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Histology of Primary Brain Tumors

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1. Introduction

Pathological classification of brain tumors is the corner stone 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.

I: Tumors of Neuroepithelial Tissue		II: Tumors of non-Neuroepithelial Tissue
A: Glioma	C: Neuronal and mixed neuronal-glial tumors	A: Tumors of the meninges
1. Astrocytic tumors	Ganglioglioma and gangliocytoma	1. Meningiomas
Pilocytic astrocytoma	Desmoplastic infantile ganglioglioma/astrocytoma	Benign Meningioma variants
Pilomyxoid astrocytoma	Dysembryoplastic neuroectodermal tumor	Atypical
Pleomorphic astrocytoma	Central neurocytoma	Clear cell
Sub-ependymal giant cell astrocytoma	Extra-ventricular neurocytoma	Chordoid
Fibrillary astrocytoma	Cerebellar liponeurocytoma	Anaplastic
Anaplastic astrocytoma	Papillary glio-neuronal tumor	Papillary
Glioblastoma	Rosette forming tumor of the 4 th ventricle	Rhabdoid
Gliomatosis Cerebri	D: Choroid plexus tumors	2. Primary Melanocytic lesions
2. Oligodendroglioma	Choroid plexus papilloma	3. Other Neoplasms related to meninges
3. Mixed oligo-astrocytoma	Atypical choroid plexus papilloma	Hemangioblastoma
4. Ependymoma	Choroid plexus carcinoma	B: Cranial and paraspinal nerve tumors
Myxo-papillary ependymoma	E: Tumors of the pineal region	C: Germ cell tumors
Sub-ependymoma	Pineocytoma	D: Tumors of the sellar region
Cellular ependymoma	Pineal parenchymal tumor of intermediate differentiation	E: Hematopoietic cell tumors
Clear cell ependymoma	Pineoblastoma	
Tanycytic ependymoma	Papillary tumor of the pineal region	
B: Embryonal tumors	F: Other neuroepithelial tumors	
Medulloblastoma	Angiocentric glioma	
CNS- primitive neuroectodermal tumor	Chordoid glioma of the 3 rd ventricle	
Atypical teratoid rhabdoid tumor	Astroblastoma	
Cribriform Neuroepithelial Tumor (CRINET); This tumor is a recently described neuroepithail 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”.

Figure 1. There is proliferation of piloid cells with elongated cytoplasmic processes. Rosenthal fibers are acidophilic processes seen in these areas (arrow).

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 oligodendroglial like proliferation can be encountered, especially in the posterior fossa tumors. Various forms of vascular proliferation can be seen including reactive vascular

Figure 2. The microcystic areas are composed of proliferation of protoplasmic astrocytes. Eosinophilic granular bodies are seen in these areas (red arrow). Multinucleated giant cells are sometimes seen in pilocytic astrocytoma (black arrow).

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 anotherwise 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 pursued 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.

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 lacks 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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