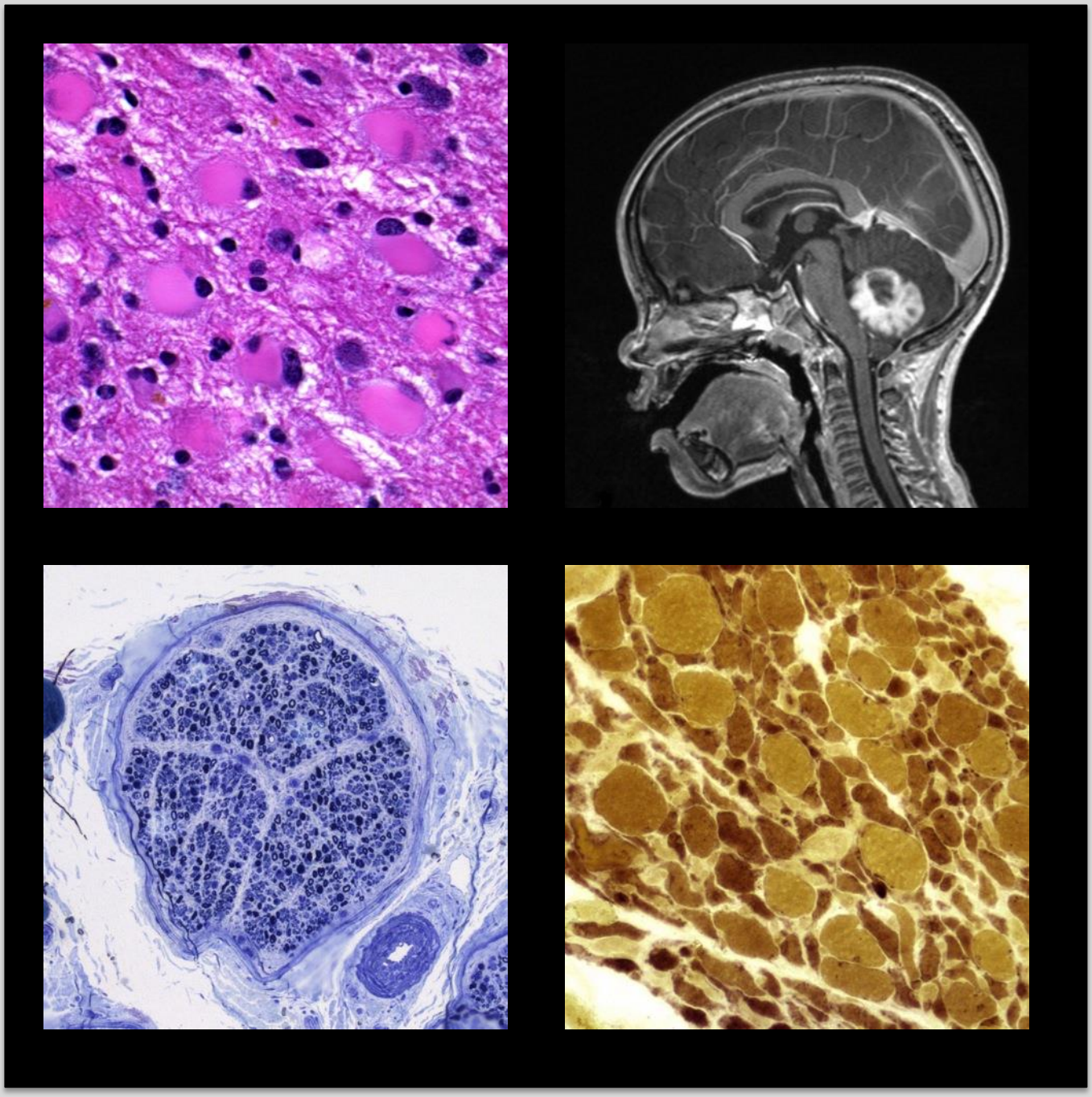
Beginner's Guide to Neuropathology



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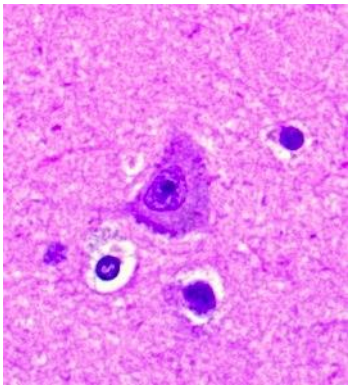
Chapter 1: Normal Histology of the Central Nervous System – *How to tell what your looking at…*

Before attempting to tackle abnormal pathology of the CNS, one first needs to become familiar with the normal histology of the nervous system. Below is a concise description of the basic cellular elements of the brain.

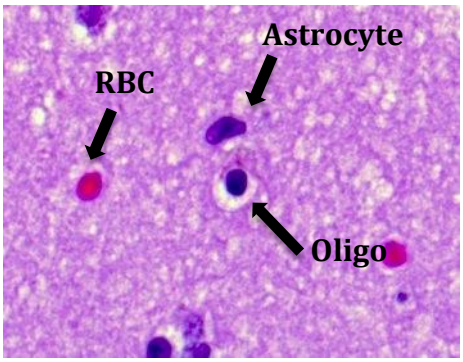
Neuropil: A generic term denoting the pink, fibrillar background seen throughout the brain. Comprises a mixture of cellular processes (i.e. axons, dendrites, astrocytic processes). In gray matter, neuropil consists primarily of astrocytic processes and neuronal dendrites. In white matter, axons (most myelinated) predominate. Except for neurons, the cytoplasm of cells in the CNS lies amongst the neuropil, and individual cells are seen as "naked nuclei" lying amongst neuropil.



