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1. Introduction

Pathological classification of brain tumors is the cornerstone upon which the management plan and treatment strategy depends. It is the pathologist who defines the “target” at which the rest of the clinical team members aim their “weapons”. Despite of the great advancement of the ancillary studies, the simple H&E stained slide remains an invaluable mean in the diagnosis, classification and stratification of primary brain tumors. Slides should be interpreted in correlation with patient’s age and clinical presentation. Radiological findings substitute the macroscopic/gross description in other organs and assessment of the location (supratentorial, infratentorial, intra-ventricular), growth pattern (circumscribed versus infiltrative, solid versus cystic), enhancement pattern (non-enhancing versus enhancing), and the presence or absence of edema, necrosis, calcification should all be consolidated with the microscopic findings in formulating the final diagnosis. The need for an expert neuropathologist is becoming crucial in reviewing the cases before commencing on treatment [1-3]. The importance of multidisciplinary clinics/teams cannot be overemphasized and neuropathologist plays a central role in these clinics [4, 5]. In less developed countries, telemedicine and twinning programs as well as affiliation with recognized international experts may offer an accessible and relatively affordable tool which can help narrowing the knowledge and practice gaps, thus providing patients in these countries with better standards of care [6, 7].

This chapter aims at providing a concise yet comprehensive description of the histology of the most common neuroepithelial primary central nervous system tumors, based on the most recent pathological classification of tumors of the CNS; 2007 WHO Classification of Tumours of the CNS [8]. The morphological features as well as the most useful immunohistochemical stains that can be used to support the diagnosis will be provided. In primary brain tumor there is a considerable overlap in diagnostic features and morphological criteria that are used to grade the tumor, which although is not the primary intention of this chapter, will be alluded to briefly for sake of completeness.
Primary brain tumors are divided into 2 major groups, neuroepithelial and non-neuroepithelial tumors. Table-1.

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</table>

Cribriform Neuroepithelial Tumor (CRINET): This tumor is a recently described neuroepithelial tumor and is not part of the WHO classification of primary brain tumors.

Table 1. WHO classification of tumors of the nervous system (2007) [8]
2. Neuroepithelial group of tumors

2.1. Glial tumors

This is by far the most common group of central nervous system tumors, both in adults and pediatrics. They are thought to originate from the brain framework cells; the glial cells. This group is divided into several tumor families which are further divided into entities, patterns and variants based on the presumed cell of origin and the growth pattern.

2.1.1. Astrocytic tumors

Circumscribed astrocytomas

a. Pilocytic astrocytoma (PA)/pilomyxoid astrocytoma (PMA)

Pilocytic astrocytoma (PA) is assumed to arise from reactive astrocytes [9], this tumor predominates in children in the first decade of life and is the prototype of circumscribed tumors. It typically involves midline structures most commonly the cerebellum followed by optic pathway, hypothalamus, basal ganglion and thalamus but can occasionally arise elsewhere. The morphological features are at large similar regardless of the site of origin with one exception; the optic pathway glioma. Typically this is a biphasic tumor with compact and microcystic areas, the proportion of which may vary from one tumor to the other. Proliferation of bipolar spindle “piloid” cells with long fibrillary processes is seen mostly within the compact areas “Figure 1”.

The microcystic areas, on the other hand show protoplasmic-like astrocytes with multi-polar short cytoplasmic processes and small cell body with round to oval bland nuclei “Figure 2”.

Areas with oligodendrogial like proliferation can be encountered, especially in the posterior fossa tumors. Various forms of vascular proliferation can be seen including reactive vascular
proliferation, vessels with hyalinized walls and granulation tissue like vessels, none of which carries a prognostic significance. Conspicuous pleomorphic cells, some of which appear multinucleated can be seen focally within tumor and are not associated with unfavorable outcome. Rosenthal fibers which correspond to thick, tortuous bright acidophilic cytoplasmic processes of variable length are seen mostly in the compact areas, while eosinophilic granular bodies predominate in the microcystic foci, both of which representing products of degeneration [9]. Calcifications with psammoma like spherules, perivascular inflammatory infiltrate and hemosiderin-laden macrophages are detected in few tumors. Scattered mitotic figures and foci of infarction-type necrosis can be identified in otherwise typical pilocytic astrocytoma. However; unlike fibrillary astrocytoma neither of these features warrant a higher grade diagnosis [10]. Areas with diffusely infiltrative growth pattern with entrapment of normal ganglion producing the “trapped neuron” appearance, can be seen in some tumors. In addition; infiltration into the overlying leptomeninges can sometimes be encountered [9].

Cases that exhibited anaplastic features and persued a more malignant behavior are reported in the literature, especially but not exclusively following radiotherapy [11]. The presence of increased mitotic activity per high power field, hypercellularity, endothelial proliferation and/or palisading necrosis should alert the pathologist to such a possibility. The diagnosis of “anaplastic pilocytic astrocytoma” is the term proposed by the WHO book for such tumors [8, 9]. Atypical pilocytic astrocytoma is, on the other hand assigned to few tumors that display few mitotic figures in conjunction with hypercellularity and marked nuclear atypia [8, 11].

Tumor cells are typically reactive with glial fibrillary acidic protein (GFAP) and vimentin. Reactivity for synaptophysin but not other neuronal markers is seen in some cases [10]. Neurofilament protein (NFP) highlights occasional axons in the background or can be totally negative thus is helpful in confirming the circumscribed nature of the tumor. Rosenthal fibers are reactive for GFAP but not NFP in support of their origin from astrocytic processes. This typically takes the form of positivity at the periphery of the fiber, with negative central core.
In Masson Trichrome special stain they appear bright red. Eosinophilic granular bodies (EGBs) on the other hand are positive for PAS diastase, which highlights their variably-sized granular appearance. Pilocytic astrocytomas are typically negative for P53 and EGFR, an important differentiating point from low and high grade diffuse astrocytoma; respectively [10, 12]. MIB-1 labeling index is variable and can range from 1-8% [10, 13], and this does not seem to be associated with prognosis [14]. BRAF immunostain has been recently described in some cases. However; this is not helpful in determining BRAF duplication [10], the genetic signature of pilocytic astrocytoma.

Pilomyxoid astrocytoma (PMA) is a distinctive tumor that occurs mostly in infants in the hypothalamic/ supra-sellar region. As the name implies this tumor manifests prominent myxoid stroma that can be highlighted with alcian blue stain and a monomorphic piloid astrocytes that arrange themselves in a distinct perivascular growth pattern with sun-ray like orientation “Figure 3”.

Figure 3. Distinct perivascular pseudorosette is seen in this case of pilomyxoid astrocytoma.

