WNT-Activated Medulloblastoma in A 6-Year-Old Boy

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Abstract

Background: Medulloblastoma is the most common malignant brain tumor of childhood. Prognosis is mostly favorable, but may be affected by histological and molecular subtypes. Long-term therapy-related morbidity also remains a significant concern.

Case Presentation: A 6-year-old boy with brainstem/midline cerebellum tumor. Histopathology found area of necrosis, sheets of malignant undifferentiated round cells with hyperchromatic nuclei and scanty cytoplasm, no nodule and no anaplasia. Immunohistochemistry found p53 wild-type staining pattern along with β-catenin diffuse cytoplasmic and focal nuclear staining. This indicated a diagnosis of WNT-activated medulloblastoma, World Health Organization (WHO) grade IV, with classic histological features.

Discussion: WNT-activated medulloblastomas with classic histological features and no anaplasia were reported to have the most favorable prognosis. The current patient showed negative staining for GFAP, Olig2, EMA, H3K27M, EZHIP, and LIN28A, with retained staining for INI1 and BRG1, thus excluding several differential diagnosis such as atypical teratoid/rhabdoid tumor, embryonal tumor with multilayered rosettes, small cell glioblastoma, Ewing sarcoma, high-grade neuroepithelial tumor with BCOR alteration or diffuse midline glioma. Histopathology in combination with immunohistochemical and molecular subtyping of medulloblastoma can help to refine diagnosis, exclude differential diagnosis, and improve counseling in regards to overall prognosis.

Introduction

Medulloblastoma is defined by the WHO as an embryonal neuroepi¬thelial tumor arising in the cerebellum or dorsal brainstem, presenting mainly in childhood and consisting of densly packed small round undifferentiated cells with mild to moderate nuclear pleopmorphism and a high mitotic count.[1] This condition is the most common malignant brain tumor of childhood.[2] In the United States, approximately 350 new pediatric cases of medulloblastoma are diagnosed every year, which represents about 30% of all pediatric brain tumors and 7–10% of all brain tumors.[3] The incidence of medulloblastoma is estimated to be 0.7 per 100 000 children per year with a male predominance, wherein the relative risk is 1.5 times higher in males. They can also occur in adults, although more than 70% of all medulloblastoma cases are found in children younger than 18 years old.[1,4] The majority of cases arise in children with a median age of 9 years, and a peak in

incidence between the ages of 3 and 7 years.[5]

This condition was initially described as cerebellar glioma until Bailey and Cushing named it medulloblastoma in 1925.[6] However, medulloblastoma has now been included in the group of embryonal neuroepithelial tumor (grade IV) of the World Health Organization (WHO) classification.[7] In modern classification, medulloblastoma represents a heterogeneous tumor with multiple subtypes. Medulloblastoma share a primitive embryonal phenotype, composed of malignant tumor cells which are dominated by neuronal antigen expression.[5] This highly invasive embryonal neuroepithelial tumor has a tendency to disseminate throughout the central nervous system early in its evolution. Prognosis is mostly favorable with a 5-year overall survival of approximately 75%, however, this might be affected by the histological and molecular subtypes, and long-term therapy-related morbidity also remains a significant concern.[5,8]

Diagnosis is mostly based on imaging and histopathological findings, while immunohistochemistry and molecular analysis can help to characterize the molecular subtype of medulloblastoma. This molecular characterization of medulloblastoma can help to better assess the risk or prognosis, and to refine treatment options.[5,8,9] Combination of histologic findings and immunohisto-chemistry may also help to exclude possible differential diagnosis.5 In view of that, this article will report a case of WNT-activated medulloblastoma in a 6-year-old boy with the main focus on the histopathological and immunohisto-chemical findings.

Case Report

A brainstem/midline cerebellum tumor tissue biopsy from a 6-year-old boy was evaluated in the histopathology laboratory. Routine H&E staining, special staining and immunohistochemical studies were performed after formalin fixation and paraffin-embedding. Light microscopy examination of the sections showed some brain tissue and tumor with extensive area of necrosis. Viable areas of tumor showed sheets of malignant undifferentiated round cells with hyperchromatic nuclei and scanty cytoplasm. No definite nodule formation can be seen. No anaplasia was seen. Mitoses were easily identified.

