**Medullomyoblastoma: A Case Report and Literature Review of a Rare Tumor Entity**

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**Abstract.** Background: Medullomyoblastoma (MMB) is a very rare medulloblastoma (MB) variant consisting of primitive neuroectodermal cells intermixed with cells featuring myogenic differentiation. MMBs are a subtype of primitive neuroectodermal neoplasm (PNET) predominantly occurring in children. Case Report: We describe a case of a one-year-old girl who presented with headache, emesis and ataxia. The symptoms had started seven weeks before hospital admission. Magnet resonance imaging of the brain was performed, and revealed a lesion with a maximal diameter of 5 cm, located in the cerebellum close to the vermis. Histologically, the poorly-differentiated lesion was diagnosed as a type of PNET, but it was the immunohistochemical staining that assured the diagnosis of MMB. Results: Immunohistochemistry and interphase fluorescence in situ hybridization (I-FISH) were performed on formalin-fixed paraffin-embedded tissue. FISH did not reveal any amplification of CMYC or NMYC. No nuclear expression of β-catenin was detectable. Discussion: Since MMB is a very rare tumor entity, standard treatment today is the same as that for conventional MB due to the lack of larger study series. Some authors assume that MMBs behave especially aggressive in comparison to conventional MBs. Therefore, new treatment regimes should be tested to optimize the prognosis of MMB. Further data is needed to determine the differences between MB and MMB.

Medullomyoblastoma (MMB) is a medulloblastoma (MB) variant consisting of primitive neuroectodermal cells intermixed with cells featuring myogenic differentiation (1, 2). This tumor entity was first described by Marinesco and Goldstein in 1933 (3). MMBs are very rare lesions, with only 47 cases reported since its first description (4). They are primitive neuroectodermal tumors (PNETs), also known as embryonal neuroepithelial neoplasms (5). According to the WHO classification of brain tumors of 2007, PNETs are listed as embryonal tumors (6). Embryonal tumors comprise of the MB and its subtypes (desmoplastic/nodular MB, MB with extensive nodularity, anaplastic MB and large-cell MB), subtypes of CNS PNETs (namely neuroblastoma, ganglioneuroblastoma, medulloepithelioma and ependymoblastoma) and the atypical teratoid/rhabdoid tumor (6). General characteristics of PNETs are dissemination through the cerebrospinal fluid, poor differentiation, high mitotic activity and high apoptosis (7). PNETs account for approximately 5% of all neoplasms of the CNS (7).

**MB and related tumors.** MB was first described as a tumor entity by Bailey and Cushing in 1925 (2). This tumor occurs mainly in children, but is also found in adults (8). An analysis on the incidence of CNS tumors in 1964 among 155 children showed that MBs occur at a younger age than other intracranial tumors do. If a boy under 5 years of age presents with a tumor in the posterior fossa, he is almost certainly suffering from MB (9). The location is most frequently in the cerebellum, close to the cerebellar vermis. Histologically, MBs are characterized by small cells with round nuclei, rich in chromatin, and the cell bodies cannot be distinguished from each other. In about one third of such lesions, rosette-like configurations of the tumor cells can be found. MB cells generally stain positively for synaptophysin and β-tubulin. Clinically, patients suffer from increased intracranial pressure and typical cerebellar symptoms such as ataxia, vertigo and headache. The present 5-year survival rate after surgery, radiation and chemotherapy ranges from 50-80%.

The melanotic MB is the rarest type of MB. The neuroectodermal cells exhibit intracytoplasmic melanin...
pigment (10, 11). In some melanotic MBs, the melanotic cells form tubules or papillae, but the melanotic tumor cells can also be randomly dispersed within the tumor tissue (2).

MB with extensive nodularity (MBEN) is a subtype that is associated with a better prognosis compared to conventional MB (12, 13). The growth pattern is lobular and there are reticulin-free zones within the lesion that contain a population of small neurocytic cells (1).

Large-cell MB is a variant containing monomorphic, eosinophilic cells with large and round nuclei and distinct single nucleoli (2, 12). For large-cell MBs with an especially high degree of nuclear pleomorphism and high mitotic counts, the term “anaplastic MB” is used (7).

Medulloepithelioma (ME) and ependymoblastoma. Medulloepithelioma (ME) is classified as a highly malignant embryonal tumor entity, corresponding to WHO grade IV (1). Histologically, the lesion features gland-like epithelial structures, but also has the potential for glioneuronal and even mesenchymal differentiation (bone-, cartilage- or muscle-like tissue) (7, 9). These differentiation variants occur especially in those areas of the tumor, where the cells form ependymoblastoma-like rosettes (14). The tumor cells in MEs, which are mitotically active, are cuboidal or columnar in shape with oval, hyperchromatic nuclei and several nucleoli (7, 14).

Ependymoblastoma is usually located in the periventricular zone, and is normally large and clearly circumscribed (14). The key morphological feature for the diagnosis of ependymoblastoma is the presence of ependymoblastic rosettes (7). In large part, ependymoblastomas consist of small, undifferentiated cells. Mitotic activity is high and necrotic areas are frequently found (7).

