Medulloblastoma: Pathology

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17.1 Introduction

Medulloblastoma generally affects patients in the first two decades of life, accounting for about a fifth of all intracranial neoplasms of childhood [1]. According to the 2007 WHO classification [2] of tumors of the central nervous system, it belongs to primitive embryonal grade IV tumors (Table 17.1).

It mostly appears undifferentiated, but differentiation along different cell lineages (neuronal, glial, mesenchymal, melanotic) can sometimes be observed. This tumor shows wide heterogeneity from the histological and molecular point of view, reflecting distinct biological behavior and prognosis.

Its relationship with primitive neuroectodermal tumors (PNET) has changed over time. Since 1983, in fact, with the classification proposed by Rorke [3], they were considered a unique entity, being all pediatric cerebral high-grade undifferentiated neuroepithelial tumors and sharing an alleged common ontogenic origin. Despite many similarities, for the first time in 2000, the WHO [4] issued a classification where medulloblastoma was distinguished from other embryonal tumors, and more recently, a molecular distinction of these tumors from PNETs has been demonstrated on the basis of microarray techniques [5].

Also the histological framework has changed with the last classification: two variants (medullomyoblastoma and melanotic medulloblastoma) have been excluded as distinct entities and one (medulloblastoma with extensive nodularity) has been added; moreover, anaplastic medulloblastoma and the large-cell variant have been separated into two different categories.

The actual classification, therefore, includes five variants: classic, desmoplastic/nodular, with extensive nodularity, anaplastic, and large cell.

Table 17.1 Embryonal tumors (From: the 2007 WHO classification of tumors of the central nervous system)

Embryonal Tumors
Medulloblastoma
Classic
Desmoplastic/nodular medulloblastoma
Medulloblastoma with extensive nodularity
Anaplastic medulloblastoma
Large-cell medulloblastoma
CNS primitive neuroectodermal tumors (PNET)
CNS neuroblastoma
CNS ganglioneuroblastoma
Medulloepithelioma
Ependymoblastoma
Atypical teratoid/rhabdoid tumor

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Although currently risk and therapy stratification of patients is essentially based on clinical criteria (age, metastatic spread, and extent of surgical resection) [6], there is already an established consensus on histology and molecular genetic to play a relevant role for prognosis and rationalization of treatment protocols [7–10]. For example, desmoplastic variant is generally considered less malignant than classic one [7, 11], and medulloblastomas with extensive nodularity and anaplastic variant are poles apart, having the best and worst prognosis respectively. In the first case, thus, a lightening of adjuvant therapies may be justified to reduce long-term side effects without changing the outcome. However, between these two extreme entities, histology alone is inadequate for correct diagnostic and prognostic assessment, and at the same time, several transcriptional profiling studies have suggested the existence of multiple distinct molecular subgroups (*wingless*/WNT, *sonic hedge-hog*/SHH, groups 3 and group 4) that differ in their demographic distribution, genetic features, and clinical outcomes; their corresponding histological phenotypes can be variable [12]. Only in some cases a closer correspondence between histology and molecular subgroup can be found. Classic medulloblastoma, for example, is variably related to all four subgroups, and it also poses problems of differential diagnosis with teratoid/rhabdoid tumor on the bases of morphology alone [12]. For this reason, immunohistochemistry and sequencing technologies, although more expensive, should always be performed.

17.2 Origins and Historical Findings

The first description of this tumor, with the name of spongioblastoma multiforme, is to be referred to Globus and Strauss at the beginning of the last century [13]. The current nomenclature "medulloblastoma" was coined in 1925 by Bailey and Cushing [14, 15] for its similarity with embryonal medullary velum. They speculated that the progenitor cell was the "medulloblast" [16], a supposed multipotent cell, distinct from spongioblast and neuroblast but able to differentiate along both lineages. To date, the precursor cell remains unknown and a matter of debate among neuropathologists. Microarray studies, however, demonstrated the existence of a strong link between medulloblastoma and normal cerebellum embryogenesis [17, 18]. In particular, mutations affecting the different cells and signal pathways (mainly SHH and WNT) that generate the different cellular layer of the cerebellum may produce different medulloblastoma variants. In fact, the tumor expresses immunohistochemical markers belonging either to the primary germinal zone (i.e., subventricular zone of the cerebellar anlage: calbindin-D28K, parvalbumin, nestin, vimentin, and GFAP) or to the secondary germinal zone (i.e., the granule neuron precursor cells that invade rostrally across the cerebellum anlage to produce the external germinal layer: $p75^{NTR}$, TrkC, Zicl, and Math1) [21]. These two immunohistochemical profiles are mutually exclusive [19–22]: the former is usually associated with the classic variant and the latter with the desmoplastic variant.

17.3 Macroscopic Aspects

The tumor generally appears as a soft, fleshy, and pink or gray mass but firm and well circumscribed in the desmoplastic variant; sometimes necrosis is observed, especially in the large-cell variant. Cysts can be found in 2–20 % of cases [23] and multiple microcysts are more often observable compared to single large cyst. Calcifications are detected in 10–20 % of cases [24] and a spontaneous tumor hemorrhage is found only in 3–5 % of medulloblastomas [23].

In most cases, the lesion is localized on the midline of the cerebellum, generally originating from the inferior medullary velum or from the roof of the fourth ventricle.

Lateral cerebellar location is observed more often in older children, in adults [25], and in the desmoplastic variant, while brainstem and cerebellopontine angle locations are exceptional [26].