Few mitotic figures can be detected. Unlike pilocytic astrocytoma, there is no biphasic growth pattern, Rosenthal fibers or eosinophilic granular bodies and infiltration into adjacent brain parenchyma is more prominent [15]. Interestingly; some PMA cases have matured into pilocytic astrocytoma following several recurrences [16], suggesting a close relation between both tumors. The tumor cells demonstrate strong and diffuse positivity for GFAP and vimentin and focal positivity for synaptophysin. Neurofilament protein highlights the limited infiltration into adjacent parenchyma [17]. MIB-1 labeling index is around 5%, although higher figures would still be compatible with the diagnosis.

b. Pleomorphic xantho-astrocytoma (PXA)

PXA is a superficially located tumor with close relation to the meninges that predominates in the temporal lobe. It occurs in children and young adults with history of epilepsy [18]. Morphologically it is a composite tumor with a variegated appearance in which spindle cells closely intermingle with small and large mononuclear and multinucleated bizarre tumor giant...
cells with acidophilic cytoplasm “Figure 4”. Intra-nuclear cytoplasmic pseudo-inclusions are frequently seen in the giant cells. Cytoplasmic lipidization in the form of intra-cytoplasmic droplets that occupy much of the cytoplasm and displace the organelles and glial filaments to the periphery is seen in tumor cells scattered through the tumor, hence the “xantho” prefix.

**Figure 4.** Multinucleated tumor giant cells are seen (right lower) admixed with cells with intracytoplasmic fine lipid droplets (arrow).

These lipidized cells can be prominent or alternatively can only be scattered through out the tumor substance. Oil-red O confirms the intra-cytoplasmic lipid content on fresh material. An infiltrating astrocytoma pattern is seen at the deeper aspect of the tumor and this does not affect the outcome [19]. Invasion of the overlying meninges can be encountered in some tumors, creating resemblance with meningioma. Striking positivity for reticulin stain with fibers surrounding groups of cells or individual cells is seen in many tumors; probably representing a reaction to infiltration of the meninges. The blood vessels show peri-vascular lymphoplasmacytic infiltration. Eosinophilic granular bodies, but not Rosenthal fibers can be seen scattered within the tumor substance. Despite of this alarming appearance mitotic figures are not seen and necrosis is at best focal; important discriminating features from giant cell glioblastoma [20]. GFAP labels the tumor cells including the giant cells, and is displaced to the periphery in lipidized cells. Positivity for synaptophysin, NFP and CD34 in tumor cells has been noted in some cases, rendering separation from ganglioglioma difficult [18, 20]. PXA with anaplasia is reserved for tumors showing no or rare degeneration, increased mitoses ≥5 MF/10HPFs and atypical mitoses [14]. MIB-1 and P53 are not helpful in predicting more aggressive tumors, i.e. PXA with anaplasia [21].

c. **Sub-ependymal giant cell astrocytoma (SEGA)**

This intra-ventricular tumor is typically associated with tuberous sclerosis complex. It exhibits proliferation of three cell types; large gemistocytes -like cells with perivascular pseudorosette pattern, long spindle fibrillary astrocytes arranged in broad fascicles and giant cells, some with ganglioid appearance “Figure 5”.

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Clinical Management and Evolving Novel Therapeutic Strategies for Patients with Brain Tumors150
Calcification is noted in some cases and can be prominent in long standing ones [22]. Various combinations of glial and neuronal markers are reported in different cell population. Co-expression of GFAP, neuron-specific enolase (NSE) and synaptophysin is noted in tumor cells, including the spindle cells, while NFP is usually positive in ganglioid cells only. Mitosis, vascular proliferation and necrosis do not seem to affect the prognosis [23, 24].

Diffuse astrocytoma

This group of tumors is composed of proliferation of astrocytes that diffusely infiltrate pre-existing brain parenchyma, thus precluding successful attempts at complete excision and cure. In addition; there is a natural tendency for progression and transformation from lower into high grades. On a rising scale of malignancy these tumors are divided into the following entities:

a. Fibrillary astrocytoma (FA)

FA is at the lower end of the malignancy scale, and can raise diagnostic difficulties with reactive gliosis on one hand and circumscribed low grade astrocytoma on the other. Morphologically there is proliferation of “well-differentiated” fibrillary astrocytes with elongated, irregular and hyperchromatic nuclei exhibiting angulated contours with many coma-shaped forms that lack nucleoli “Figure 6”. Thin cytoplasmic process originate from the cytoplasm and form the mesh-like fibrillary background. Morphological variation include the proliferation of gemistocytic and protoplasmic astrocytes. Gemistocytes contain a globular acidophilic cytoplasm with distinct membranous accentuation, eccentric irregular nuclei and thick cytoplasmic processes. Protoplasmic astrocytes on the other hand show multi-polar cytoplasmic processes and grow in a myxoid background, forming microcysts [25]. Features of anaplasia are lacking and mitoses are generally not detected [25, 26]. GFAP positivity is seen both as haphazardly crossing processes in which “naked” tumor nuclei are enmeshed, and as dense cytoplasmic rim positivity surrounding the nuclei. Gemistocytes demonstrate diffuse cytoplasmic GFAP positivity with
membranous accentuation; an important discriminating point from mini-gemistocytes seen in oligodendroglioma (see below). To support the infiltrating astrocytoma diagnosis NFP, P53 and IDH1 can be used. Neurofilament protein is useful to highlight the infiltrative growth pattern “Figure 7”.

Figure 7. Neurofilament protein immunostain highlights the neuronal processes, with negative tumor cells in between confirming the infiltrative nature of the tumor.

P53 may be strongly positive in tumor cell nuclei versus the negative/ minimal staining in gliosis. [27]. Recently; IDH1 antibody is reported to be positive in all infiltrating gliomas (astrocytoma, oligodendroglioma and mixed oligo-astrocytoma) with granular cytoplasmic reactivity pattern [20, 28]. MIB-1 labeling index is low, although the cut-off value is not exactly determined (see below) [29].

A recently described morphological pattern is the “glioneuronal tumor with neuropil-like islands”, in which nodules of well differentiated neurocytic cells are embedded within and
surround acellular synaptophysin-positive neuropil islands. These are seen focally in what is an otherwise typical infiltrating astrocytoma of either fibrillary or anaplastic types [15]. There is a relative abrupt transition between both components [30]. In these islands the cells are positive for synaptophysin and NeuN, while the neuropil in the background displays granular positivity for synaptophysin [17].

b. Anaplastic astrocytoma (AA)

AA occupies an intermediate position between fibrillary astrocytoma and glioblastoma. Features of anaplasia include higher cellularity, greater degree of pleomorphism and increased proliferation. The exact number of mitotic figures needed to separate this from FA is still debatable and this feature should be evaluated in relation to the amount of tissue sample examined. While the presence of a single mitotic figure in a small stereotactic biopsy justifies assigning grade III to a tumor, the presence of a single mitotic figure in an ample biopsy after careful searching and deeper sections might not be as relevant. In one study; >3MF/10HPFs was the cut-off value proposed [27]. Ancillary studies might help in defining the proliferative activity of a tumor and can be used to support the diagnosis of AA. Although cut-off values are variable an elevated MIB-1 labeling index (>9%) and proliferative activity as measured by PHH3 mitotic index (>4per 1000 cells) were found to be supportive of AA diagnosis over FA, in which MIB-1 and PHH3 labeling indices were low (≤ 9% and ≤4 per 1000 cells) [27]. In addition; MIB-1 labeling index prognostic value independent from histologic grade was reported [14], which might be indicative of an early anaplastic transformation [31], even in the absence of detectable mitoses.

c. Glioblastoma (GBM)

This is the most malignant and unfortunately the single most common primary brain tumor. The essential features for the diagnosis of GBM are microvascular proliferation (MVP) and/or necrosis whether palisading or not. Microvascular proliferation is loosely defined to include endothelial hypertrophy, endothelial hyperplasia and glomeruloid vessels, in which multilayered tufts of proliferating endothelium are accompanied by smooth muscles and pericytes “Figure 8” [32].