Immunohistochemical stains showed patchy reactivity for synaptophysin. There was negative staining for glial fibrillary acid protein (GFAP), OLIG2, epithelial membrane antigen (EMA), H3K27M, EZHIP, and LIN28A. There was retained staining for INI1 and BRG1. P53 showed a wild-type staining pattern. Beta-catenin showed diffuse cytoplasmic and focal nuclear staining. The NanoString expression profiling classifies this tumor as WNT activated

Discussion

A 6-year-old boy with a brainstem/ midline cerebellum tumor was diagnosis with WNT-activated medulloblastoma WHO Grade IV based on histologic findings and results of immunohisto-chemical studies. This tumor showed classic histological features with extensive area of necrosis and sheets of malignant undifferentiated round cells with hyper-chromatic nuclei and scanty cytoplasm. Neither definite nodule formation nor anaplasia was seen, and mitoses were easily identified. WNT-activated medullo-blastoma accounts approximately for 10% of all cases, is typically found in children between the age of 7 and 14 years old, and has an excellent prognosis with standard therapeutic approaches.[7,10]

Medulloblastoma is a high-grade embryonal neoplasm that composed of small round undifferentiated cells disposed in densely packed groupings and exhibits mild to moderate nuclear pleomorphism and a high mitotic index.[7,10] This primitive, small round blue cell tumor of the neuronal lineage may also demonstrates scattered apoptotic cells and foci of necrosis.

Neuronal differentiation is evidenced by diffuse synaptophysin positivity in most tumors, although focal glial, melanotic, or myogenic differentiation can be observed. Histologic subtypes of medulloblastoma include classic, large cell, anaplastic, nodular/desmoplastic, and extensive nodularity. The great majority of WNT-activated medulloblastoma has classic morphology at light microscopy, as was the case in the current patient, which denotes a low-risk tumor. The classic variant are by far the most frequent encountered in clinical practice, accounting for 72% of all reported medulloblastoma cases.[5,7]

Tumors with classic histology are characterized by cells with minimal cytoplasm and dense basophilic nuclei present in diffuse sheets. Homer Wright (neuroblastic) rosettes may also be seen.[4] Intrinsic desmoplasia is rare in classic variant tumors, and when desmoplasia presents it is typically associated with involvement of the leptomeninges by tumor. Similarly, nodules of differentiation are rare, and when present are not outlined by pericellular collagen as detected by reticulin staining.[5]

This tumor did not show any anaplastic features, and only very few cases of WNT-activated medulloblastoma were reported to show large cell/anaplastic pattern.[10] Cytological pleomorphism, increased nuclear size, brisk mitotic activity, and cell wrapping are considered as the key features of anaplasia in medulloblastomas. Anaplasia has been reported to be associated with poor prognosis in patients with medullo-blastoma. An increasing degree of anaplasia is significantly associated with shorter relapse-free survival time. Slight anaplasia might not influence prognosis, but patients with moderate and severe anaplasia were reported to have significantly worse outcome.[11]

Beyond histology, medulloblastoma classification may also be based on molecular differences and signaling pathways driving tumor development. Gene expression and methylation profiling is the gold standard for defining molecular groups of medulloblastoma.[10] The 2016 World Health Organization Classification of Tumors of the Central Nervous System has divided medulloblastoma into four molecular subtypes: WNT-activated, sonic hedgehog (SHH)-activated, group 3, and group 4.[7] Immunohistochemical markers help stratify medulloblastomas into each of the molecular subgroups: WNT-activated tumors typically show classic histology and immunostaining positive for β-catenin aberrantly located in cell nuclei; SHH-activated frequently show nodular/ desmoplastic histology and immuno-staining positive for GAB1; Group 3 and Group 4 tumors commonly have either classic or large cell/anaplastic histologic features and negative GAB1 and nuclear β-catenin immunostaining.[12]