In case of aggressive growth (Fig. 17.1), the mass can reach the surface of the cerebellar hemispheres, the floor of the fourth ventricle, often causing obstructive hydrocephalus, and infiltrate the leptomeninges. Medulloblastoma thus tends to spread via cerebrospinal fluid pathway (Fig. 17.2)

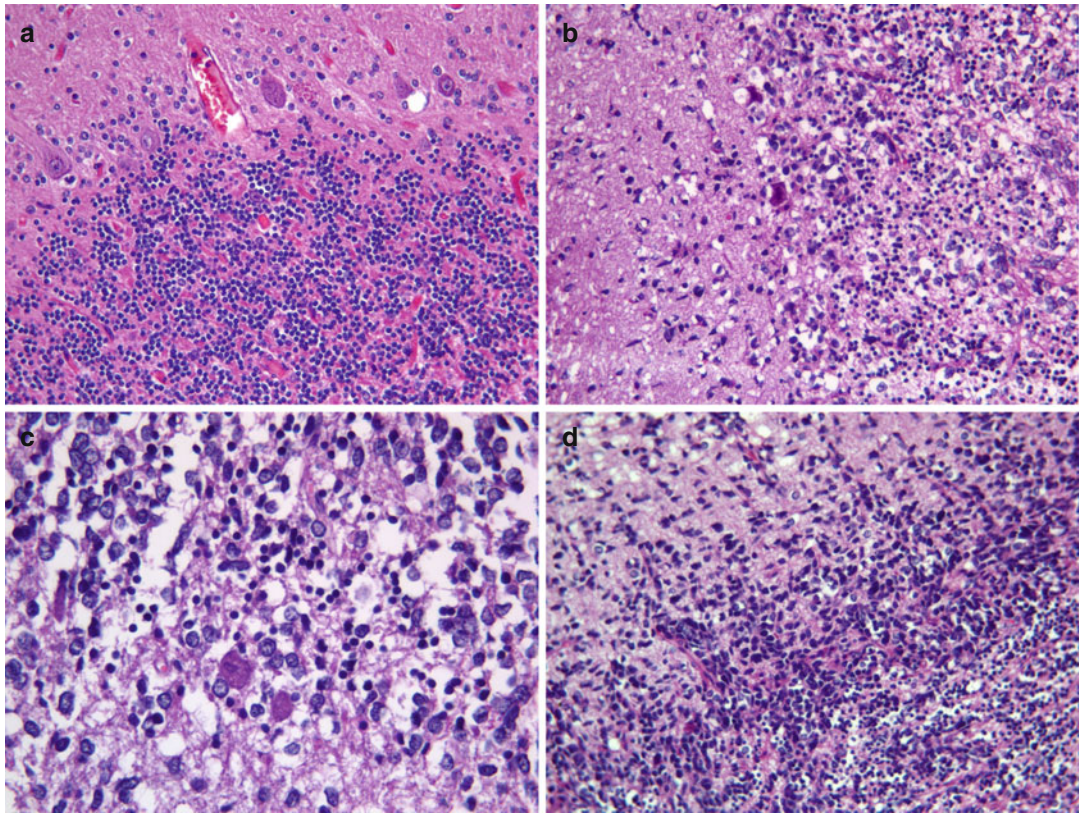

Fig. 17.1 (**a**) Normal cerebellum. (**b**) Infiltrative pattern: tumor cells (*right*) invade cerebellar cortex. (**c**) The cells of medulloblastoma with a larger and irregular nucleus intermingle with the regular, lymphocyte-like cells of the internal granular layer of the normal cerebellum. (**d**) Neoplastic cells arranged in columns, at the level of the molecular layer. Hematoxylin and eosin stain: **a**, **b**, and **d** (20×), and **c** (40×)

along neuraxis generating distinct tumor nodules (e.g., the "drop metastases" among lumbar nerve roots) or, less frequently, a thickening of the pial or ventricular surface ("icing" of leptomeninges) [27]. Metastatic spread outside central nervous system is possible even if very rare [28–30], and the most common sites are bone, bone marrow, and lymph nodes; peritoneal dissemination through ventriculoperitoneal shunt is also reported [31].

17.4 Microscopic Aspects

17.4.1 Classic Medulloblastoma

Classic histology represents about 70 % of all medulloblastomas, mainly belonging to the molecular WNT subgroup (97 %), but even, to a lesser extent, to group 3 and group 4 [32], affecting the prognosis.

It is a highly cellular neoplasm (Figs. 17.3, 17.4, and 17.5), composed of small round or oval-shaped cells, with hyperchromatic nuclei and little apparent cytoplasm [27]. Molding of the nuclei can be observed because of the high cellular density, even if it is a peculiarity of the anaplastic variant. Mitotic activity is usually conspicuous.

Necrosis and angiogenesis are variably present, but they are generally modest and lower than those seen in high-grade gliomas. Cells may be organized into rows, lobules, and twisted bundles or form neuroblastic (Homer-Wright) rosettes (Fig. 17.6). The latter are observed in not more than 40 % of cases and consist of tumor cell nuclei arranged in a radial fashion around a central tangle of fibrillar processes [27]. Like in neuroblastoma, pinealoblastoma, and primitive