Neurons: The cells in the CNS that show the greatest degree of variability. Range from large cells with obvious neuronal features ("pyramidal" neurons such as Betz cells and Purkinje cells) to small cells nearly impossible to distinguish from lymphocytes (developing neuroblasts, mature granule neurons of the cerebellum). Here are some ways to tell that a cell is a neuron:

1) Visible perinuclear cytoplasm, often with tiny bluish granules (Nissl substance, aggregates of RNA) in the cytoplasm.
2) Larger nucleus with open, often granular chromatin.
3) Prominent nucleoli.

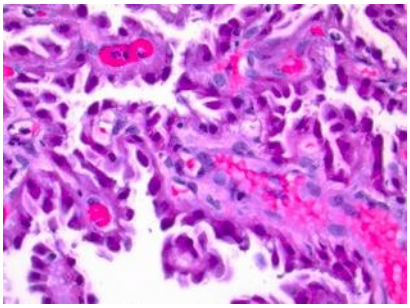
Obviously, the presence of significant numbers of neurons should be seen only in gray matter structures (e.g. cortex, deep nuclei). Regarding neoplasia, there are no pure "malignant" neuronal neoplasms. However, dysplastic neurons occasionally partake in neuroglial neoplasms. Neuronal dysplasia is defined as **abnormal neuronal clustering**, increased **nuclear size variability** (anisonucleosis), and **binucleation**. Remember that otherwise unremarkable neurons are often entrapped in infiltrative glial neoplasms ("innocent bystanders"); their presence does not imply a dysplastic ganglionic component.



Astrocytes: Astrocytes serve a supportive role in the CNS, with diverse functions including regulation of the blood-brain barrier, maintenance of extracellular homeostasis (metabolic regulation), and formation of the large part of the structural framework of the brain. Normal astrocytes are seen as "bean-shaped", elongate ovoid nuclei measuring ~15 microns in length (approximately twice the diameter of an oligodendroglial nucleus or RBC). The nuclear membrane should be nice and smooth, and the chromatin smooth. As with most cells in the CNS, astrocytes present as "naked nuclei" in a background of neuropil. On smear preparations, one should see long, thin cytoplasmic processes. On an H&E-stained section, visible perinuclear cytoplasm is typically homogenous and eosinophilic, and always pathologic (e.g. neoplastic or reactive). On a glial fibrillary acidic protein (GFAP) stain, the cytoplasm should stain convincingly. Neoplastic astrocytes retain their "bean-shaped architecture", yet show atypical features (nucleomegaly, irregular nuclear contours, hyperchromasia). There are two main types of astrocytes: 1) Protoplasmic astrocytes lie predominantly in the gray matter, and have numerous short, thin, highly-branching processes. 2) Fibrillar astrocytes occupy the white matter, and have longer processes with a paucity of branches.

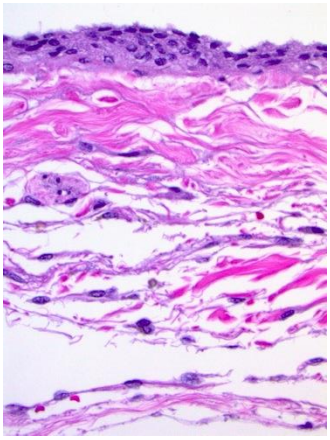
Oligodendroglia: Serve a supportive role in the CNS. Oligodendroglia send out sheets of lipid-rich cytoplasm, which wraps several adjacent axons, forming the **myelin sheath**. While they lie primarily in white matter, lesser numbers can also be found in gray matter structures. They are visible as small, round "naked nuclei" lying amongst neuropil. Their nuclear diameter is similar to that of an RBC (~ 8 microns). The nuclei are round and hyperchromatic. Oligodendroglia often cluster around neurons, and are occasionally seen in chains running perpendicular to the cortical ribbon. In young children who are actively myelinating, one may see perinuclear cytoplasm in a cape-like distribution ("superman cells"). Neoplastic oligodendroglia largely retain the round nuclear shape, yet show variable nucleomegaly and nuclear membrane irregularities. The cytoplasm of oligodendroglia (both normal and neoplastic) reacts with GFAP, reflecting glial origin.

Ependyma: Columnar epithelium that surrounds CSF-filled spaces. In younger individuals, the ependyma is ciliated. With age, the ependyma loses its ciliation. In the spinal cord, nests and small tubules of ependyma are often found in the region of the obliterated central canal. In pathologic conditions (e.g. aqueductal stenosis), disorganized ependymal nests often lie in the damaged areas.



Choroid plexus: The lesser known of the glia family. Nonetheless, the cells lining the choroid plexus show evidence of glial differentiation (i.e. GFAP immunoreactivity). The cells form a cuboidal, **hobnail-type lining** over thin fibrovascular cores. A helpful point is that benign choroid plexus lining is hobnailed, while the choroid plexus neoplasia shows a smooth, flattened lining. These cells actively secrete CSF. Interestingly, choroid plexus neoplasms may over-produce CSF, resulting in communicating hydrocephalus. With age, the fibrovascular cores of the choroid plexus tufts tend to become sclerotic and calcified.

Blood vessels: Innumerable small blood vessels and capillaries are present throughout the brain parenchyma. The larger vessels are largely restricted to the subarachnoid space; most vessels deep in the brain parenchyma are capillaries. A higher density of capillaries in the neocortex give it a brown gross appearance ("gray matter"); the white matter has relatively fewer blood vessels. Tight junctions between the endothelial cells comprise the most important part of the blood brain barrier.



Meninges: Leptomeninges (lepto = thin) (picture left) consist of the pia mater and arachnoid. The pia mater consists of a single-cell layer of thin, simple cells, and lies in direct contact with the underlying brain parenchyma. The arachnoid consists of a loose collection of fibroblasts, capillaries, empty space containing CSF, and occasional meningothelial rests (top of image). The meningothelial rests are the putative precursors for meningiomas. Thus, while the tumors are typically dural based, meningiomas most likely arise from the arachnoid layer. The dura mater consists of a thick layer of collagen and fibroblasts, which merges imperceptibly with the overlying cranial periosteum.