As the original name implies glioblastoma “multiforme” is characterized by heterogeneous cell population with proliferation of fibrillary, gemistocytic and scattered tumor giant cells “Figure 9”.

On the basis of their origin GBM is divided into primary (type II) and secondary (type I) types. Primary GBM is a tumor of elderly patients, is characterized by short presenting history and it arises de-novo with no detectable pre-existing lower grade tumor. Secondary GBM on the other hand affects younger patients with prolonged history and is typically preceded by a lower grade astrocytoma. Prognosis seems to be better for the secondary tumors. Whether a tumor is primary or secondary GBM cannot be predicted on basis of morphologic features. However; the presence of large vessel thrombosis with large areas of infarction-like necrosis seems to be more prevalent in primary GBM. Immunohistochemically; reactivity for PS3,
MGMT and IDH1 is more frequent in secondary GBM, while positivity for EGFR is more common in primary GBM [32].

Several GBM variants and patterns are described some of which might be prognostically relevant, Table-2.

Giant cell glioblastoma (GCG)

GCG accounts approximately for 1.5-5% of GMB cases [32]. This is characterized by the predominance of bizarre markedly enlarged, often multinucleated tumor giant cells that tend to grow in cohesive pattern with rich reticulin-positive stroma, accounting for the deceptively circumscribed nature of the tumor seen radiologically. GFAP tends to be strongly positive in many of the tumor cells. Up to 90% of these tumors are positive for P53 [20]. Recently; it was shown that CD34 can be positive in giant cell glioblastoma, thus losing its discriminating power.
from pleomorphic xanthoastrocytoma; its main differential diagnosis [33]. Giant cell glioblastoma is claimed to carry a slightly better prognosis than classical GBM [20].

Gliosarcoma (GS)

This is a well-circumscribed, biphasic tumor that brings morphological remembrance to “carcinosarcoma” in other sites. There is a near mutually exclusive staining for GFAP and reticulin in the glial and mesenchymal components; respectively [34]. In the glial component a clear GFAP-positive, reticulin-free usually fibrillary and sometimes gemistocytic astrocytes proliferation is seen with necrosis and vascular proliferation. The sarcoma component, on the other hand is typically GFAP-negative, and reticulin-rich. This component may be fibroblastic with proliferation of long bundles of malignant spindle cells, or can show heterologous component including smooth muscle, adipose tissue, cartilage and osteoid formation [32].

Glioblastoma with oligodendroglial component (GMB-O)

This is thought to represent a variant of glioblastoma with a probable better prognosis [35]. Its relation to the mixed oligo-astrocytic tumors is discussed below. The essential component for establishing this diagnosis is the presence of an oligodendroglial component in addition to the astrocytic component in association with necrosis [15]. In 15-20% of tumors 1p/19q co-deletion is detected.

Small cell glioblastoma (SCG)

This is characterized by proliferation of deceptively bland, uniform, small, round to slightly elongated cells with minimal atypia, but with brisk mitoses. Of note is the rarity of microvascular proliferation and necrosis in most cases [20]. GFAP is at best focally positive in thin cytoplasmic processes. Resemblance to anaplastic oligodendroglioma is further accentuated by the presence of tumor cell satellitosis, chicken-wire vascular proliferation and microcalcifications [15, 20]. The disconnection between the bland cytology and the brisk mitosis should act as a clue in this differential diagnosis. Furthermore; immunoreactivity for EGFRvIII supports the diagnosis of small cell GBM [20].

Glioblastoma with primitive neuroectodermal tumor (PNET)-like component

In this variant proliferation of a clone of primitive cells reminiscent of PNET/medulloblastoma is seen, sometimes forming discrete nodule. The cells have high nuclear cytoplasmic ratio and exhibit frequent neuroblastic and Homer-Wright rosettes. Features of anaplasia with cell-cell wrapping, increased cell size with prominent nucleoli are seen in a subset of cases; thus bringing resemblance to anaplastic/large cell medulloblastoma (see below). Mitotic activity is brisk. Immunohistochemistry shows diffuse staining for neural markers including synaptophysin and NeuN and in many cases P53. GFAP is positive only in occasional cells. MIB-1 labeling index shows a nearly diffuse positivity (almost 100%) [31, 36].

Adenoid glioblastoma

This is an extremely rare variant that brings metastatic carcinoma into the differential diagnosis. There is glandular-metaplastic component that intermingles with the better defined glial
component. Reactivity for a variety of cytokeratins including CK7 can add further to the confusion [32, 37].

Granular cell glioblastoma (GCA)

This is a deceptively bland tumor with proliferation of astrocytes showing abundant granular PAS-positive cytoplasm and regular nuclei, so they can be confused with macrophages. Reactivity with GFAP is the rule with few cases displaying EMA but not cytokeratin positivity. P53 can be positive in few cases [32].

Table 2 summarizes the clinicopathological features of GBM variants (From Miller et al with modification) [32]

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Features</th>
<th>1ry</th>
<th>2ry</th>
<th>Fib</th>
<th>Gem</th>
<th>GCA</th>
<th>GC</th>
<th>GS</th>
<th>SCA</th>
<th>GBM-O</th>
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<tr>
<td>Peak age (decade)</td>
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<td>6-7</td>
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</tbody>
</table>

1ry, primary; 2ry, secondary; Fib, fibrillary; Gem, gemistocytic; GCA, granular cell astrocytoma; GC, giant cell; GS, gliosarcoma; SCA, small cell astrocytoma; GBM-O, GBM with oligodendrogial features; …, no data available; -, absent; +/-, infrequent; + to ++, increasing frequency; PVI, perivascular inflammation.

Table 2.

d. Gliomatosis cerebri

This entity has been shifted to join astrocytic tumors in 2007 classification. By definition, it is an infiltrative tumor involving at least 2 lobes but lacking mass effect. When crossing from one
side to the other it causes widening of the corpus callosum. Microscopically; there is an infiltrative glioma, usually corresponding to grade III anaplastic astrocytoma and occasionally to oligodendroglioma. Rarely grade II fibrillary astrocytoma or grade IV glioblastoma can be encountered. Characteristically; the infiltrating malignant cells preserve the underlying structures intact without destruction. P53 can highlight the tumor cells and MIB-1 labeling index is variable reflecting the grade of the tumor [38, 39].

2.1.2. Oligodendroglioma

This is characterized by proliferation of monotonous cells with regular round, uniform nuclei with delicate chromatin, sharply defined nuclear membrane and inconspicuous nucleoli, brining a “highly-uniform” appearance on low power examination. In formalin-fixed tissue there is clearing artifact creating “haloes” around tumor cell nuclei due to shrinkage of the cytoplasm; a useful diagnostic clue, although not an absolute criteria for diagnosis “Figure 10” [31].