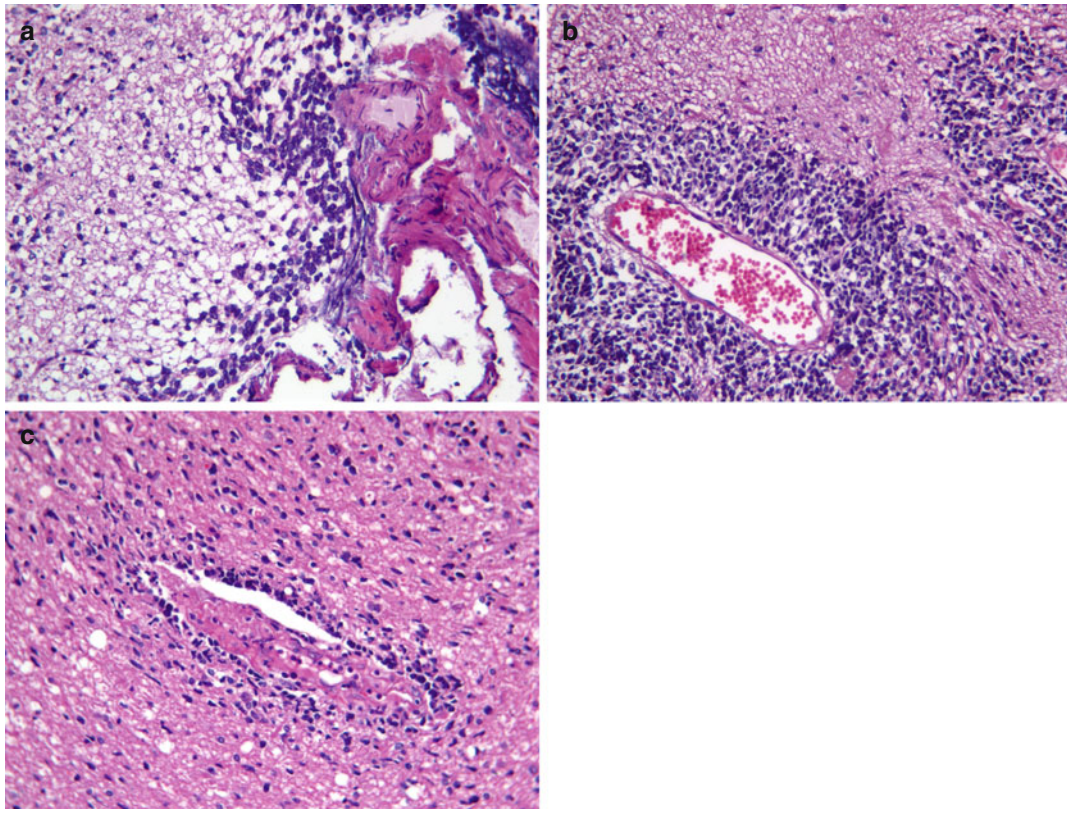

Fig. 17.2 Tumor cells fill the subarachnoidal space (**a**) and reenter the brain along perivascular spaces (**b**, **c**). Hematoxylin and eosin stain (20×)

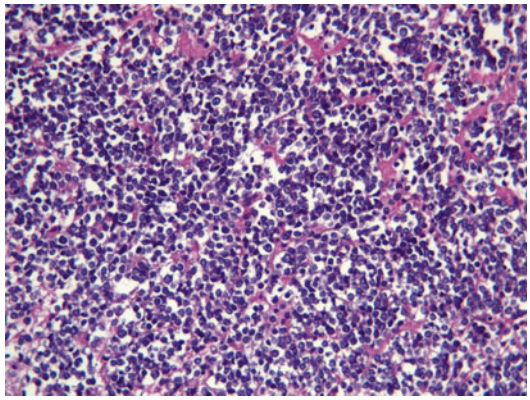

Fig. 17.3 Classic medulloblastoma. Densely cellular tumor, with non-nodular growth pattern. Hematoxylin and eosin stain (40×)

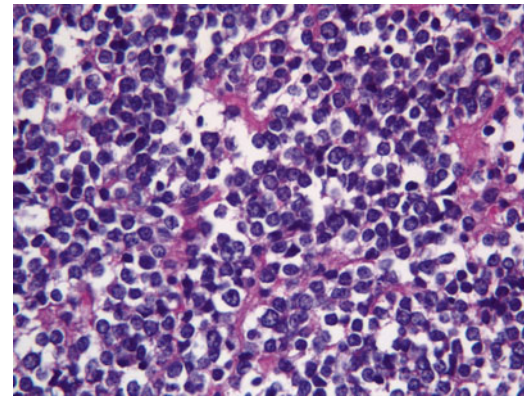

Fig. 17.4 Classic medulloblastoma. Sheets of cells with bland cytology and uniform distribution. Hematoxylin and eosin stain (63×)

neuroectodermal tumors of bone, they represent a phenotype of neuronal differentiation. Another possible structure is the "pseudorosette," where fibrillar processes are projecting toward a central blood vessel, resembling "spokes around the hub of wheel."

Neuronal differentiation is the most common aspect, but morphological evaluation based on

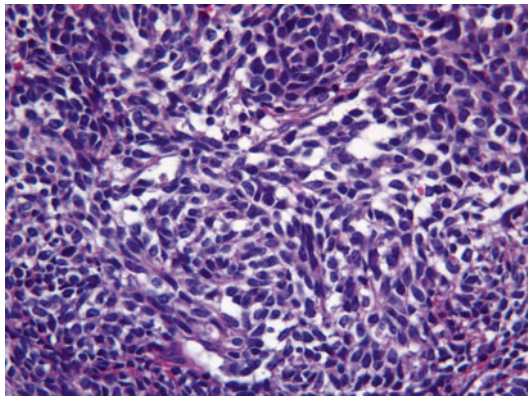

Fig. 17.5 Classic medulloblastoma with mild cytological atypia and minimal nuclear pleomorphism. Hematoxylin and eosin stain (40×)

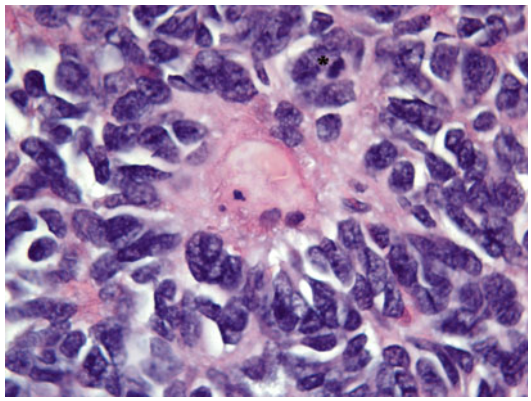

Fig. 17.6 Classic medulloblastoma. Detail of a Homer-Wright rosette: cells disposed in a radial fashion around a central core of fibrillar material. Note the mitotic figure (*). Hematoxylin and eosin stain (63×)

routine hematoxylin and eosin staining alone is not sufficient to reveal it. Immunohistochemistry becomes essential. In about 7 % of tumors, neurocytic or ganglion cells are found [18]. Glial differentiation is less frequent, and it is represented by mature glial cells with astrocytic phenotype, with eosinophilic cytoplasm and cell processes. Ependymal differentiation, on the contrary, is exceptional.