WNT-activated tumors are characterized by expression of WNT pathway genes, contain mutations in exon 3 of the CTTNB1 gene in approximately 85%–90% cases, and exhibit loss or partial loss of chromosome 6 in 85%–90% cases. APC mutations can be identified in a high proportion of WNT-activated medulloblastoma lacking CTTNB1 mutations.[5] Other genes frequently mutated in this molecular subtype include TP53 (12.5% cases), SMARCA4 (27% cases), KMT2D (12.5% cases) and DDX3X (50% cases).[5,10,13,14] Around 85% MDB that are characterized by WNT pathway activation show monosomy 6 and/or harbor a CTNNB1 mutation in exon 3, and these genetic alterations determine the positive immunoexpression for beta-catenin antibodies in tumor cell nuclei.[10] The current patient showed a wild-type staining pattern of p53 expression. This TP53 mutations do not appear to carry the same poor prognosis in WNT tumors as they do in the SHH molecular group.[10,15] WNT-activated medulloblastoma are associated with a favorable prognosis in the pediatric population, whereas the prognosis in adults with this tumor subtype is still uncertain.[5]

The diagnosis of medulloblastoma should be considered in the context of any embryonal brain tumor in the cerebellum, cerebellar peduncle, or fourth ventricle. Rarely other malignant tumors with small cell morphology can be encountered in this region, such as atypical teratoid/rhabdoid tumor (ATRT), embryonal tumor with multilayered rosettes (ETMR), small cell glioblastoma, Ewing sarcoma, or high-grade neuroepithelial tumor with BCOR alteration (HGNET-BCOR). These can typically be excluded by a combination of subtle histologic findings or immunohistochemistry, using lineage markers or entity specific stains.[5]

The possibility of ATRT or ETMR can be suspected in the presence of specific histologic features such as rhabdoid cells or ependymoblastic rosettes, respectively. Immunohistochemistry can be of use in the absence of these specific histologic features. Malignant tumor other than medulloblastoma usually will not express neuronal markers such as synaptophysin or NeuN apart from ETMR and rarely ATRT. Furthermore, ETMR typically express high levels of LIN28A, whereas ATRT typically show loss of INI1 and Brg1 exprission, and is also found to have a polyimmunophenotype, where several different antigens such as EMA, smooth muscle actin, and GFAP are being co-expressed at the same time.[5]

Small cell glioblastoma and medulloblastoma are usually hard to distinguish. However, widespread expression of GFAP, Olig2, or SOX10 and the absence of neuronal antigen expression favors the diagnosis of astrocytoma, while only a minority subset of medulloblastoma tumor cells may express Olig2 or SOX10. High-grade neuroepithelial tumor with BCOR alteration and Ewing sarcoma can usually be differentiated from medulloblastoma by BCOR or EWSR1 FISH immunohistochemistry, respectively.[5] Additionally, for tumor that arises in midline structures, diffuse midline gliomas may be considered as a differential diagnosis.

H3K27M mutations are the hallmark of diffuse midline gliomas, and thus the absence of this mutation may help exclude this diagnosis.[16] The immunohistochemical evaluation of EZHIP may also be considered to exclude the diagnosis of diffuse midline gliomas H3K27-mutant with EZHIP overexpression and posterior fossa ependymoma, group PFA (PFA-EPN).[17]

The current patient showed negative staining for GFAP, Olig2, EMA, H3K27M, EZHIP, and LIN28A, with retained staining for INI1 and BRG1, thus excluding all the aforementioned differential diagnosis.

Conclusions

Stratification of patients with medulloblastoma into low-risk and high-risk groups would enable more precise therapeutic intervention, so that the extent of treatment could be tailored to the degree of biologic aggressiveness. Histopathologic subclassification of medulloblastoma can help modify therapeutic planning, while molecular characterization of medulloblastoma is becoming increasingly important to help establish diagnosis, to exclude differential diagnosis, and to predict prognosis. Molecular subtyping based on genetic alterations, methylation profiles, and transcriptional patterns can better predict prognostic outcomes than histology alone and is increasingly used for medulloblastoma classification in clinical practice. WNT-activated medulloblastomas are defined by activating mutations in the WNT/β-catenin signaling pathway, often associated with the loss of chromosome 6, and have the most favorable prognosis.

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