![Figure 10](http://dx.doi.org/10.5772/52356)

Figure 10. A case of oligodendroglioma with monotonous fried-egg appearance, chicken-wire vascularity and scattered calcification (arrow).

However; a small eccentric acidophilic cytoplasm can sometimes be appreciated. Hypertrophy of the cortical vessels leads to the development of the characteristic chicken-wire vascular proliferation [35]. Micro-calcification, extensive infiltration of the cortical structures with perineural satellitosis and microcysts with basophilic mucinous contents are additional diagnostic features [20]. In the anaplastic variant; the vascularity becomes more prominent leading to the development of a nodular growth pattern at low power magnification. The cells become larger and exhibit more abundant cytoplasm with vesicular nuclei and prominent nucleoli; yet they retain their uniform appearance. There is increased cellularity with increased mitosis (≥6 MF/10HPFs), microvascular proliferation and necrosis. Important companions are the glio-fibrillary oligodendrocytes and the mini-gemistocytes “Figure 11”.

![Image](http://dx.doi.org/10.5772/52356)
Minigemistocytes with whorling GFAP positive filaments. The tumor cells can be positive for GFAP. This is especially seen in the perinuclear staining in glio-fibrillary oligodendrocytes and the diffuse cytoplasmic staining in the mini-gemistocytes, thus potentiating confusion with infiltrating astrocytoma, or mixed oligo-astrocytoma [20]. In most cases, P53 [25] and vimentin [40] stains are negative thus helping in sorting out the differential diagnosis with astrocytoma. A notable pitfall is the positivity of oligodendrogial tumors for neural markers including NeuN [41, 42], and synaptophysin which reacts with a para-nuclear dot-like positivity [31].

2.1.3. Mixed oligo-astrocytoma

Mixed oligo-astrocytoma is one of the most common tumors associated with considerable diagnostic difficulty and inter-observer variability [31]. A mixture of oligodendrogliaoma and infiltrative diffuse astrocytoma is seen. Both components can be spatially separated (compact variant) or they can be intermixed (diffuse variant). The minimum percentage of each component needed to establish the diagnosis is debatable, although a minimum of 10% astrocytic component of either fibrillary or gemistocytic morphology was used in some studies [43]. In the anaplastic variant, the tumors are highly cellular with pleomorphism and nuclear atypia, mitosis (≥6 MF/10HPFs) and/or microvascular proliferation [31] which could be identified in either or both components. Recent literature supports the up-grading into glioblastoma in the presence of necrosis (see above) [17, 35].

2.1.4. Ependymoma

a. Myxo-papillary ependymoma

This is a slowly growing tumor that is almost exclusively seen in the cauda equina and filum terminale of young adults. It is composed of hypo- and hypercellular areas. The hypocellular areas show abundant mucicarmine-positive mucinous matrix with scattered epithelioid-appearing cells. The hypercellular areas are formed of tumor cells arranged in papillary structures. Cystic spaces filled with alcian-blue, PAS positive mucin separate the tumor cells from the blood vessels “Figure 12”.

Figure 11. Minigemistocytes with whorling GFAP positive filaments. The tumor cells can be positive for GFAP. This is especially seen in the perinuclear staining in glio-fibrillary oligodendrocytes and the diffuse cytoplasmic staining in the mini-gemistocytes, thus potentiating confusion with infiltrating astrocytoma, or mixed oligo-astrocytoma [20]. In most cases, P53 [25] and vimentin [40] stains are negative thus helping in sorting out the differential diagnosis with astrocytoma. A notable pitfall is the positivity of oligodendrogial tumors for neural markers including NeuN [41, 42], and synaptophysin which reacts with a para-nuclear dot-like positivity [31].
In myxo-papillary ependymoma, alcian-blue positive cores surround vessels and cells grow in between forming sheets and sometimes perivascular psuedorosettes. The cells are bland with processes radiating to the walls of the vessels and are arranged in single or multiple layers. Cribriform areas, sheets of cells and cells with clear cytoplasm can occasionally be encountered, creating resemblance to metastatic carcinoma. Pleomorphic cellular features, proliferation of vascular spaces, mitosis or necrosis are not seen, even in more aggressive tumors [44]. Tumor cells are reactive for GFAP and S-100 and MIB-1 labeling index is low. A potential pitfall is positivity of the cells for pancytokeratin (AE1/AE3), cam 5.2 and cytokeratin 7 [45]. EMA can show cytoplasmic positivity in few tumor cells, similar to the pattern seen in other ependymoma (see below).

b. Sub-ependymoma

This mostly arises in the 4th followed by lateral ventricles [46]. Many cases are asymptomatic and discovered incidentally, although symptoms of increased intra-cranial pressure are the presenting features in others [47]. Morphologically; this is a well-delineated tumor that is characterized by nodules of clustered isomorphic cells arranged against a fibrillary background alternating with hypocellular fibrillary areas. Vague perivascular rosettes can be seen “Figure 13”.

Focal cystic degeneration is noted [48], as well as vascular hyalinization, nuclear pleomorphism and calcification [46]. This distinctive pattern may frequently be admixed with classical ependymoma (See below). No mitotic figures, vascular proliferation or necrosis is detected in most tumors. GFAP is diffusely positive in these cases. MIB-1 labeling index is extremely low approaching zero [46].

c. Cellular ependymoma;

This is characterized by the presence uniform monomorphic cells extending their fine processes radially to the walls of blood vessels creating a fibrillary cellular free zone around the
vessels and forming perivascular pseudorosettes. True rosettes and ependymal canals, where clusters of ependymal cells are arranged around a lumen resembling spinal canal, are less commonly encountered “Figure 14”.

Feature of anaplasia include diffuse hypercellularity with diffuse nuclear pleomorphism, vascular endothelial proliferation, palisading necrosis, increased mitosis (usually ≥5MF/10HPFs) and elevated MIB-1 labeling index (≥20.5%) [27, 49]. Necrosis, in the absence of palisading, is a common feature in posterior fossa tumors, and is not a poor prognostic feature [31]. Interestingly; the identification of sub-ependymoma like areas in infratentorial ependymoma seems to be associated with adverse outcome [14]. Another important microscopic feature is the focal hypercellular nodules, in which focal increase in cellularity is associated with nuclear pleomorphism and an increase in mitosis. In the absence of diffuse changes, these
nodules are not associated with an adverse prognosis and as such may not warrant assigning a higher grade to the tumor [49]. GFAP is variably positive in tumor cells, especially in perivascular processes. EMA [50] and CD99 show characteristic dot-like perinuclear cytoplasmic positivity [51]. Other positive stains include other intermediate filaments like vimentin and desmin [27].

d. Clear cell ependymoma
This is a tumor that predominates supratentorially and displays an enhancing cystic component in the majority of cases. It is characterized by proliferation of sheets of cells with round nuclei and prominent, clear haloes. Focal ependymal perivascular pseudorosettes may be seen but true rosettes and canals are not typical. Features of anaplasia including increased cellularity, mitosis and microvascular proliferation, and at least focal necrosis are frequent. Reactivity for GFAP with perivascular accentuation, dot-like cytoplasmic EMA and CD99 staining should all help in reaching the appropriate diagnosis. MIB-1 labeling index is increased especially in areas of increased mitosis. [52]. Clear cell ependymoma should be differentiated from oligodendroglioma [20, 52].

e. Tanycytic ependymoma
This is primarily a tumor of the spinal cord, but occasional cases may arise from the third ventricle or the hypothalamus. Tanycytic ependymoma posses an “astrocytoma-look”, with solid proliferation of spindle cells with elongated processes and with at best focal ill-defined ependymal pseudorosettes. The nuclei are uniform, round to oval with salt and pepper chromatin, similar to other ependymoma “Figure 15”.