Rarely differentiation along mesenchymal line can occur. Medulloblastoma (classic, desmoplastic, and anaplastic) with foci of myogenic phenotype, with long cytoplasmic processes and striated muscle fibers, may be observed. This entity, in the previous WHO classifications, was named medullomyoblastoma [33–35] and considered as a distinct variant; according to the current WHO classification (2007), the pathology report in these cases should refer to "medulloblastoma with myogenic differentiation" [2].

Another rare phenotype, previously described as a distinct variant, is melanotic medulloblastoma [18, 36, 37], now simply termed "medulloblastoma with melanotic differentiation" [2]. It is characterized by epithelioid pattern and the presence of cytoplasmic melanin pigments that have been proved to be both neuromelanin and oculocutaneous types. However, melanotic and medullomyoblastoma phenotypes can even coexist [38].

Cell proliferation in most classic medulloblastomas is generally high although variable [9, 39].

17.4.2 Desmoplastic Medulloblastoma

Desmoplastic/nodular variant accounts for about 16 % of cases, with a significantly higher prevalence in adults and infants (42 %) than in children (9 %) [32]. SHH molecular subgroup expresses this phenotype in the great majority with a good prognosis in infants and intermediate in others [12].

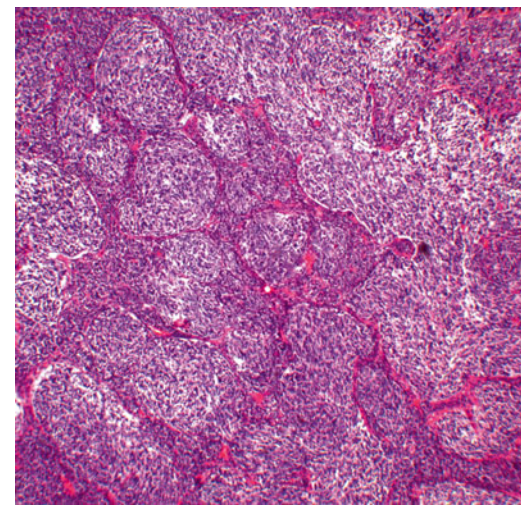

Fig. 17.7 Nodular/desmoplastic medulloblastoma, characterized by the alternating of pale and dark areas (hematoxylin and eosin stain; 10×)

It is characterized by coexisting of both nodular reticulin-free areas ("pale islands") and desmoplasia (Figs. 17.7 and 17.8). Only one of these architectural elements, detectable separately in all variants of medulloblastomas, does not allow to classify it as desmoplastic [18]. They should be considered as distinct biological microenvironments [45] with different degrees of mitosis, apoptosis, and differentiation. Nodular areas appear as round or elongated zones of tumor cells, placed on a neuropil-like background, with neurocytic neuronal differentiation (Figs. 17.9 and 17.10), poor proliferation, and scattered apoptotic cells. In some cases, nodule formation can be very focal with uninterrupted sheets of tumor cells, so there may be diagnostic problems because it is difficult to establish how many nodules or desmoplasias (Fig. 17.11) are required to make a correct diagnosis [45].

Desmoplasia is a pericellular reticulin-rich network that may represent also a reactive phenomenon like in leptomeningeal invasion [40]. Tumor cells in internodular regions tend to be more undifferentiated, sometimes with focal anaplasia, to be pleomorphic and mitotically

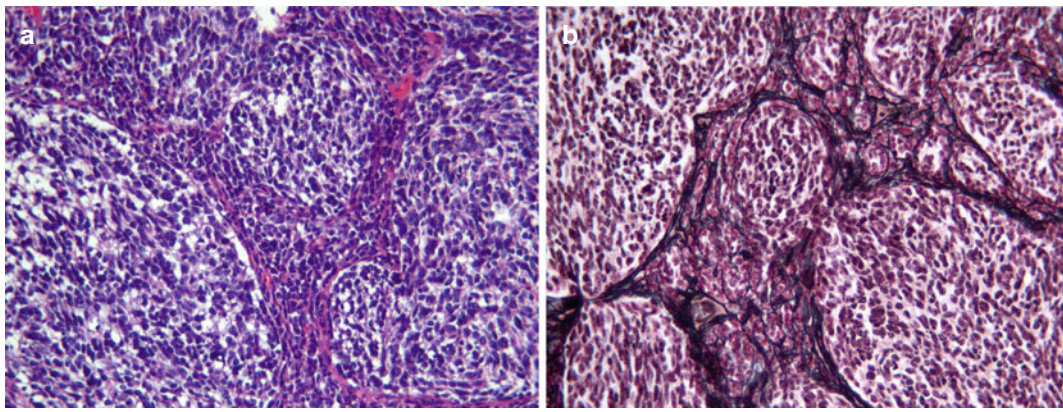

Fig. 17.8 Nodular/desmoplastic medulloblastoma. (**a**) Nodular areas appear as round or elongated zones of tumor cells, in contrast with the internodular regions where cells appear more undifferentiated. Hematoxylin and eosin stain (40×). (**b**) Alternation of "pale islands," reticulin-free, and dark zones, rich in reticulin (40×)

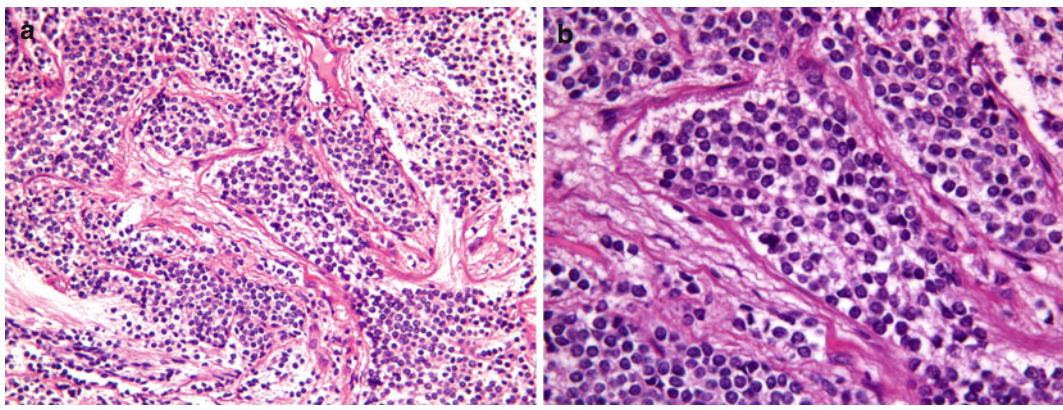

Fig. 17.9 Nodular/desmoplastic medulloblastoma. (**a**, **b**) Intranodular neurocytic differentiation. Hematoxylin and eosin stain (20× and 40×)