Chapter 2: General Concepts in Neuropathology – *Why we're different!*

Neuropathology varies from general surgical pathology in several key ways…

- **Margins are not an issue in neuropathology**, for several reasons (hooray!!!).
    - With a few exceptions, real estate in the brain is quite valuable. Many neurosurgical resections result in motor, sensory, or other post-operative functional deficits. As such, resection of additional brain parenchyma surrounding the lesion for the purpose of "clear margins" isn't such a good idea. Thus, neurosurgeons often aim for gross total resection (i.e. all the tumor that they can see, post-operative scan negative for residual tumor).
    - Many intracranial neoplasms are not "surgically-treatable" tumors. This is due to the fact that many gliomas are diffusely infiltrative. That is, even if you resect the bulk of the tumor, there are nearly always single neoplastic cells that have spread down various pathways, escaping the scalpel to fight another day. An example is a glioblastoma that I encountered at autopsy during fellowship. The bulk of the tumor was in the frontal lobe. However, microscopic examination of the brain and spinal cord showed occasional neoplastic astrocytes present throughout the cerebral hemispheres, brainstem, reaching as far caudally as the lumbar spinal cord. Complete surgical resection of the neoplasm would have required removal of the entire brain and spinal cord!
    - Thankfully, our intraoperative consultations tend to be limited to lesion identification (no margin assessment), and our specimens are never inked. I once inked a sacrum resected for a chordoma, and my Neuropathologist attending teased me incessantly for days.

- **Correlation with neuroradiology is essential in establishing a correct diagnosis**. The radiology is our "gross examination". Just as a clinician must interpret an abnormal serum potassium level in the context of the entirety of the clinical details, and a pathologist must consult radiology for evaluation of a bone tumor, interpretation of a neuropathologic specimen without consideration of the neuroradiologic features is an absolute invitation for disaster. Here are some illustrative examples:
    - Pilocytic astrocytomas often show proliferating vessels, and may even contain significant cytologic atypia and rare mitotic figures. There are unfortunate examples of unwitting pathologists who have diagnosed pilocytic astrocytomas as "glioblastoma" due to these features. A consultation with the neuroradiology would have demonstrated a cystic mass in the cerebellum, and most likely would have saved the patient from unnecessary cranial irradiation and the pathologist from the ensuing litigation.
    - Biopsies from the edge of a glioblastoma (away from the enhancing component) often show only infiltration by few atypical astroglial cells. If a pathologists sees only a few atypical infiltrating astrocytic cells, and does not correlate with the radiologic finding of a heterogenously-enhancing component, the lesion could easily be grossly under-graded and there would be a "delay in diagnosis".

- Neuropathology intraoperative consultations often place a great degree of emphasis on the "**smear preparation",** slide upon which the tissue of interest is crushed and sheared apart, and the lesional cells are literally stretched and torn apart from their neighbors. The purpose is to assess how the cells relate to each other, and to examine the presence and quality of the cytoplasmic processes. Touch preparations are of little use in assessing neuropathologic specimens, as touch preps do not adequately separate the cells from one another.

- Neuropathologists often take the baseline pathologist "quirkiness" to the extreme. Individuals with eccentric appearances (think of a vagrant Albert Einstein), odd beliefs, and unusal affect are often seen wandering amongst the halls during Neuropathology meetings (present company not excluded).

Chapter 3: Amateur Neuroradiology

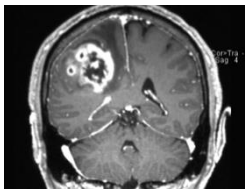
As previously discussed, practicing neuropathology requires at least a basic understanding of neuroradiology. Here are a few key points…

- As a general rule, head **CT scans are useless** to Neuropathologists, with two exceptions:
    1. Head CT scans are great for blood – useful for evaluating intracranial hemorrhage
    2. Head CT scans are great for calcifications – if you have a sellar region mass in a young patient, the presence of intralesional calcifications **strongly suggests** craniopharyngioma

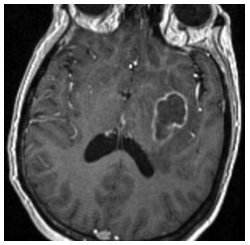
- Here is a simplified explanation of the different MRI sequences…
    - T1: Good for evaluating normal anatomy; gray matter is dark, white matter is light
    - T2: Good for evaluating relative liquid content (things like cytotoxic, vasogenic, or interstitial edema); gray matter is light, white matter is dark, CSF is very bright
    - FLAIR: Just like T2, but CSF is suppressed (dark); excellent for edema
        - T2 and FLAIR are great for evaluating for areas of pathology; increased signal often implies edema (or other abnormal conditions such as infiltrating glial neoplasia)
    - Contrast: Gadolinium administration shows you areas of **abnormal vascular permeability**, as gadolinium is normally unable to cross the blood brain barrier

- What is the differential diagnosis for **ring-enhancing lesions** of the brain? *Remember abnormal vessels! See images on right…*
    - Glioblastoma: Irregularly-enhancing, often white matter based tumors. Variable wall thickness. Microvascular proliferation causes enhancement. Often crosses midline along white matter tracts.
    - Abscess: Thin, "egg shell like" enhancing rim. Abscesses are often embolic in etiology, thus tend to be located at gray-white junction. Another helpful point is that the ring is often thinner in the deeper aspect (abscesses often rupture into the ventricles).
    - Metastatic carcinoma: Abnormal vessels "feeding" the carcinoma result in contrast enhancement. Similar to abscesses in that lesions tend to be at gray-white junction. Also often present as multiple discrete lesions.
    - Subacute infarction: Particularly a consideration if in a region of increased susceptibility to hypoxic-ischemic brain injury (e.g. watershed distribution, deep gray nuclei, and vascular distribution.
    - Tumefactive demyelination: Tends to affect white matter (greater myelin density). Often presents as an open "c-shaped" ring. Patient demographics are helpful (young, often female patients).
    - Radionecrosis: The history of previous radiation (~ 6 months → 2 years) is helpful. A biopsy is often necessary to exclude recurrence of malignancy.
    - Contusion: Clinical history is leading. Likely related to organizing hemorrhage.