Figure 15. Tanycytic ependymoma is composed of “piloid” like tanycytes with only vague perivascular pseudorosettes noted.

Strong GFAP positivity is seen in the elongated processes. Other positive markers include S-100, vimentin and CD99 [20].
2.2. Embryonal tumors

They all share proliferation of small round blue cells with increased mitosis and apoptosis. This group includes

a. Medulloblastoma

This is a primitive neuroectodermal tumor that arises from the cerebellum. It is the most common malignant brain tumor in children and the most common embryonal tumor. Medulloblastoma is thought to originate from a primitive cell type in the cerebellum. The multipotent progenitor cells of ventricular zone that forms the innermost boundary of the cerebellum is the postulated origin of the classical medulloblastoma, while the external germinal layer that lines the outside of the cerebellum; the external granular layer, is the postulated origin of the desmoplastic medulloblastoma [53].

Several morphologic sub-types are recognized, some of which are prognostically relevant:

- Classic medulloblastoma; is the most common variant, and represents 66% of cases [54]. It is composed of densely-packed cells with hyperchromatic, round, oval or carrot-shaped nuclei with minimal cytoplasm “Figure 16”.

Figure 16. Sheets of tumor cells with Homer-Wright rosettes (right side) and neurocytic nodules (left) can be encountered in typical medulloblastoma.

The cells are usually arranged in diffuse sheets, but trabeculae, spongioblastic pattern, Homer-Wright rosettes and nodules can be identified. Necrosis, sometimes palisading, may be seen in some tumors, and has been identified as an adverse prognostic feature [55].

- Desmoplastic/nodular medulloblastoma (DNM) and medulloblastoma with extensive nodularity (MEN); both of these variants share the presence of reticulin-rich desmoplastic component and a reticulin-free, nodular component showing comparatively extensive neurocytic differentiation, fibrillary background, less mitoses and frequent apoptosis “Figure 17”.
Both variants are claimed to be associated with better prognosis [54]. DNM can be seen in children and adults and represents 25% of cases of medulloblastoma. MEN, on the other hand, is characteristically seen in infants, where it accounts for 57% of medulloblastoma in this age group and is associated with excellent outcome. Whereas the reticulin-rich component predominates in DNM, and the presence of any percentage of nodularity and desmoplasia qualifies the tumor for DNM subtype [56], the reticulin-free differentiating component predominates in MEN, representing 96-100% of the tumor [57]. Thus MEN might be perceived as an exaggerated form of DNM [15]. Importantly, the borders between the nodules and the surrounding desmoplasia are usually sharp [54]. The presence of desmoplasia due to infiltration of the meninges in the absence of nodules does not qualify the tumor as DNM [57] and vice versa; the identification of less-delineated neurocytic nodules in the absence of desmoplasia i.e. biphasic medulloblastoma is considered a variation of classical or sometimes anaplastic/large cell medulloblastoma morphological patterns that are not associated with improved outcome in some [54], but not all studies [55]. Immunohistochemistry helps further confirming both growth patterns. The pale islands are synaptophysin positive with low MIB-1 labeling index, while the inter-nodular areas are at best focally positive for synaptophysin with high MIB-1 labeling index, in keeping with presence or absence of neuronal differentiation; respectively.

- Anaplastic/large cell medulloblastoma; these are closely related variants that frequently co-exist and account for 17-24% of cases of medulloblastoma [54, 57]. In anaplastic medulloblastoma there is marked nuclear pleomorphism with angular, crowded pleomorphic cells with nuclear molding, cell-cell wrapping and numerous mitotic and apoptotic figures “Figure 18”.

**Figure 17.** Desmoplastic medulloblastoma with pale islands and internodular area giving a reactive lymph node like appearance.
Figure 18. Anaplastic medulloblastoma with frequent cell wrapping (lower right), apoptosis and abnormal mitosis.

The nuclei are twice to three times the size of an RBC in moderate to severe anaplasia, thus varying in size from 18-21 micrometers; respectively [57, 58]. Hyperchromasia per se is not a defining feature of anaplasia. The large cell variant on the other hand is characterized by large spherical cells possessing round vesicular nuclei and prominent central nucleoli “Figure 19” [57, 58].

Figure 19. In large cell medulloblastoma; the cells have abundant cytoplasm, vesicular nuclei and prominent nucleoli.

Anaplasia is considered diffuse when seen involving every low power field, otherwise it is considered focal. It is the diffuse, moderate to severe anaplasia that is associated with poor prognosis. Anaplastic/large cell features can be detected in what appears to be DNM or in recurrent classical medulloblastoma. The presence of features of DNM, Homer-Wright rosettes or previously classical medulloblastoma is not incompatible with the diagnosis of anaplasia [31, 57, 58].
• “Medulloblastoma with myogenic differentiation” and “medulloblastoma with melanotic differentiation” are considered morphological patterns with divergent differentiation that can be seen in any of the medulloblastoma variants, but with no effect on prognosis. Respectively; desmin and myogenin positive rhabdomyoblasts and S-100 positive melanotic tumor cells are seen in both patterns, hence the nomenclature [15].

In medulloblastoma, the tumor cells are positive for synaptophysin in up to 80% of cases, while microtubule-associated protein 2 antibody (MAP2) is seen in cases with weak synaptophysin reactivity [27]. CD99 is usually negative in contrast to peripheral PNET [59]. GFAP reactivity can be seen in medulloblastoma cells in a perinuclear pattern and this might carry adverse prognosis [27]. Diffuse positivity for P53 (strong nuclear stain in > 50%), ErbB2 (strong membranous staining in ≥ 50% of tumor cells) and survivin (nuclear stain) is associated with poor prognosis [56, 60-62]. TrK-C (strong cytoplasmic staining in >50% of tumor cells) and beta-catenin (either diffuse, strong cytoplasmic and nuclear or nuclear staining in cell clusters of at least 10% of nuclei among others with negligible or weak staining) are associated with improved outcome [60, 63, 64]. MIB-1 labeling index is variable but with a mean that ranges between 46.5-59.03%. The prognostic importance of elevated MIB-1 labeling index varies from one study to another [56, 60], with higher figures reported among anaplastic/large cell variant, and correlating with poor outcome [65].

b. CNS-primitive neuroectodermal tumor (CNS-PNET)

This is a heterogeneous group of poorly-differentiated primitive small round blue cells that can be seen supratentorially, in the brainstem or in the spinal cord. Divergent differentiation along neuronal/ ganglio-neuronal, epithelial or ependymal lines can be seen occasionally, hence the neuroblastoma/ CNS ganglioneuroblastoma, medulloepithelioma and ependymoblastoma variants; respectively [15]. The presence of necrosis adversely affects the outcome [14]. Embryonal tumor with abundant neuropil and ependymoblastic rosettes (ETANTR) is a newly described variant that is considered a hybrid tumor where both neuroblastic and ependymoblastic differentiation co-exist. Characteristically; ETANTR has been reported to have extra-copies of chromosome 2 [66] and 19q amplification [67].