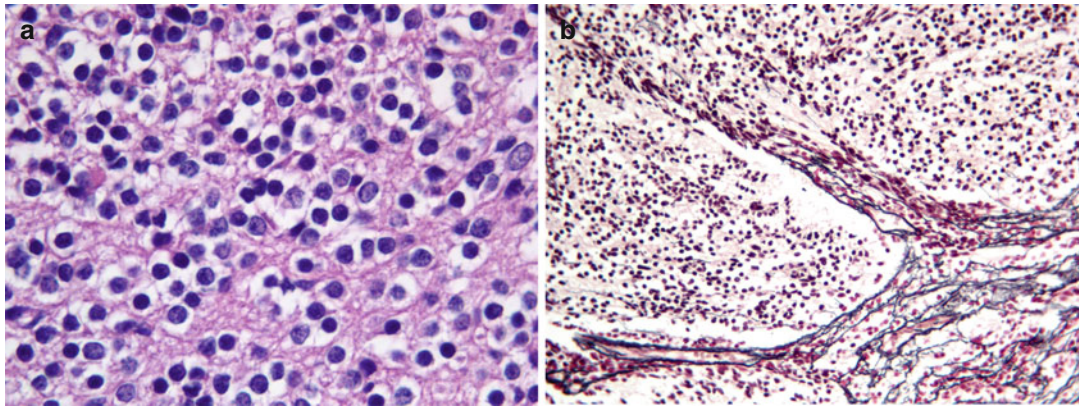

Fig. 17.10 Nodular/desmoplastic medulloblastoma. (**a**) Round bland cells with perinuclear halo. Hematoxylin and eosin stain (63×); (**b**) Nodular pattern highlighted by reticulin stain (20×)

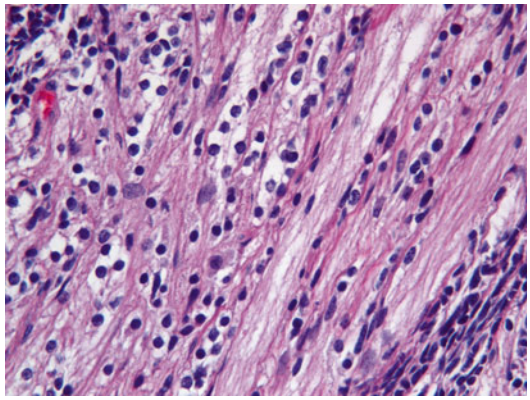

Fig. 17.11 Desmoplastic component. Streaming pattern of neoplastic cells (hematoxylin and eosin stain; 63×)

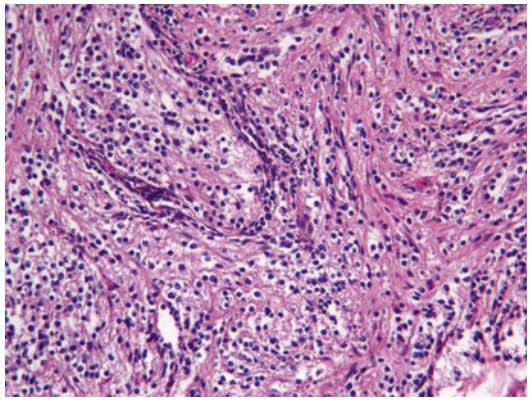

Fig. 17.12 Medulloblastoma with extensive nodularity. Large nodules of neoplastic cells with neurocytic differentiation interrupted by poor extranodular tissue. Hematoxylin and eosin stain (20×)

active, with greater nuclear/cytoplasmic ratio than nodular zones and a higher Ki67 (MIB1) Labeling Index [41].

17.4.3 Medulloblastoma with Extensive Nodularity (MBEN)

It is an uncommon variant, closely related to desmoplastic one [2] that was previously termed "cerebellar neuroblastoma" [42] and accounts for about 3 % of cases [43]. It occurs mainly below the age of 3 years, and it is associated to a good prognosis [44].

It may be considered as the most differentiated form of desmoplastic medulloblastoma (MB) [45] in which reticulin-free nodules are particularly large and numerous, while desmoplasia is markedly reduced or absent (Fig. 17.12). Intranodular cells show neurocytic differentiation and nuclear uniformity with features that resemble those of central neurocytoma. Occasionally, after radiotherapy and/or chemotherapy, medulloblastomas with extensive nodularity may evolve into a ganglioglioma [46].

17.4.4 Large Cell and Anaplastic (LCA)

These two histologies represent a morphophenotypical and biological continuum; for this reason

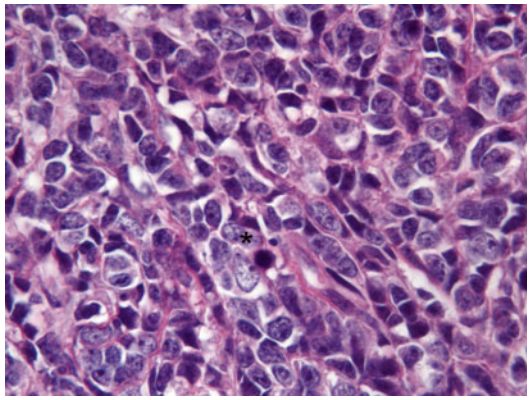

Fig. 17.13 Large-cell medulloblastoma. Large round cells with a vesicular nucleus and generally a prominent single nucleolus. Note the mitotic figure (*). Hematoxylin and eosin stain (63×)

