Medulloblastoma with Extensive Nodularity: Case Report and Review of the Literature

Abstract
Medulloblastoma, in addition to being the most common high grade brain tumor of childhood, is the prototype of the embryonal (primitive) neoplasms of the central nervous system. These neoplasms are highly cellular, poorly differentiated, and mitotically active tumors with resemblance to the developing embryonic nervous system. They are highly aggressive and are designated to the highest grading (IV) in the World Health Organization's Classification of Tumours of the Central Nervous System. It usually presents as an expansile mass in the cerebellum or fourth ventricle (posterior fossa location) in a mostly pediatric population. Historically, they are composed of densely packed cells with round to oval, hyperchromatic nuclei, sometimes forming neuroblastic rosettes. The Medulloblastoma with extensive nodularity is a variant that accounts for 3% of all medulloblastomas and is characterized by the same histologic features with alternating well-differentiated nodules of retinoblastoma free stroma, which represent regions of neural maturation. It is associated with a good prognosis, especially in the patient group that it affects most commonly (<5 years), the same group which presents a poor clinical outcome in cases of classic medulloblastoma.

Case Report
This is the case of a 7 month old boy with no history of systemic illness and born to a 20 year old G2P2A0 mother by cesarean section one week prior to admission he presented with eye-staring, bulging fontanel, irritability, vomiting, and irritability, which was evaluated by a pediatrician and treated for an upper respiratory infection. He persisted with symptoms and worsening irritability and was brought to the ER, where a head CT revealed a large posterior fossa mass and severe hydrocephalus. An MRI (Figure D) confirmed the mass and presented extension through the foramen magnum with compression of the pons and midbrain. The next day the patient underwent surgery with gross tumor resection achieved. Tissue was submitted for intraoperative consultation, which was diagnosed as a Small blue round cell tumor, favoring Medulloblastoma with Rhabdoid tumor in the differential diagnosis. Histologic sections stained with hematoxylin and eosin (H&E) revealed a markedly nodular neoplasia (Figure A). The nodules consisted of a homogeneous population of neurocyte-like cells with granular chromatin and small nuclei, arranged in rows (streaming) in a fine fibrillary background (Figure B). Surrounding the nodules was a more pleomorphic population showing hyperchromasia (Figure C). Immunohistochemical stains revealed a nodular distribution of Synaptophysin (Figure E) and a perinodular distribution of high Ki-67 (primitive) neoplasms of the central nervous system. These neoplasms are highly cellular, poorly differentiated, and mitotically active tumors with resemblance to the developing embryonic nervous system. They are highly aggressive and are designated to the highest grading (IV) in the World Health Organization's Classification of Tumours of the Central Nervous System. It usually presents as an expansile mass in the cerebellum or fourth ventricle (posterior fossa location) in a mostly pediatric population. Historically, they are composed of densely packed cells with round to oval, hyperchromatic nuclei, sometimes forming neuroblastic rosettes. The Medulloblastoma with extensive nodularity is a variant that accounts for 3% of all medulloblastomas and is characterized by the same histologic features with alternating well-differentiated nodules of retinoblastoma free stroma, which represent regions of neural maturation. It is associated with a good prognosis, especially in the patient group that it affects most commonly (<5 years), the same group which presents a poor clinical outcome in cases of classic medulloblastoma.

Discussion
Medulloblastoma with extensive nodularity (MBEN) has been described in the literature as a subtype of medulloblastoma with an expanded desmoplastic (or nodular) architecture. These nodules or pale islands represent widespread neurocytic maturation of the embryonal cells that compose classic medulloblastomas (CMB), as demonstrated by synaptophysin staining and paucity of Ki-67 staining, signifying diminished proliferation. In contrast to CMB, MBEN presents in a younger population (<3 y/o) vs 7 y/o) and exhibits a dramatically better prognosis [95% vs 42% 5-year overall survival (OS)], evidenced by the rarity of metastasis at diagnosis (17% vs. 37%).

Molecular characterization of medulloblastomas has achieved great strides in the last few years, pointing towards a directed therapy directed in the near future. Defects in the Sonic Hedgehog (SHH) pathway (commonly PTCH1 mutations) have a high incidence in the desmoplastic group of MB (which includes MBEN), whereas aberrant signaling in the Wntless (WNT) pathway (frequently CCNB1 mutations) is associated to CMB. Additionally MYC overexpression has been associated to subtypes with poor prognosis (Anaplastic and Large Cell MBs).

Different theories have been proposed to as MBs cell of origin. Classically the two more dominant ones have been 1.) a common origin in the external granular layer of the cerebellum and 2.) derivation from subependymal matrix cells (PNET concept). Recent studies have demonstrated that a subgroup of MBs presenting SHH alterations originate from granular neuron progenitors and others have found a separate germinal zone origin for subgroups of MBs with defects in the WNT pathway, showing that different subgroups have different cells of origin. The cells of origin of other subgroups have not been elucidated.

Due to its aggressive nature, CMB’s have traditionally been treated with a combination of surgery and high dose radio- and chemotherapy, associated with increased morbidity. MBEN’s have been successfully treated with surgery and chemotherapy alone, with recurrence rates [9% vs 5 year event-free survival (EFS)]. Treatment targets have been in development since 2005 against the Smoothen homologue (SMO) protein which works as an activator of the SHH pathway and is a critical component of the hedgehog signaling pathway involved in medulloblastoma development.

The purpose of this presentation is to highlight this entity's histological and immunological profile due to the scarcity of its presentation in the local literature and to present the latest achievements that have been portrayed in the scientific literature to treat these cases.

References
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