CNS-PNET can show positivity for synaptophysin, GFAP and occasionally dot-like cytoplasmic EMA, according to differentiation [68]. Of note is the total negativity for CD99 in contrast to the peripheral type PNET tumors [69].

c. Atypical teratoid/rhabdoid tumor (AT/RT)

This tumor predominates in infants and can be seen in supratentorial and infratentorial compartments. Growth pattern are predominantly diffuse in most cases with reticular and papillary patterns noticed in few [70]. The typical cell, “rhabdoid cell” is seen in most but not all tumors and is not an absolute prerequisite for establishing the diagnosis. It is a large cell with eccentric acidophilic cytoplasm, vesicular nucleus with prominent nucleolus, reminiscent of “rhabdomyoblasts” hence the name. Intra-cytoplasmic spherical filamentous inclusions are identified in a proportion of rhabdoid cells “Figure 20”.

Histology of Primary Brain Tumors
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Figure 20. Typical case of AT/RT composed of cells with eccentric acidophilic cytoplasm and vesicular nuclei with prominent nucleoli. Note the myxoid background in the lower left corner.

Other common cellular components included large pale cells and primitive small round blue cells. Pale cells are characterized by vesicular nuclei, prominent nucleoli, and granular vacuolated wispy or water clear cytoplasm lacking intra-cytoplasmic inclusions, while small cells are cells with high nuclear:cytoplasmic ratio reminiscent of medulloblastoma/PNET [42, 71]. Admixture of all three cell components is noted in most cases. However, cases composed entirely of one cell type are not uncommon. Variable mesenchymal structures including myxoid changes, chondroid, lipoblastic and spindle cells elements can be seen. Occasional cases may contain glandular or papillary structures as an evidence of epithelial differentiation. Dystrophic calcifications and necrosis can be identified in some tumors.

Nowadays; the diagnosis of AT/RT can be confirmed by loss of INI1/BAF47 immunostain in tumor cells nuclei with appropriate positive normal endothelial and mononuclear cell control in the background [42]. In the rare instances of retained INI1/BAF47 nuclear stain, which is seen in 2% of cases, positivity for a panel of other markers can help in suggesting the diagnosis. A panel of EMA, synaptophysin, GFAP, vimentin, smooth muscle actin and pan-cytokeratin can show various combination of positive staining and thus can be of help in suggesting the diagnosis [27]. Confirmation by cytogenetics for monosomy 22 may be warranted in such cases. Notably is the absence of desmin [72]. MIB-1 labeling index ranges between 30-50%.

2.3. Neuronal and mixed neuronal-glial tumors

This is the most heterogeneous and rapidly expanding group of tumors with many newly recognized and added entities. As the name implies, many tumors are composed of a mixture of glial and neuronal components.

a. Ganglioglioma (GG) and gangliocytoma

Frequently presenting as long standing chronic seizure, this biphasic tumor is most commonly located in the temporal lobe and is seen mostly in children and young adults. This is a variably circumscribed tumor with intimate mixture of disfigured and dysplastic neurons and neo-
plastic glial cells of varying proportions. The ganglion cells are characterized by cyto-architectural disorientation with sub-cortical localization, abnormal aggregations and clustering. Morphologically; the neurons show abnormal forms with frequent cytomegaly, bi- and multinucleation, prominent nucleoli, and peri-membranous condensed Nissl substance [73]. The glial component can vary as well from pilocytic to diffuse astrocytoma to oligodendroglioma like component “Figure 21” [73, 74]. This is the proliferative component that ultimately determines the biological behavioral of GG. Tumors composed predominantly of ganglion cells, which are devoid of a glial component are termed gangliocytomas [73, 74]. Dysplastic calcification (globules or incrustation), eosinophilic granular bodies and increased reticulin meshwork can be seen in the background. Perivascular lymphocytes and scattered parenchymal plasma cells are common supportive features. An atypical or anaplastic ganglioglioma is rarely encountered and can arise either de novo or at recurrences of a previously diagnosed GG [74]. The presence of cellular atypia and pleomorphism, microvascular proliferation, necrosis and elevated MIB-1 labeling index supports the diagnosis of anaplastic ganglioglioma [17, 73]. It was suggested to lable tumors exhibiting features of anaplasia without necrosis as atypical GG[74]. Gemistocytes identified in some tumors might represent an additional feature of anaplasia [74].

**Figure 21.** Ganglioglioma with dysplastic ganglion cells that are haphazardly oriented with abnormal aggregation of Nissl substance in the cytoplasm. Perivascular lymphocytic infiltrate is seen.

Immunohistochemically; the dysplastic ganglion cells are positive for synaptophysin, with peri-somatic synaptophysin reactivity, chromogranin A, neurofilament protein and MAP2 [74-76], while the glial component is positive for GFAP. Dysplastic ganglions frequently fail to react with NeuN, a potentially useful marker to differentiate dysplastic from normal neurons [42]. CD34 is reported to be positive in up to 80% of tumors; labeling the dysplastic neurons, being less frequently positive in atypical and anaplastic tumors [74]. MIB-1 labeling index is seen in the glial component and is usually <1% [77] and labeling index >5% is associated with a more aggressive behavior (see above). P53 is reported in only atypical/anaplastic tumors [74, 77].
b. Desmoplastic infantile ganglioglioma/astrocytoma (DIG/DIA)

DIG is a massive, supratentorial tumor that primarily affects infants, usually younger than 6 months of age. It is characterized by superficial leptomeningeal attachment, multiple conspicuous cysts, firm consistency and focal infiltration into adjacent brain parenchyma without clear plane of resection [78]. Microscopically; there is admixture of fibroblasts, neuroastroglial cells and primitive cells, all enmeshed within a desmoplastic stoma, that can be highlighted by reticulin and Masson’s trichrome stains [79]. The proportion of the different cellular components varies from one tumor to the other. The astroglial cells are the most abundant cell component, especially in regions of desmoplasia, are characterized by strap-like to polygonal, GFAP positivity. The neuronal cells; on the other hand are more frequently seen in the less desmoplastic areas, with proliferation of small abortive neurons to occasional polygonal ganglioid cells with prominent nucleoli and Nissl substance that are reactive with synaptophysin and NFP. The proportion of the small primitive cells can vary from scattered to a considerable amount in some tumors. It is within these areas that rare mitosis and foci of micro necrosis, but not endothelial proliferation can be detected [78, 79]. However; regardless of their amount; this tumor continues to carry a favorable prognosis in most cases. MIB-proliferative index is low with a mean of 6.5% [79]. There has been reported cases in the literature in which the prognosis was not as favorable and resulted occasionally in patient’s death [80]. DIA shares with DIG the desmoplasia and the astrocytic components, but not the neuronal or the primitive cells [78].

