high-grade glioma or ependymoma if confused with a supratentorial PNET. DNA methylation profile defines the diagnosis.[14] In infratentorial lesions, medulloblastoma and ependymoma have to be excluded first. They studied

brain magnetic resonance imaging (MRI) characteristics of embryonal tumors, which distinguished them from other molecular diagnosed tumors and found the embryonal tumors have similar edema changes, definition of margins, and size as the non-embryonal tumors and are thus radiologically indistinguishable.

Histopathology

All embryonal tumors are classified as WHO IV.[11] The term PNET is not used anymore. The genetic/molecular analysis of each tumor is essential. The histopathological changes are still important for the initial recognition of the tumor and the intraoperative consultation. Immunohistochemical staining shows specific characteristics in each tumor.

Embryonal tumor with multilayered rosettes shows abundant neuropil and true rosettes, and have amplification of the C19MC region on chromosome 19.[10] They show small multilayered round blue cells with pseudostratified neuroepithelium around a central lumen, which can be empty or contain eosinophilic debris. The nucleus of cells is away from the lumen. Histochemistry is positive for vimentin, cytokeratin, and CD99. It can be focally positive for epithelial membrane antigen (EMA). Synaptophysin, neuron-specific protein, and neurofilament protein are positive for the neuropil. Those tumors classified as embryonal tumors, NOS, should be closely worked up because they may be classified into other tumor entities using current diagnostic techniques.[15] The Ki-67 labeling index is very high.

ATRT usually shows a loss of SMARCB1 (INI1) protein immunoreactivity. They have three groups (ATRT-TYR frequent at infratentorial regions in very young children, ATRTMYC prevalent at the supratentorial area in older children, ATRT-SHH at both ages).[6] They can be positive for EMA and vimentin.

CNS neuroblastoma with FOXR2 activation is highly cellular with small cells with hyperchromatic nuclei surrounded by a clear halo. Areas of neuropil, neurocytic cells, or ganglion cells are seen. Vascular pseudorosettes, nuclear palisades, and Homer Wright rosettes are commonly found. It can have microvascular proliferation.

CNS Ewing sarcoma family tumor with CIC alteration is densely cellular with small round cells. The tumor has both alveolar and fascicular patterns of growth. It does not have markers of differentiation.[2][3]

CNS high-grade neuroepithelial tumor with MN1 alteration shows a mixture of solid and pseudopapillary patterns with pericellular hyalinization. Commonly expressed glial fibrillary acidic protein (GFAP).

CNS high-grade neuroepithelial tumor with BCOR alteration shows a combination of spindle to oval cells with perivascular pseudorosettes and fibrillary processes. Commonly expressed GFAP. They are highly cellular with a thin-walled capillary network.[2][3]

Medulloepithelioma show neuroepithelial cells with papillary arrangement that may mimic the embryonic neural tube. It can have necrosis and hemorrhage.

History and Physical

Patients with embryonal tumors usually present with signs of increased intracranial pressure, which may include headache, nausea, vomiting, irritability, and lethargy in decreasing order of frequency.[8] They can also show visual problems, seizures, hemiparesis, cerebellar signs, and cranial nerve palsies.

The location of the tumor, supratentorial or infratentorial, is important for the manifestation of symptoms. Those with an infratentorial location usually develop hydrocephalus with headache, vomiting, irritability, and lethargy. Ataxia or other cerebellar signs and cranial nerve palsies are common. They rarely have seizures. In supratentorial locations, vomiting, seizures, and headaches are common. Hemiparesis is present if the tumor affects the cortical motor areas or the descending tracts. The presentation is also affected by age. Younger patients present irritability, vomiting, and visual problems. Those older than three years usually show headaches, vomiting, and ataxia.[8]

These aggressive tumors have a short prediagnosis interval between the first symptoms and the radiological diagnosis, with a median of 20 days.[8] Infratentorial tumors, high-grade tumors, and those in younger patients have the shortest

intervals.

A complete physical examination with emphasis on the neurological evaluation is essential. The neuro-ophthalmologist must evaluate visual problems as they are challenging to identify in younger patients.

Evaluation

Brain MRI shows a large, demarcated, solid mass with surrounding edema, often with significant mass effect. On T1-weighted images, they are hypointense but sometimes can be isointense; on T2-weighted images, they are isointense to hypertense, and the T1-weighted images with contrast shows patchy contrast enhancement.[10] Some tumors can show areas with blood products, microcalcifications, and necrotic-cystic components. They have restricted diffusion due to the high cellularity of the tumor. These characteristics are similar to high-grade gliomas, making molecular diagnosis very important.