Specific features of MMB. MMBs are found in the cerebellum (5). They occur in children, predominantly in males, mostly before the age of seven years while adults are rarely affected (1). Typical of MMBs is a biphasic configuration with a small-cell, undifferentiated neuroectodermal and a loosely-textured part. The lesion is rich in collagen, myoblasts and myocytes (1). Sometimes, these two elements are not clearly separated from each other. Usually, a pattern of myogenically differentiated cells occurs between the undifferentiated cells (15). Myoblastic cells can either exhibit striates or a globular blast-like morphology (1). Therefore, Leedham and colleagues proposed that MMBs can be seen as a variant of rhabdomyosarcomas (11).

The neuroectodermal tumor cells in MMBs are usually polygonal with eosinophilic cytoplasm and eccentric nuclei (16). MMBs often exhibit necrotic areas and apart from neuroectodermal and myoblastic components, there can be islands of cartilage and sometimes epithelial, gland-like structures (16) or even neuronal/ganglionic, glial/astrocytic or melanotic differentiation (4, 16). Some regions in the tumor may appear similar to classic MB or might display nodular/desmoplastic or large-cell/anaplastic features (4).

MMBs are positive for actin and desmin, when evaluated by immunohistochemistry (14). There is also variable positivity for vimentin, glial fibrillary acidic protein (GFAP), cytokeratin (CK), epithelial membrane antigen (EMA), smooth muscle actin (SMA) and synaptophysin (16). Typical molecular alterations in MMBs are isochromosome 17q and CMYC amplification (4).

The prognosis of patients with MMB has been assumed to be especially poor (4). However, survival times have improved with the development of modern treatment strategies (4). Since MMBs are very rare tumors, there is not much experience regarding response rates to treatment. In a report regarding six cases of MMB, all patients underwent surgery followed by radiotherapy and after that, different regimes of chemotherapy were provided (e.g. either neoadjuvant chemotherapy or four adjuvant high-dose chemotherapy courses) (4). Generally, treatment regimes in these six cases of MMB were similar to that of classic MBs (4). The authors of these case reports suggested that MMBs should be treated like MBs because the outcome in the six reported cases of MMB was comparable to that of MBs (4). In contrast to previous reports, this finding suggests that MMBs are not especially aggressive (4).

About myoglobin. Myoglobin is a heme protein of low molecular weight (17,800 Daltons) (16, 17). Myoglobin is a member of the hemoprotein superfamily, with members such as hemoglobin, neuroglobin and cytoglobin (11). Its main functions are oxygen storage and transport (18). Furthermore, MGB is a scavenger for free radicals (11). Myoglobin is found exclusively in striated muscle (18). Tumors with rhabdoid differentiation (e.g. rhabdomyosarcomas) stain positively for myoglobin by immunohistochemistry (11, 18).

Case Report

Patient description. In August 2011, a one-year-old girl presented with headache, emesis and ataxia. The symptoms had started seven weeks before admission to hospital. Magnetic resonance imaging of the brain was performed, and revealed a lesion with a maximal diameter of 5 cm, located in the cerebellum close to the vermis. The tumor was well-circumscribed and isointense to the adjacent cortex on T1-weighted imaging. There were signs of edema and of a moderate obstructive hydrocephalus. Macroscopically, no necroses were found. Histologically, the poorly-differentiated lesion was diagnosed as a type of PNET, but based on morphology with myogenic differentiation and immunohistochemistry, the diagnosis of MMB was made. Before any further therapy could be started, the girl died, 3 weeks after the diagnosis was made.
Histology and immunohistochemistry. Paraffin sections (3-5 μm thick) were de-waxed and stained with hematoxylin and eosin (H&E) and immunostaining following standard procedures. H&E-stained brain tumor tissue sections were evaluated for their characteristics. Immunohistochemistry was performed on the formalin-fixed paraffin-embedded tissue sections with a primary monoclonal antibody to β-catenin (1:1000, clone 14, BD Transduction Laboratories, Franklin Lakes, USA).

The tumor was also stained for smooth muscle actin, myoglobin, MIB 1, S 100, INI 1, synaptophysin and EMA. In our scoring system "+" equals weak positivity, "++" equals distinct positivity and "–" equals a negative score.

Interphase Fluorescence in situ hybridization (I-FISH). I-FISH was performed on formalin-fixed paraffin-embedded tissue. Commercially available probes were used (NMYC: 2p24/LAF (2q11), CMYC: 8q24/SE8 D8Z1, Kreatech, Amsterdam, The Netherlands). Signals were counted for 200 non-overlapping tumor cell nuclei. Single-cells were defined as amplified (test probe: control probe ratio >4:1), gained (>1:1 and ≤4:1) or balanced (1:1; haploid, diploid or hyperdiploid).

Results of histological analysis. Histologically, the tumor was poorly-differentiated. Many mitoses and a high degree of cellular pleomorphism were seen (Figure 1). The main component was neuroectodermal, so it was assumed, that the lesion was a form of PNET, namely a MMB, due to the presence of areas with myogenic differentiation. To assure the diagnosis, immunohistochemistry was performed.