c. Dys-embryoplastic neuroectodermal tumor (DNET)

The essential diagnostic features of this peculiar epilepsy-associated tumor are the combination of cortical localization, multi-nodular architectures with nodules composed of glial cells of either astrocytic or oligodendrogial or a mixture of both, foci of dysplasia in the adjacent cortex and the “specific glioneuronal elements” [81]. These are composed of bundles of axons lined by small S-100 positive, GFAP-negative oligodendrocytes with normal appearing neurons floating within pale eosinophilic interstitial fluid i.e. “floating neurons”, all arranged in columns perpendicular to the overlying cortex, and is strikingly similar from one case to another. Thin capillaries run within the columns. When sectioned perpendicular to the columns; the capillaries are seen to be rosetted by the oligodendroglial cells with the “floating neurons” in between. Calcification can sometimes be seen. Two morphological forms exist; the simple and complex forms [81]. In the simple form; only the “specific glioneuronal elements” are seen within the cortex. The complex form, on the other hand; features the glial nodules and/or cortical dysplasia in addition to the “specific glioneuronal elements”. The nuclei of the oligodendrocytes within the nodules are frequently voluminous and multilobated “fleurettes-like”, while the astrocytic component is usually in the form of pilocytic astrocytoma, sometimes accompanied by the “vascular arcade” proliferation typically seen in cerebellar pilocytic astrocytoma. Fibrillary astrocytoma, of both grades II and III like features can also be seen. The presence of morphological features of anaplasia in the form of rare mitosis and necrosis can occasionally be seen. MIB-1 labeling index is mostly negative in the simple form with rare reactive cells in the complex form, although higher labeling index can be seen in some cases according to the type and grade of the glioma seen within the nodules [81]. Cases can still be
diagnosed as DNET even in the absence of histological appearances previously described, if all of the following clinical and radiological features are fulfilled including 1) partial seizure with or without secondary generalization beginning before the age of 20 years, 2) no neurological deficit or stable congenital deficits, 3) cortical topography of the lesion as demonstrated by MRI and 4) absence of mass effect on imaging. The underlying spectrum of histopathologic entities that can be seen include mostly pilocytic and fibrillary astrocytoma [82].

d. Central neurocytoma
This tumor typically occupies the lateral ventricles or less commonly the third ventricle in young adults without significant invasion into the adjacent brain tissue [83]. It is characterized by proliferation of uniform round cells, embedded within and focally separated by a fibrillary background, the “neuropil” giving an overall monotonous appearance “Figure 22”.

Figure 22. Typical neurocytoma with monotonous tumor cells with vesicular chromatin and delicate capillary-sized vessels. The background is fibrillary.

The tumor cells grow in sheets, clusters, “Indian filing” but rarely rosettes. The fibrillar areas can be seen to form acellular aggregates, bringing resemblance to pineocytomatous rosettes (see below). The nuclei are round to oval with finely speckled chromatin and occasional prominent nucleoli. The cytoplasm is scanty and can be acidophilic or rarely clear. Calcification, which is seen throughout the tumor, and delicate-branching capillaries bring resemblance to oligodendroglioma. Occasional cases show ganglion cells [17]. Mitosis is scarce and there is usually no necrosis [15]. When present such features warrant the diagnosis of atypical neurocytoma. Synaptophysin is strongly and diffusely positive in both the neurocytes and neuropil. NeuN shows strong nuclear stain in tumor cells [42]. Other positive neural markers include neurofilament protein and MAP2. Leu-7 can be positive but it is not specific as is staining for neuron-specific enolase (NSE). Chromogranin is typically negative in both the neurocytoma cells and neuropil [84]. Occasional positivity for GFAP can be seen in some tumors [83]. MIB-1 labeling index is < 2% in typical cases [83]. An elevated MIB-1 labeling index >3% correlates with poorer outcome [14].
e. Extra-ventricular neurocytoma (EVN)

EVN shares morphologic and immunophenotypic features with central neurocytoma. It arises, however from the parenchyma, mostly in the cerebral hemispheres in adults [15, 84]. In addition, Ganglion cell differentiation is a more frequent occurrence, being described in more than half of the cases and can be either focal or diffuse [17, 84]. Frequent reactivity for GFAP is seen in nearly half of cases [84].

f. Cerebellar liponeurocytoma

This is another biphasic tumor that occurs in adults. Originally described in the posterior fossa mostly in the cerebellar hemispheres, cases with identical morphological features are also being reported supratentorially, arising from the lateral ventricle [85]. Morphologically a well differentiated neurocytic component composed of uniform round nuclei and minimal cytoplasm is admixed with mature lipomatous component. Thin and occasionally hyalinized vessels can be detected in the tumor as well as dispersed foci of neuropil. The tumor is diffusely reactive for synaptophysin, NSE and NeuN. Other neuronal markers including chromogranin and NFP can be focally positive. The lipomatous component shows cytoplasmic reactivity for NFP, chromogranin, occasionally for GFAP and S-100 rimming the vacuoles. MIB-1 labeling index is low (<1%) in the majority of cases [17].

g. Papillary glio-neuronal tumor (PGNT)

This tumor is characterized by pseudopapillae and less frequently by papillae, with hyalinized cores lined by a single or multiple layers of hyperchromatic GFAP positive, S-100 positive astrocytes that exhibit acidophilic cytoplasm. These are separated by sheets of synaptophysin positive, Neu-N positive mature neuronal cells in the inter-papillary areas. The neurocytic component includes neurocytes with vesicular nuclei and clear cytoplasm, ganglionoid cells and ganglion cells [15]. A fibrillary or mucoid matrix is seen in the background and can form nodules outside the papillary regions [30]. Sharp demarcation from the adjacent brain is seen.

Mitoses is rare or absent and microvascular proliferation and necrosis are not seen. MIB-1 labeling index is low usually in the range of 1-2%.

h. Rosette forming tumor of the 4th ventricle (RGNT)

This is another example of hybrid glial/neuronal tumor, that arises in midline structures, mostly but not exclusively the 4th ventricle. It often shows involvement of the surrounding periventricular tissue [30]. The neural component shows neuropil-rich rosettes and perivascular pseudorosettes that are lined by synaptophysin-positive neurocytes with clear cytoplasm. A microcystic component with blue mucinous extracellular matrix is sometimes described [17]. The glial component is in the form of pilocytic astrocytoma with Rosenthal fibers and eosinophilic granular bodies [15]. No nuclear atypia or mitosis is seen. However; vascular proliferation of the type seen in pilocytic astrocytoma can be encountered and should not lead to the suggestion of anaplasia [30]. Reactivity for NSE and MAP2 can be seen in the neural component, while GFAP and S-100 are positive in glial component. MIB-1 labeling index is low.
2.4. Choroid plexus tumors

These tumors originate within the ventricular system, and are composed of “epithelial-like” cells reminiscent of choroid plexus [86].

a. Choroid plexus papilloma (CPP)

This is the most frequent entity in this group of tumors and is characterized by papillae lined by a single layer of bland looking cuboidal to columnar epithelial-like cells with abundant acidophilic cytoplasm, bland basal, round to oval nuclei [15]. Tubular or solid growths may occasionally be encountered [86]. Rare mitotic figures, microscopic infiltration into adjacent brain but not necrosis can be seen [14, 17]. Oncocytic changes, melanin deposition, calcification, ossification, and xanthogranulomatous changes may occasionally be encountered [86].

b. Atypical choroid plexus papilloma (atypical CPP)

This recent addition is characterized by preservation of the papillary architecture similar to papilloma, but with increased mitotic activity of ≥ 2 mitoses per 10 high power fields “Figure 23” [15, 87].