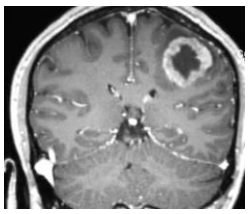
- What is the differential diagnosis for a **cystic mass with an enhancing mural nodule**?
    - Hemangioblastoma: Cerebellum > retina & spinal cord. Von Hippel Lindau (VHL) gene -3p - mutations.
    - Pilocytic astrocytoma (PA): Cerebellum > thalamus/hypothalamus, optic tract, spinal cord.
    - Ganglioglioma: Superficial temporal lobes. Often has clinical history of seizures.
    - Pleomorphic xanthoastrocytoma (PXA): Superficial temporal lobes. Seizures again.



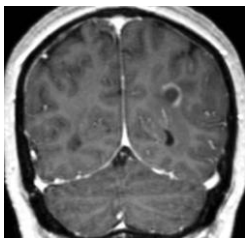
Glioblastoma



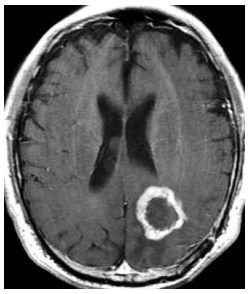
Abscess



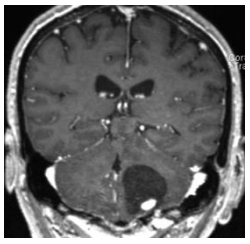
Metastatic carcinoma



Tumefactive demyelination



Radionecrosis



Cyst with enhancing mural nodule - PA

Chapter 4: Statistical Neuropathology – *Location, location, location…*

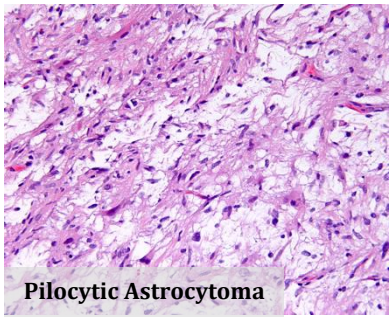
Let this serve as a guide. This list is definitely not all encompassing…

Location	Children	Adolescence/Middle Age	Old
Cerebrum (Parenchymal)	Pilocytic astrocytoma Ganglioglioma Pleomorphic Xanthoastrocytoma DNET PNET (supratentorial Medulloblastoma) Infiltrating astrocytoma Teratoma (rare[2], +/- congenital)	Pilocytic astrocytoma Pleomorphic xanthoastrocytoma Oligodendroglioma Infiltrating astrocytoma Anaplastic astrocytoma Glioblastoma (rare) Demyelination	Glioblastoma Metastatic carcinoma Metastatic melanoma Lymphoma (DLBC) Oligodendroglioma Infarct
Cerebrum (dural-based)	Rare	Meningioma Solitary fibrous tumor Hemangiopericytoma Metastatic carcinoma Lymphoma Plasmacytoma	Meningioma Metastatic carcinoma Hemangiopericytoma Solitary fibrous tumor Lymphoma Plasmacytoma
Intraventricular (Non-cystic)	Ependymoma Meningioma Choroid plexus papilloma Choroid plexus carcinoma	Ependymoma Meningioma Central neurocytoma SEGA Choroid plexus papilloma	Ependymoma Meningioma
Cysts	Colloid cyst (3rd) Arachnoid cyst (anywhere) Choroid plexus cyst (lateral) Epidermoid cyst (anywhere) Dermoid cyst (anywhere) Neurenteric cyst (spinal cord) Rathke cleft cyst (sellar region)	Same	Same
Sellar region	Rare	Pituitary adenoma Craniopharyngioma Rathke cleft cyst Germinoma Teratoma Yolk sac tumor Metastatic carcinoma Langerhan's cell histiocytosis	Pituitary adenoma Metastatic carcinoma Meningioma
Cerebellopontine angle	Rare	Schwannoma Meningioma *Neurofibroma* Epidermoid cyst	Same (+ metastatic carcinoma)
Cerebellum	Medulloblastoma Pilocytic astrocytoma Ependymoma AT/RT	Pilocytic astrocytoma Ependymoma Hemangioblastoma Metastatic melanoma	Metastatic carcinoma Lymphoma Metastatic melanoma
Spinal cord (parenchymal)	Ependymoma Pilocytic astrocytoma	Same (+ Hemangioblastoma) (+ infiltrating astrocytoma)	Metastatic carcinoma Infiltrating astrocytoma
Spinal cord (Dural)	Meningioma	Meningioma Nerve sheath tumors Mesenchymal tumors; SFT, HPC	Meningioma Metastatic carcinoma Nerve sheath tumors Plasmacytoma
Cauda equina region	Rare	Meningioma (classic) Myxopapillary ependymoma Paraganglioma	Same (+ metastatic carcinoma)

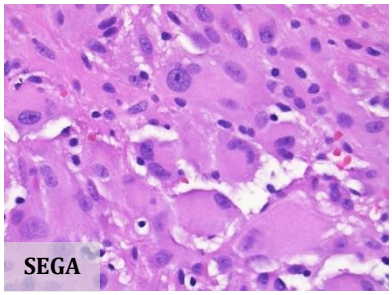
**** Notice that metastatic carcinoma is included in nearly every site for the elderly. *Keep that in mind…* ****