High proliferation rates with many MIB-positive tumor cells and positivity for S100, INI 1 and synaptophysin were observed on immunohistochemical staining. Weak positivity for SMA was found (Table 1). The tumor was negative for EMA. A few parts of the lesion were also positive for myoglobin (Figure 2). This finding clearly showed muscular differentiation, leading to the diagnosis “MMB”. Interestingly, in the immunohistochemistry no nuclear expression of β-catenin was detectable (Figure 3).

FISH did not reveal any amplification of CMYC or NMYC. Both regions showed a predominantly balanced ratio of NMYC/CMYC and control signals. Whereas for CMYC, a considerable number of hyperdiploid cells was observed, for NMYC, in addition to mainly diploid cells, some cells with copy number gains were found (Figure 4).
Figure 2. Biopsy material from the MMB. A: Hematoxylin-eosin (HE) staining (magnification: 40×), B: myoglobin staining features distinct positivity (magnification: 40×), C: H&E staining (magnification: 60×), D: myoglobin staining (magnification: 60×), E: MIB 1 (magnification: 20×), F: EMA (magnification: 20×), F: INI-1 (magnification: 20×), G: myoglobin staining (magnification: 20×), H: myoglobin staining (magnification: 20×).

Figure 3. No nuclear expression of β-catenin was detectable in the cells (magnification: 40×).

Figure 4. In addition to mainly diploid cells, some cells with copy number gains of NMYC were found.
acoustic neurinoma (19). The tumor normally arises in the infratentorial compartment. Primitive neuroectodermal cells have differentiated into rhabdomyoblastic components in MMBs: MMBs may be a variant of teratoid tumor, or multipotent endothelial or mesenchymal cells near or within the tumor undergo rhabdomyoblastic differentiation (20-22). A more recent theory proposes, that PNET cells themselves, within the MB, have the potential for rhabdomyoblastic differentiation (23). Current findings favor this new hypothesis, since genetic similarities between MB and MMB have been found in FISH analyses. MMB seems to be an MB subtype in which primitive neuroectodermal cells have differentiated into rhabdomyoblasts, still displaying the same molecular patterns as MB cells (4).

Genetic alterations in chromosome 17, e.g., losses or deletion of 17p, often leading to an isochromosome 17q, are the most frequent alterations described in MB. MB may also feature amplifications of CMYC or NMYC. Most teratoid/rhabdoid tumors display mutation or deletion of the INI-1 gene, but so far, INI-1 alterations have not been found in MB (4). Helton et al. showed, that MMBs also display alterations in chromosome 17, such as isochromosome 17q or monosomy 17 (4). Polysomies of chromosomes 2, 8, 17 and 22q were also found in MMB. CMYC amplification can be also found (4). Interestingly, the neuroectodermal components of MMB do not differ in FISH results from the rhabdomyoblastic components (4).

There is evidence, that MMB does behave especially aggressively and that treatment should therefore be more radical (4). This still needs to be investigated in larger patient series.

Discussion

MB subtypes are difficult to distinguish from each other because morphology and immunohistochemical staining of the various subtypes can be similar. Careful review of histology and immunohistochemical profiling is essential to avoid making the wrong diagnosis. Since the first description of MMB, only 47 additional cases of this entity have been described in the literature (4). The current treatment recommendation is the same as for classic MB, consisting of surgical resection, followed by adjuvant chemotherapy and radiotherapy (4). Summarizing all previous data about MMB, about 90% of the patients were aged less than ten years, and only three were adults (4). Average survival was less than two years, but in some cases, survival times were considerably longer, e.g. more than fifteen years, the longest survival time ever documented, reported by Helton et al. (4). The tumor normally arises in the infratentorial compartment. Previous data reported the involvement of the cerebellar vermis and hemispheres, the fourth ventricle, the cerebellopontine angle and the brainstem (4). The cerebellopontine angle can also be the primary location of MMB, according to a case report of an MMB in the cerebellopontine angle that mimicked acoustic neurinoma (19).

There are several theories about the origin of rhabdomyoblastic components in MMBs: MMBs may be a variant of teratoid tumor, or multipotent endothelial or mesenchymal cells near or within the tumor undergo rhabdomyoblastic differentiation (20-22). A more recent theory proposes, that PNET cells themselves, within the MMB, have the potential for rhabdomyoblastic differentiation (23). Current findings favor this new hypothesis, since genetic similarities between MB and MMB have been found in FISH analyses. MMB seems to be an MB subtype in which primitive neuroectodermal cells have differentiated into

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<th>Table 1. Positivity or negativity in stainings of bioptic material from the MMB.</th>
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Scores for smooth-muscle antibody (SMA), myoglobin (MGB), mindbomb E3 ubiquitin protein ligase 1 (MB-1), S100 protein, neuron-specific enolase (NSE), RING finger-like protein Ini1 (INI-1), synaptophysin (SYN) and epithelial membrane antigen (EMA). + = weak positivity, ++ = distinct positivity, – = negative.

References


Received July 17, 2012
Revised September 16, 2012
Accepted September 18, 2012