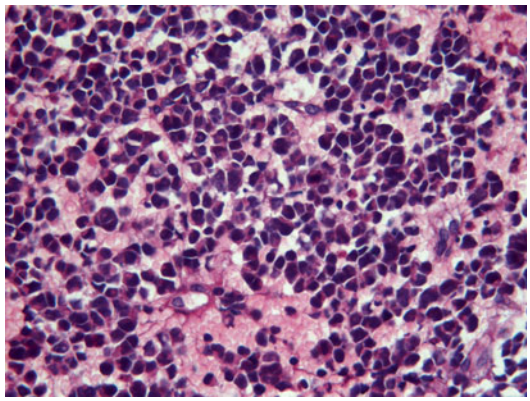

Fig. 17.14 Large-cell/anaplastic medulloblastoma. Large polyhedral cells which are densely packed with a paving-like pattern. Hematoxylin and eosin stain (40×)

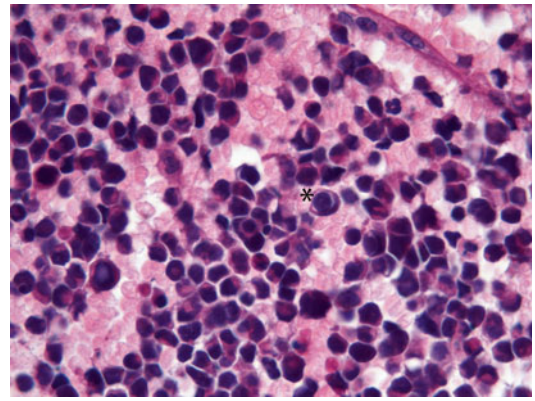

Fig. 17.15 Large-cell/anaplastic medulloblastoma. Nuclear pleomorphism and molding. Note the cell-cell wrapping (*). Hematoxylin and eosin stain (63×)

in literature, they are usually considered as a single macrogroup (LCA tumors) [7].

Their prevalence accounts for 10 % of MBs, and it is lower in adults (3 %) [32]. They are equally associated to all the molecular subgroups except for WNT tumors in which a link is rarer, or among infants where the tumor always correspond to group 3, with poorer prognosis [32].

Large-cell medulloblastoma is composed of lobules or sheets of large round cells (two to three times greater than conventional small cells), with a vesicular nucleus and generally a prominent single nucleolus (Fig. 17.13). In some regions, large cells can be polyhedral and densely packed with a paving-like pattern.

Anaplastic medulloblastoma (Figs. 17.14 and 17.15) is characterized by nuclear molding, cell-to-cell "wrapping," nuclear pleomorphism [18, 47], and a peculiar apoptotic activity that can be so extensive to form small "lakes" [47].

Large-cell medulloblastoma always contains areas with anaplastic phenotype. When histology is dominated by this phenotype, anaplastic medulloblastoma variant is configured [18]. This entity was introduced in the 2007 WHO classification [2], and histological progression from non-anaplastic to anaplastic medulloblastoma is documented even within the same tumor [2, 8, 33, 48].

17.5 Immunohistochemistry

Medulloblastoma is mainly an undifferentiated neoplasm, referring solely on the light microscopic appearance, but at the immunohistochemical and ultrastructural level, it must be considered a neoplasm with neuronal or neuroblastic phenotype. Sometimes a differentiation toward glial lineage is detectable, almost exclusively after immunohistochemical investigation.

Clear positivity to synaptophysin (Fig. 17.16), class III β-tubulin, microtubule-associated protein 2 (MAP2), cromogranin, NSE, and NeuN may variably be observed [49, 50], especially in the fibrillar cores of

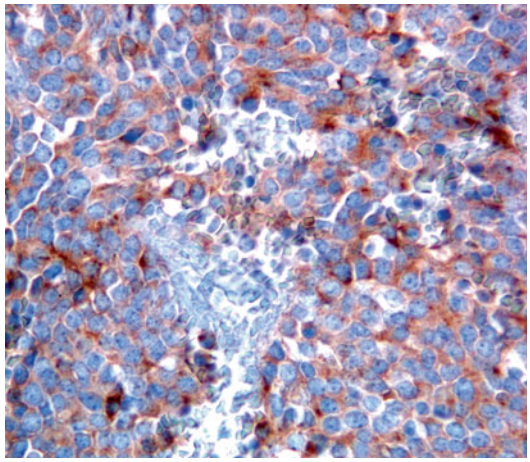

Fig.17.16 Synaptophysin. Granular cytoplasmic immunoreactivity

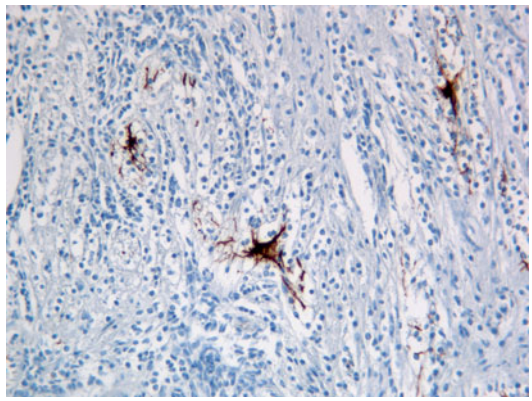

Fig. 17.17 GFAP. Rare entrapped glial cells reactive for GFAP

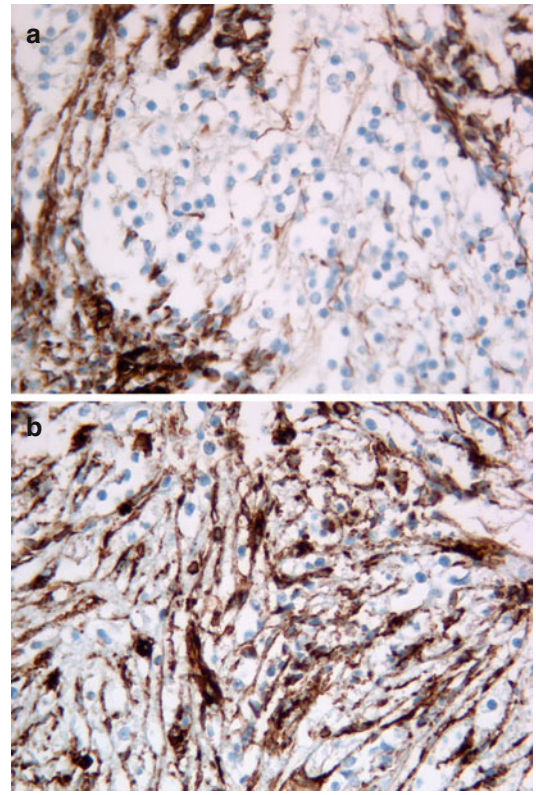

Fig. 17.18 Vimentin. Immunophenotype in the (**a**) nodular variant and in the desmoplastic area (**b**)