Chapter 5: Neoplastic Neuropathology – *Translation: "Brain tumors"*

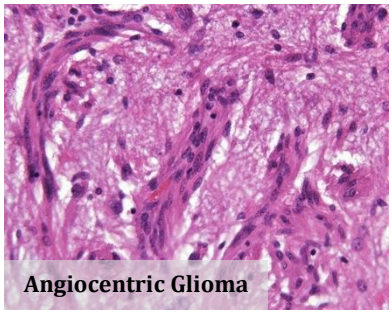
Glial Tumors - Astrocytic Derivation


Pilocytic Astrocytoma

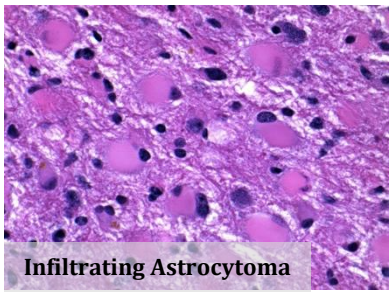
Pilocytic Astrocytoma (WHO I): Most common pediatric brain tumor.
Localization: Cerebellum, thalamus, optic pathway, and spinal cord are common sites.
Radiology: Often **cyst with enhancing mural nodule**. Or may be solid enhancing mass.
Pathology: Non-infiltrating glioma comprising a proliferation of bland, "hair-like" (mildly-atypical bean-shaped nuclei) with bipolar hair-like processes. Low power shows biphasic architecture, with microcystic and fascicular areas. **Rosenthal fibers** (eosinophilic elongate structures) and **eosinophilic granular bodies** are frequently seen. Perivascular chronic inflammation is common. May have "degenerative" nuclear atypia. Mitoses should be absent. Should not infiltrate brain parenchyma. Ki-67 labeling index should be low (< 2.5%)
Miscellaneous: Must distinguish from reactive gliosis surrounding a brain lesion ("piloid gliosis"), which looks remarkable similar (Rosenthal fibers and all!)


SEGA

Subependymal Giant Cell Astrocytoma (SEGA; WHO I): Patients with **tuberous sclerosis**.
Localization: Medial aspect of lateral ventricles. May obstruct foramen of Monroe.
Radiology: Variable enhancement (not ring) may show calcifications
Pathology: Pleomorphic proliferation of "**confused cells**". This means that although the cytoplasm looks astrocytic (homogenous, eosinophilic), the nuclei often have neuronal features (granular chromatin, prominent nucleoli). Although there may be significant nuclear pleomorphism, mitoses should be absent and the Ki-67 labeling index should be low (ugly tumor, good prognosis). Tumor often contains dystrophic calcifications.
Miscellaneous: Rare tumor. Beware of atypia. May be over-called as glioblastoma!

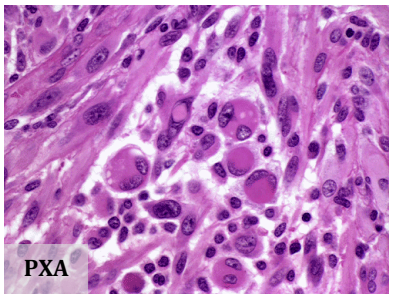

Angiocentric Glioma

Angiocentric Glioma (WHO I): The most recently described brain tumor. Seen most often in children and young adults. Rare! Causes seizures!
Localization: Cerebral hemispheres
Pathology: Low-grade infiltrating glioma with astrocytic ("bean-shaped") nuclear features. The characteristic finding is the **tumor cells wrapping around and "coating" the outside of blood vessels** (angiocenricity, pictured right). GFAP positive. Also shares some phenotypic overlap with ependymoma (dot-like perinuclear reactivity)
Miscellaneous: Rare tumor. Not likely to be seen on boards…


Infiltrating Astrocytoma

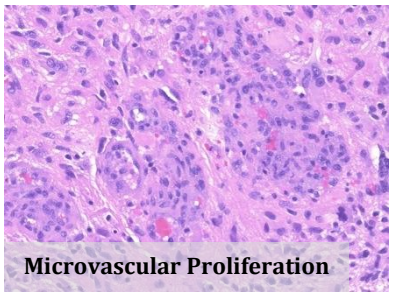
Infiltrating Astrocytoma (WHO II): Defined by infiltration of brain parenchyma
Clinical: Younger adults (~ 4th decade), cerebral hemispheres most common site
Radiology: Abnormal FLAIR/T2 signal with mass effect, often in white matter. **No contrast enhancement**!
Pathology: Scattered (often hypocellular) infiltrating atypical astrocytic ("bean-shaped) nuclei. Atypia = enlargement, hyperchromasia, nuclear membrane irregularities (benign = smooth). **No mitoses, necrosis, or microvascular proliferation**! May see neoplastic cells with prominent eosinophilic nuclei → **gemistocytes** ("stuffed cells") (see image to right). Neoplastic gemistocytes portend a worse prognosis.

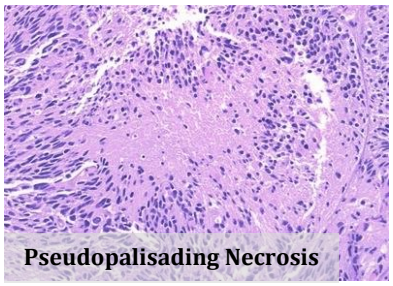
Pleomorphic Xanthoastrocytoma (PXA; WHO II): Temporal lobe tumor; **seizures**!
Clinical: Children and young adults. Involves the superficial temporal lobes
Radiology: Superficial cyst with an **enhancing mural nodule** in the temporal lobe
Pathology: Highly atypical appearing (yet mostly benign) tumor with astrocytic nuclear features. As the name implies, there is **significant nuclear atypia**. Some (not all) examples contain cells with **cytoplasmic lipid vacuoles**, hence the designation "xantho". Despite the degree of nuclear atypia, mitoses should be rare/absent, and the Ki-67 labeling index should be low. A **reticulin** stain may be helpful, as there should be increased pericellular reticulin deposition.
Misc: Occasional tumors show anaplasia, characterized by significant proliferative activity (high Ki-67, mitotic figures), and thus deserve a WHO grade III designation


