Quiz
Correct answer to the quiz. Check your diagnosis

Medulloblastoma with extensive nodularity (SHH medulloblastoma)

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Medulloblastoma is the most common CNS embryonal tumor and the most common malignant tumor of childhood. Its overall incidence is 1.8 cases per 1 million people, with a childhood incidence of 6 cases per 1 million. 77 percent of patients are less than 19 years old. Medulloblastoma occurs in the 4th ventricle and usually presents with symptoms of increased intracranial pressure (headaches, nausea, vomiting) and signs of obstructive hydrocephalus. Medulloblastoma is both histologically and genetically defined with prognosis that depends on classification.

Key words: medulloblastoma, pediatric brain tumor.

Case presentation

An 11-month old female presented to the pediatrician with an increased head circumference. Head CT was reviewed and subsequent MRI revealed a heterogeneous enhancing mass involving the medial aspect of both the right and left cerebellar hemispheres (Fig. 1). The mass extended through the posterior foramen magnum and effaced the 4th ventricle. The tumor was resected and appeared as a tan to white, firm, nodular mass measuring 4.2 × 1.8 × 0.7 cm in aggregate. An intraoperative smear and frozen section was performed. Microscopic sections were remarkable for a proliferation of small round blue cells with a pale, largely nodular architecture on HE (Fig. 2). Within the nodules, the neoplastic cells were smaller and streamed through the neuropil-like tissue. The majority of these pale nodular areas were Reticulin free (Fig. 3). Intra-nodular areas demonstrated prominent neuronal differentiation with Neu-N (not shown). The Ki-67 proliferation index was low in the intra-nodular areas (< 1%) and was high in the inter-nodular areas (approximately 30%) as shown in Fig. 4.

Discussion

Medulloblastoma is the most common CNS embryonal tumor and the most common malignant tumor of childhood. Its overall incidence is 1.8 cases per 1 million people with approximately three times higher incidence in childhood (6 per 1 million). 77 percent of patients are less than 19 years old [1].

Medulloblastoma occurs in the 4th ventricle with a different cell origin based on the molecular characteristics of the tumor. Children usually present with symptoms of increased intracranial pressure (headaches, nausea, vomiting) and signs of obstructive hydrocephalus. Another characteristic of Medulloblastoma is an increased head circumference in infants, as in this case.

Medulloblastoma is both histologically and genetically defined with prognosis that depends on classification. Based on the current 2016 WHO, there are

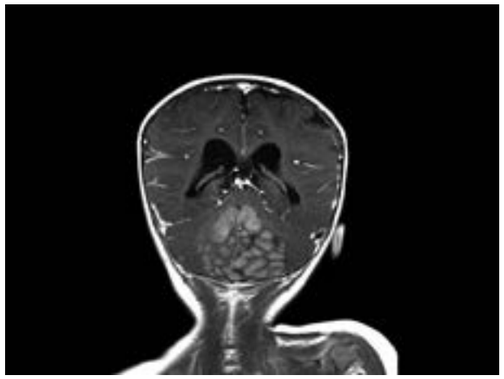

Fig. 1.

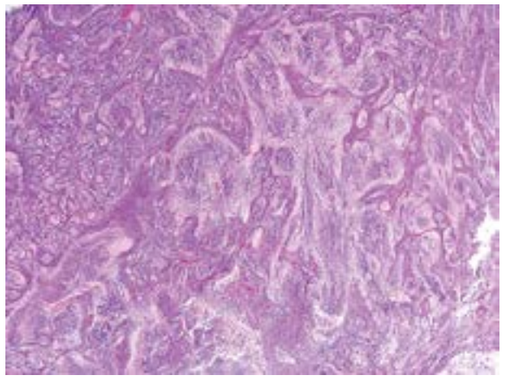

Fig. 2.