Magnetic resonance spectroscopy shows a choline peak with reduced N-acetyl-aspartate and a high ratio of choline/aspartate.[10][13]

Spinal MRI is usually required for the detection of seeding and prognosis.

Treatment / Management

The current most effective therapy in these tumors is triple therapy, which is surgical resection plus radiation and chemotherapy.[7][16] Gross total resection is always attempted as it provides better outcomes.[13] Craniospinal radiation is usually given due to the high incidence of distant leptomeningeal metastases and spinal seeding. It has been noted that long radiotherapy treatment produced the worst outcome when compared to a shorter course, especially in medulloblastomas.[17] This has yet to be proven for other embryonal tumors. This phenomenon is thought to be due to repopulation in fast-proliferating tumors. Radiotherapy is given in the 50 to 60 Gy range.

Chemotherapy varies with each protocol, but a combination of vincristine, cisplatinum, cyclophosphamide, etoposide is common. Bevacizumab is used to block the vascular endothelial growth factor. Intrathecal methotrexate and topotecan can be included in the treatment protocol. Myeloablative chemotherapy has been used in some cases, followed by hematogenic stem cell rescue.

Differential Diagnosis

ATRT: Usually found in patients under the age of two.

Ependymomas: Usually have no restriction.

High-grade gliomas: The majority are indistinguishable, and diagnosis is based on molecular characteristics. Some can have vascular endothelial proliferation and pseudopalisading necrosis.

Medulloblastomas: Have their own genetic/molecular defined groups.

Medulloepitheliomas: Usually found in very young patients.

Prognosis

Due to leptomeningeal dissemination and possible extraneural metastasis, prognosis is poor. Approximately 32% of supratentorial embryonal tumors have metastases to the spine.[12]

Several factors influence a poor prognosis, including delay in the diagnosis, poor general status, inadequate initial response to treatment.[7][16] More extensive larger tumors and those with poorly defined margins have the worst overall survival.[12]

Supratentorial high-grade glioma has a 12% five-year overall survival, which is significantly worse compared to

embryonal tumors (pineoblastomas included) with a 78.5% five-year overall survival.[18] This marked difference is crucial; therefore, it is imperative to obtain a correct molecular diagnosis to orient the patient and the family about the prognosis. The ATRT median survival is less than two years.

Complications

These tumors impose a severe burden on the patient, and many significant complications occur as a consequence of the tumor and the triple therapy received. Surgery is challenging and sometimes tricky. Radiation and chemotherapy contribute to substantial morbidity due to the ionizing radiation's effects and the adverse effects of the chemotherapeutic agents.

- Motor deficits
- Sensory deficits
- Seizures
- Neurocognitive problems
- Developmental delay
- Learning delays
- Neuroendocrine deficit (delayed puberty, hypothyroidism, low growth hormone levels)

Consultations

Consultations may be required from neuropathologists, pediatricians, neurosurgeons, hematologist-oncologists, radiation oncologists, and endocrinologists.

Deterrence and Patient Education

The previously called CNS PNET is no longer recognized. Nowadays, most tumors can be assigned to a specific category based on molecular analysis. A careful histopathological examination is required. As many high-grade gliomas are now excluded, the prognosis is nowadays better for the patient. Anyhow, the prognosis for these tumors is poor. Counseling for the patient and the parents is necessary as many of them will suffer the burden of the disease.

Enhancing Healthcare Team Outcomes

Proper diagnosis of the tumor has significant implications in the patient's clinical course and outcome.[7] Treatment and prognosis are dependent on the molecular classification of the tumor. The neurosurgeon will perform the biopsy or tumor removal while the neuropathologist and histopathologist are essential for the correct identification and diagnosis. The information obtained will be shared with the neuro-oncologist and radiation oncologist to provide the combined treatment that most of these tumors require. Nurses will assist with education and post-operative patient care, while pharmacists will give the correct and adequate chemotherapy agent to be administered to the patient.

Many patients develop hypopituitarism secondary to chemotherapy and radiotherapy; therefore, the endocrinologist has an essential role in documenting and correcting these deficiencies. Collaboration shared decision making and communication are crucial elements for the outcome in these patients. The interprofessional care provided must use an integrated care pathway combined with an evidence-based approach. Prompt recognition of signs and symptoms of the disease can aid in the prognosis and outcome.

Questions

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