PXA
http://moon.ouhsc.edu/kfung/jty1/Images/FNA0IE16-PXA-A1.gif

Anaplastic Astrocytoma (WHO III): Clinical: Middle age adults (~ 5th decade)
Radiology: Abnormal T2/FLAIR signal, mass effect, and **patchy contrast enhancement**
Pathology: Same features of infiltrating astrocytoma with increased cellularity, a greater degree of atypia, and **mitotic figures** (remember – none seen WHO grade II astrocytomas)

Glioblastoma (WHO IV):
Clinical: Older patients most common (~ 6th decade). Often involves white matter structures
Radiology: **Heterogeneous ring-enhancing mass** with surrounding T2/FLAIR signal abnormality. Tumor **crossing midline** is highly suggestive of glioblastoma.
Pathology: Atypical infiltrative astrocytic glioma with frequent mitotic figures, **microvascular proliferation**, and/or **pseudopalisading necrosis**. A few important points here. One needs to see either microvascular proliferation or necrosis. Most cases show both features, but only one is required. Second point → microvascular proliferation is not an increase in the number of vessels, but rather a thickening of the cellular coat of Pericytes. So, if you want to stain for microvascular proliferation, a smooth muscle actin (SMA) is useful (pericytes have a contractile phenotype), but a CD31 is not useful. The images to the right demonstrate microvascular proliferation and pseudopalisading necrosis.


Microvascular Proliferation


Pseudopalisading Necrosis

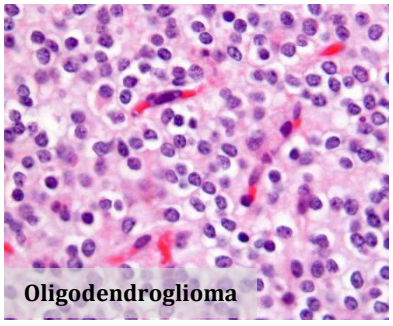
Misc:

- **Primary glioblastomas** arise de novo, typically in older patients, harbor EGFR amplification and/or PTEN mutations, and have a dismal prognosis.
- **Secondary glioblastomas** arise in the setting of a pre-existing lower-grade glial neoplasm, often over-express p53, arise in slightly younger patients, and have a marginally better prognosis.

Subtypes: Large cell, small cell, gliosarcoma, epithelioid, granular cell…

Glial Tumors - Oligodendroglial Derivation

Oligodendroglioma (WHO II): Cerebral hemispheric tumors, most often occurs in the fourth decade
Radiology: Discrete mass that does not enhance with contrast administration. Often cortical-based.
Pathology: Infiltrating glioma with nuclei that resemble oligodendroglia (**round**, mildly-atypical nuclei, not bean-shaped). May see **clear perinuclear halos**, an artifact of formalin fixation not seen on frozen sections. The background often contains a delicate "**chicken-wire**" like capillary network and **dystrophic calcifications**. The neoplastic cells often cluster around neurons, a feature called "neoplastic **perineuronal satellitosis**". Occasional mitoses may be found, but should not be markedly increased. The tumor cells variably express GFAP.


Oligodendroglioma

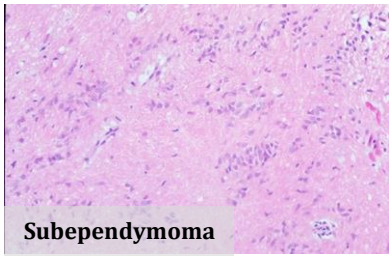
MISC: The sine qua non of oligodendroglioma is **codeletion of 1p and 19q**. Testing for 1p/19q deletion may be done by FISH or PCR, both on paraffin-embedded tissue. Presence of the co-deletion portends an improved response to chemotherapy.

Anaplastic Oligodendroglioma (WHO III): Similar features to those seen in oligodendroglioma, with the additional features of increased **cellularity**, increased **atypia**, **microvascular proliferation**, small foci of **necrosis**, and frequent **mitoses** (> 6 mitoses per 10 HPF). Worse prognosis than WHO II. 1p/19q LOH may still be seen, but not as often as in lower grade tumor.

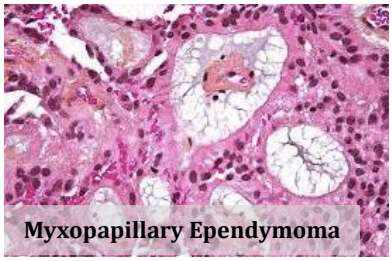
Mixed Gliomas: Every field has to have a "**waste-basket**" diagnostic category. This is neuropathology's. Tumors that show a mixture of both astrocytic (bean-shaped nuclei) and oligodendroglial (round nuclei) are often classified as "mixed" gliomas or "oligoastrocytomas". There is no agreement as to how much of each of the mixtures is required. The prognosis is uncertain, as this category is heterogeneous. In the presence of astrocytic features, 1p/19q LOH is uncommon. Avoid using this diagnostic category if possible.

Glial Tumors - Ependymal Derivation

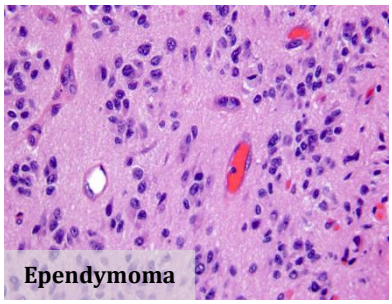
Subependymoma (WHO I): Low-grade tumor. Most often found incidentally at autopsy.
Location: **Fourth ventricle most common location**. Lateral ventricles and spinal cord less common.
Pathology: Form **exophytic intraventricular masses**. Loose clumps of round, monotonous nuclei embedded in a finely-fibrillar, lightly-eosinophilic background. Although ependymal in nature, **true or pseudorosettes are rare or absent**. Diagnosis rests upon recognition of the pattern of clumped, rounded nuclei in fibrillar background. The tumor is non-infiltrative, so no entrapped axons or neurons.