Homer-Wright rosettes and perivascular pseudorosettes and in the "pale islands" of the nodular variant; the expression of neurofilament protein is strictly tissue fixation-dependent.

GFAP (glial fibrillary acidic protein) positivity is of difficult interpretation, firstly because most of medulloblastomas contain reactive stellar-shaped astrocytes (Fig. 17.17), usually positioned around a vessel and whose long cytoplasmic processes can juxtapose to a neoplastic nucleus giving the false impression of a positive signal. Also "pale islands" of desmoplastic variant show GFAP positivity within evident network of fibrillar cells, denoting that intranodular areas represent a center of mixed neural and glial differentiation [51].

Large-cell variant never shows glial differentiation, while a strong positivity to synaptophysin, neurofilament protein, and chromogranin is often detected.

Occasionally, a photoreceptor differentiation is observed and therefore immunoreactivity to retinal-S-antigen and rhodopsin is detected.

Finally, immunophenotype of medulloblastoma may also include positivity (Fig. 17.18) to vimentin (mainly in classic form), nestin, neuronal cell adhesion molecule (NCAM), and nerve growth factor (NGF).

The Ki-67 (MIB1) antibody Labeling Index (Fig. 17.19) is among the highest detected in CNS tumors, owing to the high proliferative activity. It usually is not less than 30 % and even up to 80 %, revealing the large tumor aggressiveness. This wide range of expression, even inside the same tumor, is essentially function of the degree of differentiation. In fact, in the nodular

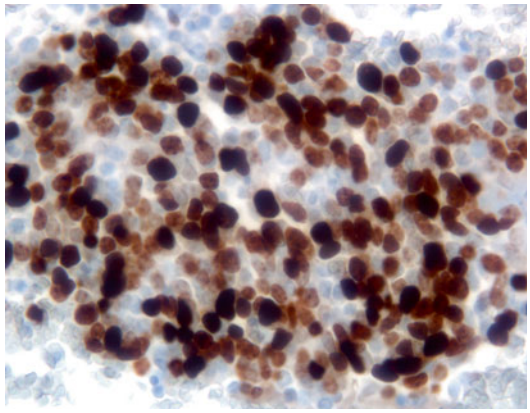

Fig. 17.19 Ki67. High Ki67 Labeling Index

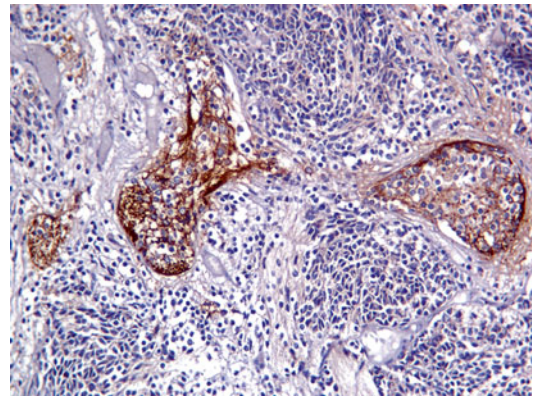

Fig. 17.21 CD133. Immunoreactivity for the stem cell marker CD133, detected inside the blades of islands in nodular medulloblastoma

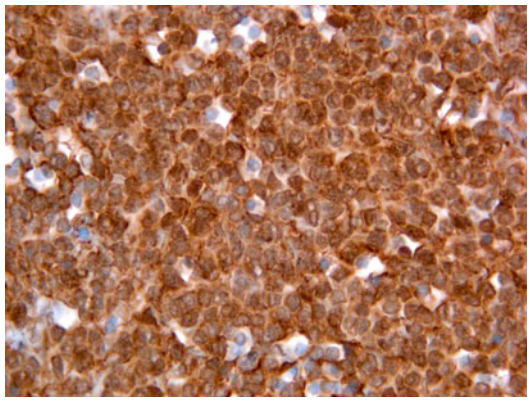

Fig. 17.20 β-catenin. Nuclear and cytoplasmic reactivity in medulloblastomas with a mutation in the β-catenin gene

variant, nodular foci, with neuronal or glial differentiation, usually show only scattered or peripheral positive nuclei, while the internodular zones explicit a much stronger signal. Higher rates are noted in the large-cell areas too.

Beyond the undoubted diagnostic utility, immunohistochemistry may play a relevant role for prognosis, patient stratification, and target therapy, although in a debated and not yet codified manner, being able to identify molecular subgroups of medulloblastoma, alternative to analysis of transcriptional profiling.

WNT subgroup medulloblastomas are characterized by nuclear immunoreactivity for both β-catenin [12, 52–57] and Dickkopf-related protein 1 (DKK1) [12, 56]. The former that also stains the cytoplasm (Fig. 17.20) generally shows a strong and diffused signal which, however, can also be moderate and patchy; DKK1 usually stains the cytoplasm.

SHH subgroup tumors are identified by cytoplasmic positivity to secreted frizzled-related protein 1 (SFRP1) [56, 60, 61], GRB2-associated-binding protein 1 (GAB1) [53], and GLI1 [56].

Both WNT and SHH subgroups are immunoreactive to cytoplasmic filamin A and YAP1 [61, 62], mainly within internodular regions of desmoplastic tumors: this panel allows to exclude a non-SHH/WNT molecular profile [53].