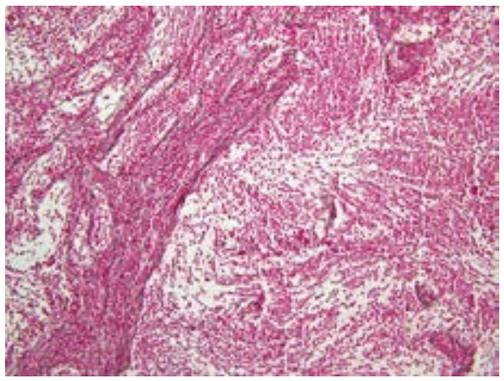

Fig. 3.

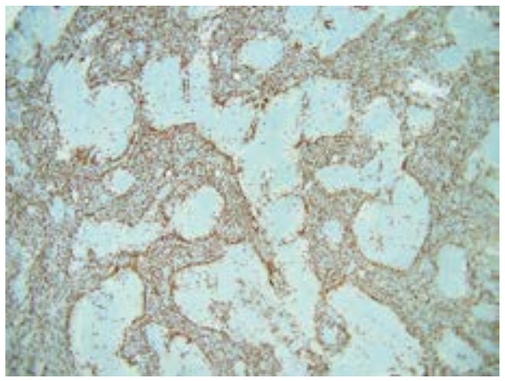

Fig. 4.

4 histologic subtypes. Classic Medulloblastoma consists of sheets and vague nodules of hyperchromatic embryonal cells that are positive for Synaptophysin. Desmoplasia is usually absent, however focal Reticulin deposition can be seen in cases with entrapped leptomeninges. Apoptotic bodies and mitoses are readily found, however cells with anaplasia or a large cell phenotype are absent. In the Desmoplastic/Nodular variant, the architecture is distinct on HE. There are numerous nodular, Reticulin free zones forming both internodular and intranodular zones. The intranodular zones have a distinct microenvironment with advanced neuronal differentiation, decreased mitotic activity, and a low proliferation index as seen in this case's Ki-67 (Fig. 4). Large, Reticulin free, pale islands predominate in Medulloblastoma with Extensive Nodularity (MBEN). In MBEN, the internodular zone is a minor component of the tumor. In Large cell/Anaplastic Medulloblastoma, the embryonal tumor has anaplasia or a large cell phenotype with severe anaplasia histologically manifested as increased cell size, cell wrapping, prominent molding, abundant mitotic activity, and apoptoses. Anaplasia should be a dominant feature of the tumor and not appear just focally. The previous WHO [2] described two additional histologic variants, Medulloblastoma with myogenic and melanotic differentiation. These were reclassified as Medulloblastoma-NOS given their rarity and tendency to occur with the classic and anaplastic/large cell types.

Michael Taylor's Lab solidified the molecular classification of medulloblastoma [3], with genetic definitions incorporating the histologic classification, copy number alterations, and frequent genetic alterations into WNT-activated, SHH-activated, Group 3, and Group 4 medulloblastoma. Activation of the WNT pathway can be demonstrated by nuclear immunoreactivity for Beta Catenin, however optimal evaluation involves detection of Monosomy 6 or a CTNNB1 gene mutation on Chromosome 3p21. Sonic Hedgehog (SHH) activated tumors usually involve *PTCH*, *SMO*, and *SUFU*, as well as amplifications of *GLI1* and *GLI2*. These are further stratified based on the presence or absence of a TP53 mutation, as TP53 mutant tumors have a worse prognosis and shorter time to recurrence for Medulloblastoma in general [4].

As most laboratories cannot perform such advanced molecular testing on these tumors, a novel diagnostic immunohistochemical method to distinguish SHH, WNT, and non-SHH/WNT tumors was developed by Dr. Ellison and his colleagues using GAP, YAP, and Filamin A [5]. Our tumor co-expressed GAB and YAP in the internodular zones, classifying the tumor as a SHH by immunohistochemistry. P53 was not overexpressed, implying the tumor was TP53 wild-type.

The authors declare no conflict of interest.

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