Subependymoma

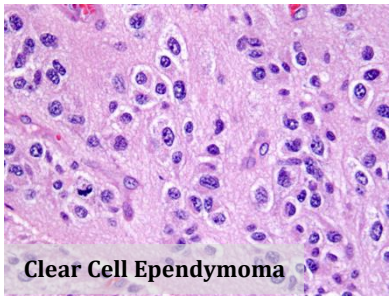
Myxopapillary Ependymoma (WHO I): Cauda equina mass with unique features
Pathology: Continuing the theme of ependymal tumors without classical ependymal features, myxopapillary ependymomas will not contain true rosettes or perivascular pseudorosettes. However, the appearance and localization are classic. The tumor comprises bland, monotonous round to spindled cells lining **pseudopapillae** with hyalinized vascular cores and **pools of lightly basophilic, Alcian blue positive mucin**. Atypia should be minimal, mitoses should be rare/absent, and features of infiltration should not be seen.


Myxopapillary Ependymoma

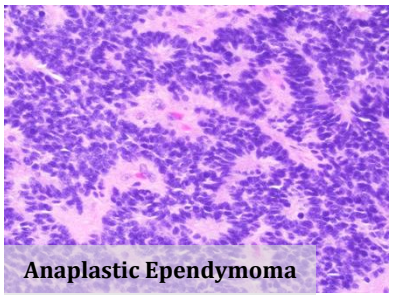
Ependymoma (WHO II): This the ependymoma that people think about…
Clinical: Common tumor, affects both children and adults. Occurs in locations with native ependymal lining (i.e. ventricles, spinal cord)
Radiology: Non-enhancing non-infiltrative mass; adjacent to or within ventricles or spinal cord
Pathology: Variably cellular, non-infiltrative glioma with rounded, non-descript nuclei. The characteristic finding is the presence of **perivascular pseudorosettes** (ependymal cells projecting their cytoplasmic processes towards a central capillary, resulting in a perinuclear, fibrillar anuclear zone) and less often **true ependymal rosettes** (centrally-oriented cellular processes with a true central lumen). A sharp brain-tumor interface is also a characteristic feature. A unique immunohistochemical finding is **dot-like perinuclear EMA immunoreactivity**, highlighting intracytoplasmic lumina (an ultrastructural finding). The degree of cellularity, atypia, and mitotic activity vary greatly between cases; see discussion of anaplastic ependymoma below.


Ependymoma

Clear Cell Ependymoma (WHO II): Ependymoma that looks like oligodendroglioma…
Clinical: Children and young adults. Supratentorial, **typically not adjacent to a ventricle**
Pathology: Round cells with perinuclear clearing (features very similar to oligodendroglioma). The way to distinguish this tumor from an oligodendroglioma is that **clear cell ependymomas are non-infiltrative**, and oligodendrogliomas are by definition infiltrative (i.e. entrapped neurons, axons). Also, ependymomas lack the characteristic chromosomal abnormality of oligodendrogliomas (1p/19q co-deletion).

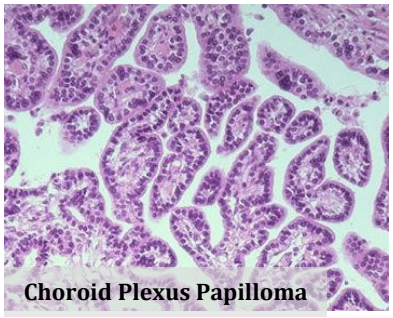

Clear Cell Ependymoma

Anaplastic Ependymoma (WHO III): No significant differences in age or location from WHO II ependymoma
Pathology: There are no defined, subjective criteria for the diagnosis of anaplasia in ependymoma. One should see multifocal increased **cellularity**, increased nuclear **atypia**, frequent mitotic figures, coagulative **necrosis**, and an **elevated Ki-67 labeling index**. Small foci of hypercellularity and increased atypia may be seen in WHO II ependymomas, and do not qualify for anaplasia. One can show the same case to two different pathologists and get two widely disparate diagnoses (a dirty little secret of the trade).

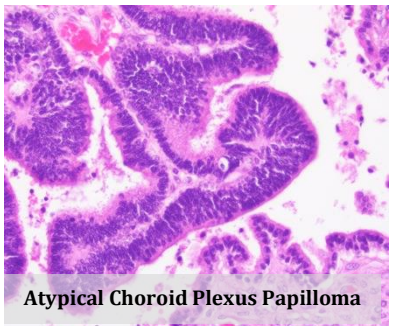

Anaplastic Ependymoma

Glial Tumors - Choroid Plexus Derivation

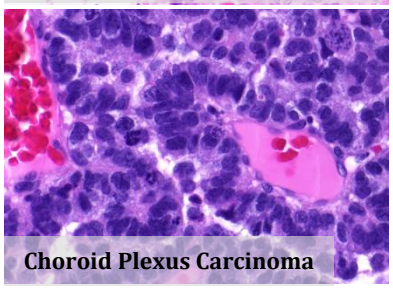
Choroid Plexus Papilloma (WHO I): Tumor closely resembles normal choroid plexus (but forms a mass)
Clinical: Affects children (~ 10 years old), **intraventricular** tumor. Interestingly, may cause **hydrocephalus** due to **overproduction of CSF**. Benign clinical behavior.
Pathology: Benign-appearing papillary neoplasm. To distinguish from normal choroid plexus, closely inspect the lining epithelium. Normal choroid plexus is lined by a cuboidal, undulating surface. Neoplastic choroid plexus is lined by a taller columnar epithelium that is smooth, **lacking the undulating surface of normal choroid plexus**. There should be no significant atypia, and mitoses should be absent or rare.


Choroid Plexus Papilloma

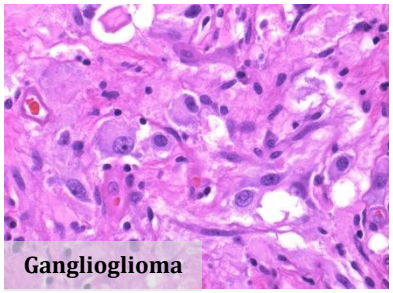
Atypical Choroid Plexus Papilloma (WHO II): Intermediate between benign and malignant…
Clinical: Seen in younger patients ~ 2-10 years old. More aggressive behavior. Intraventricular localization.
Pathology: Papillary neoplasm with **increased nuclear atypia** and easily identifiable **mitotic figures**.