![Figure 23](image)

The additional presence of at least 2 of the following features might warrant the diagnosis of atypical CPP including increased cellularity, nuclear pleomorphism, solid growth and necrosis [17]. However; these are not necessary for the diagnosis.

c. Choroid plexus carcinoma

This is the most aggressive entity in this group of tumors and is characterized microscopically by blurring of the papillae with increased cellularity and pleomorphism in addition to features of frank malignancy including brisk mitosis of >5 MF/10HPFs, and necrosis [15].
invasion into brain parenchyma is often seen [17]. PAS positive, diastase resistant variably-sized hyaline globules can be seen that are positive for alpha-1-antitrypsin [14].

The choroid plexus tumors are positive for cytokeratins, especially Cam 5.2, vimentin, S-100, transthyretin, and GFAP, with stains being more positive in papilloma versus carcinoma. Two recently described markers, stanniocalcin 1 and Kir 7.1 are claimed to be specific for choroid plexus tumors. EMA is typically negative in choroid plexus tumors [17], while CK7/CK20 show variable patterns and should be interpreted with caution [86]. MIB-1 proliferative index ranges between 1.9% in CPP to 13.8% in CPC, with higher indices correlating with poor outcome [14].

2.5. Tumors of the pineal region

a. Pineocytoma

This is a histologically bland tumor composed of mature-looking pinealocytes [17]. The cells are bland looking with amphophilic cytoplasm and round nuclei. Large fibrillary pineocytomatous rosettes and pseudorosettes can be seen. A pleomorphic variant is described with giant cells and abnormally-shaped hyperchromatic nuclei and gangliocytic cells [88]. No mitosis is seen in both variants. Immunostains are typically positive for NSE, synaptophysin, chromogranin A and neurofilaments [89]. MIB labeling index is usually zero [90].

b. Pineal parenchymal tumor of intermediate differentiation (PPTID)

This group accounts for at least 20% of tumors of the pineal gland and shows intermediate differentiation between pineocytoma and pineoblastoma [17]. They grow in sheets or lobules and are composed of uniform cells with moderate nuclear atypia. Although occasional Homer–Wright rosettes can be seen, pineocytoma-like rosettes are not reported. On the other hand; this tumor lacks the primitive cell appearance and necrosis typically seen in pineoblastoma [35]. According to the number of mitosis, proliferative index labeling and neurofilament immunostains, these tumors are divided into two prognostically different groups [17, 89]. MIB labeling index ranges between 5.2-11.2% [90].

c. Pineoblastoma

This is a small primitive tumor similar to CNS-PNET. It is hypercellular with proliferation of primitive cells with scant cytoplasm, hyperchromatic nuclei, nuclear pleomorphism and occasional prominent nucleoli. Frequent mitoses, necrosis and calcification can all be encountered [91]. Immunostains for NSE, synaptophysin, chromogranin A and neurofilaments are typically weak or negative [89]. MIB labeling index is around 36.4%-50% [90, 91].

d. Papillary tumor of the pineal region (PTPR)

This is the most recent addition to this group of tumors. It is seen both in children and adults. It grows in papillae with hyalinized cores that are lined by epithelial-like cells. The cells are large columnar to cuboidal, with pale to acidophilic cytoplasm and vesicular round nuclei, thus being different from pineal parenchymal tumors. These tumors are positive for cytokeratin, S-100 and vimentin with only focal positivity for GFAP [15]. EMA is usually negative or at best focally positive; an important feature in the differential diagnosis with ependymoma [17].
2.6. Other neuroepithelial tumors

a. Angiocentric glioma

This is probably a benign tumor that occurs in young adults with history of epilepsy. It is cortically based and is characterized by monomorphic bipolar cells with an angiocentric growth pattern, hence the name [15]. In most cases the cells tend to arrange themselves radially around blood vessels. Additionally, 2 important distinct growth patterns can be seen in a subset of cases; the arrangement of the elongated tumor cells parallel to blood vessels causing sometimes expansion of the perivascular spaces and the tendency of the tumor cells to accumulate perpendicularly beneath the pia [17]. Immunostains are positive for EMA, GFAP, S-100 and vimentin. Neuronal markers are negative.

b. Chordoid glioma of the third ventricle

This tumor usually arises from the anterior third ventricle and is characterized by cohesive clusters and cords of epithelial-like cells growing in a myxoid background [92], hence the close resemblance to chordoma and chordoid meningioma [93], from which it should be differentiated. The presence of lympho-plasmacytic infiltrate which can sometimes be heavy with abundant Russell bodies is seen at the periphery and is helpful in supporting the diagnosis. Chondroid metaplasia can occasionally be encountered [94]. Reactivity for GFAP and vimentin is the rule but with variable reactivity for S-100. EMA is positive in the infiltrating plasma cells [20, 92].

c. Astroblastoma

A well circumscribed tumor that involves mostly the cerebral hemispheres, astroblastoma is characterized by perivascular pseudorosettes with sclerosed fibrovascular cores, on which broad cytoplasmic processes of astroblasts rest “Figure 24”.

Figure 24. In astroblastoma hyalinized blood vessels are surrounded by cells with broad-based cytoplasmic processes.
This is in contrast to the fine tapering processes of classical ependymoma [20, 95]. A high grade “malignant” variant is diagnosed when hypercellularity, increased mitoses, vascular proliferation and palisading necrosis are seen, otherwise the tumor is considered a low grade or “benign” [14]. The tumor cell processes are strongly positive for vimentin and S-100, but focally for GFAP with focal membranous EMA reactivity.

2.7. Recently described tumor entities that are not included in the most recent WHO classification

a. Cribriform Neuroepithelial Tumor (CRINET)

This recently described tumor is composed of proliferation of a relatively small undifferentiated cells, arranged in cribriform, trabeculae, strands and focal compact areas exhibiting rosette formation [96]. Well defined surfaces characterize the cellular strands, which exhibit elongated nuclei but with no stratification. The cytoplasm is ill-defined and slightly acidophilic and the nuclei possess dense chromatin and lack prominent nucleoli. Mitoses and necrosis are seen. The tumor cells are immunoreactive for EMA highlights the surface as well as for vimentin, and synaptophysin with focal expression of cytokeratin and S-100. Other markers including GFAP, neurofilament, NeuN, chromogranin are negative. MIB-1 labeling index is elevated. Characteristically this tumor lack INI-1/Baf47 nuclear immunoreactivity, despite of lacking the typical features of AT/RT including eccentric acidophilic cytoplasm, cytoplasmic inclusions and vesicular nuclei with prominent nucleoli [96, 97]. CRINET seems to be associated with a better prognosis than AT/RT.

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