In fact, medulloblastomas belonging to groups 3 and 4 are usually immunonegative to all the abovementioned markers. However, group 3 and 4 tumors are identified respectively by positivity to natriuretic peptide receptor C/guanylate cyclase C (NPR3), and potassium channel Kv1.1 (KCNA1).

The association of more antibodies essentially strengthens the ascription of a medulloblastoma to a specific molecular subgroup, but there is a specific immunohistochemical panel that has been shown to have high diagnostic specificity.

Northcott et al. demonstrated that immunohistochemistry for DKK1 (WNT), SFRP1 (SHH), NPR3 (group C), and KCNA1 (group D) could univocally and reliably classify medulloblastomas,

Table 17.2 Chang's staging system for medulloblastoma

T1	Tumor less than 3 cm in diameter and limited to the midline position in the vermis, the roof of the fourth ventricle, and less frequently to the cerebellar hemispheres
T2	Tumor more than 3 cm in diameter, further invading 1 adjacent structure or partially filling the fourth ventricle
T3a	Tumor further invading 2 adjacent structures or completely filling the fourth ventricle with extension into the aqueduct of Sylvius, foramen of Magendie, or foramen of Luschka, thus producing marked hydrocephalus
T3b	Tumor arising from the floor of the fourth ventricle or brainstem and filling the fourth ventricle
T4	Tumor further spreading through the aqueduct of Sylvius to involve the third ventricle or midbrain or tumor extending to the upper cervical spinal cord
M0	No evidence of gross subarachnoid or hematogenous metastases
Ml	Microscopic tumor cells in cerebrospinal fluid
M2	Gross nodular seeding demonstrated in cerebellar, cerebral, and subarachnoid space or in the third or lateral ventricles
M3	Gross nodular seeding in spinal subarachnoid space
M4	Extraneural metastasis

in approximately 98 % of patients, into four non-overlapping molecular variants [56].

A statistical significant negative correlation of stem cell markers (CD15 eCD133) positivity (Fig. 17.21) with EFS (event-free survival) was observed [66].

17.6 Staging

The most widespread staging system is Chang's one [62]. Born in premodern neuroimaging era and later adapted to it, it was determined on surgical and autopsy findings considering the size, invasiveness, and spread outside the posterior fossa (Table 17.2). In particular, the brainstem invasion was considered an important prognostic factor also for subtotal resection.

A more recent modification is that proposed by Langston [63] that includes radiological staging and does not account for hydrocephalus and number of structures invaded (Table 17.3).

Table 17.3 Langston modification of the Chang's T

T1	Tumor <3 cm in diameter
T2	Tumor ≥3 cm in diameter
T3a	Tumor ≥3 cm in diameter with extension
T3b	Tumor ≥3 cm in diameter with unequivocal extension in to the brainstem
T4	Tumor ≥3 cm in diameter with extension up past the aqueduct of Sylvius and/or down past the foramen magnum (i.e., beyond the posterior fossa)

17.7 Cytology

The leptomeningeal disease is reported in about 30 % of medulloblastomas [64], and it is one of the major prognostic factors [6]. Therefore, the research of dissemination, by CSF cytology (lumbar and/or intracranial) together with magnetic resonance with gadolinium, plays a key role in the clinical management of these lesions.

The CSF examination generally shows small tumor cells, with a hyperchromatic nucleus; pleomorphism and apoptosis vary with the tumor grade. The little cytoplasm is often strongly basophilic especially at the level of the cell membrane [65]. Cell wrapping, or cannibalism, is also more common. In addition to the tumor cells, reactive CSF pleocytosis with prevalence of eosinophils may be evident. The differential diagnosis arises sometimes with lymphoblasts, with immature lymphocytes, and rarely with retinoblastoma. In these cases, immunocytochemical markers may be useful.

During intraoperative consultation, performing a cytologic "squash" (Fig. 17.22) can even be more useful than frozen sections.

17.8 Molecular and Cytogenetic Findings

The heterogeneity of this tumor is reflected also in the extreme heterogeneity of cytogenetic abnormalities. The most common one is the loss of all or part of chromosome 17p, often associated with duplication and translocation of chromosome 17q (isochromosome 17q). This

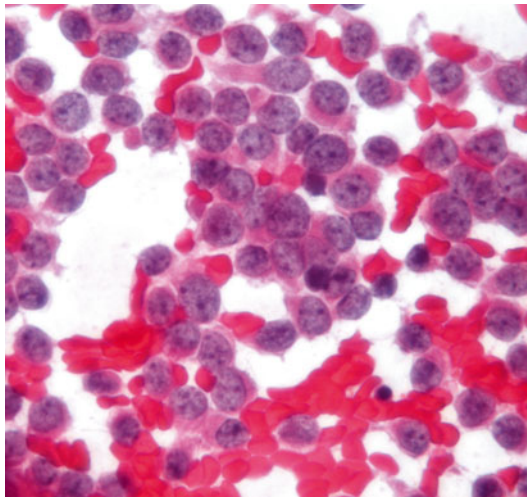

Fig. 17.22 Cytologic "squash" for intraoperative consultation. Small- and medium-sized cells with vesicular nuclei and multiple nucleoli and scant cytoplasm. Hematoxylin and eosin stain (63×)

alteration seems to be more expressed in non-nodular medulloblastomas, especially in higher-grade tumors.

High-level gains of chromosome 8q (N-*myc*) and 2p (c-*myc*) are frequently observed in anaplastic and large-cell medulloblastomas; the latter can be even characterized by amplification and overexpression of the oncogenes *c-myc* and N-*myc*. Overexpression of c-myc can also occur in non-anaplastic tumors, with negative, or unfavorable, prognostic significance.

Another molecular alteration is β-catenin nuclear positivity which characterizes the molecular subgroup of medulloblastomas associated with the activation of the WNT pathway. Immunohistochemical studies for β-catenin proved a statistical significant positive correlation with a better prognosis.

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