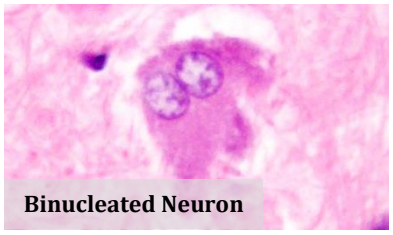

Atypical Choroid Plexus Papilloma

Choroid Plexus Carcinoma (WHO III): Malignant tumor, seen most often in infants (most < 2 y/o)
Pathology: Malignant tumor of choroid plexus derivation. The papillary architecture may be difficult to appreciate, with **solid sheets** of malignant appearing cells and focal papillae. **Mitoses** are frequent, oft atypical. May see **brain invasion** and **necrosis**.
Miscellaneous: Tumors may be congenital. Extremely poor prognosis.


Choroid Plexus Carcinoma

Confused Tumors - Neuroglial Neoplasia

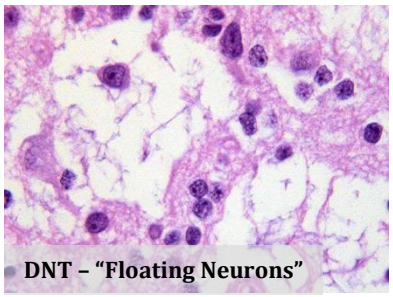

Ganglioglioma


Binucleated Neuron

Ganglioglioma (WHO II– III): Both dysplastic neurons and atypical glial components
Clinical: Rare tumors, often in adolescents/young adults. Usually involves superficial neocortex, often temporal lobes. Often presents with seizures.
Radiology: Cystic superficial mass, occasionally with enhancing mural nodule.
Pathology:

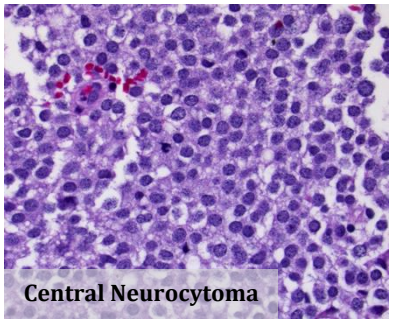
- Dysplastic neuronal component: "Ganglion" cells (neurons) that are abnormally clustered, vary in size and shape, some binucleated. These features should be noted, as one must exclude entrapped normal neurons ("innocent bystanders") entrapped by an infiltrating glioma.
- Atypical glial component: Atypical infiltrating glial component of varying degree of malignancy (WHO II-III), graded as one would an astrocytic neoplasm without a ganglionic component. Thus, the WHO grade is based upon the features of the astrocytic neoplasm.
- May also see eosinophilic granular bodies and Rosenthal fibers (similar to that seen in pilocytic astrocytoma).

Desmoplastic Infantile Ganglioglioma/Astrocytoma (WHO I): Rare tumor of infants that looks like the name implies.
Clinical: < 18 months old. Radiologic features variable.
Pathology: Atypical mixed glial and neuronal tumor with prominent desmoplasia, highlighted on reticulin stain. I've never seen one.


DNT – "Floating Neurons"

Dysembryoplastic Neuroepithelial Tumor (DNT) (WHO I): Another rare tumor of teens and adolescents.
Clinical: History of intractable seizures common.
Radiology: Nodular mass, often in the temporal lobe (adjacent to amygdala)
Pathology: These tumors are notable for their intratumoral heterogeneity and nodularity. Often see areas indistinguishable from ependymoma, oligodendroglioma, etc. There are two features that are highly suggestive. 1) **Floating neurons** (neurons which appear to "float" in pools of mucin. 2) Specific glioneuronal element (linear arrays of oligodendroglioma-like cells).
Misc: Diagnosis of this tumor requires recognition of history (seizures), location, nodularity, and characteristic histologic findings. Some consider this tumor to be a malformative (non-neoplastic) process, particularly considering the fact that some tumors arise in association with cortical dysplasia.

Neurocytic Tumors - Rare Birds


Central Neurocytoma

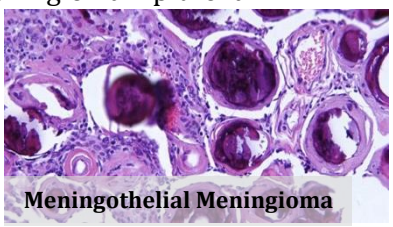
Central Neurocytoma (WHO II): Rare tumor. Most often seen in adolescents and young adults. Children rare
Radiology: **Intraventricular** mass, adherent to septum pellucidum or near **foramen of Monro**.
Pathology: Tumor consists of "**neurocytic**" cells, with round, monotonous nuclei with finely-stippled, "salt and pepper" type chromatin. The cells often have **perinuclear halos**, and thus look nearly indistinguishable from oligodendroglioma. One helpful finding is the presence of islands of slightly-fibrillar, eosinophilic **neuropil** amongst the tumor cells. May see frank ganglionic differentiation. Two things are key to the diagnosis: 1) Intraventricular location, 2) **strong, diffuse synaptophysin and neu-N immunoreactivity** in the neoplastic cells (not seen in oligodendroglioma). No infiltration of brain parenchyma.
Miscellaneous: The previously reported "intraventricular oligodendrogliomas" in the clinical literature are most likely all misdiagnosed central neurocytomas.

Gangliocytoma (WHO I): Rare tumor of children and young adults; presents with seizures.
Radiology: Tumor presents most often in temporal lobe
Pathology: Non-infiltrative tumor consisting solely of dysplastic ganglion cells (dysplasia = pleomorphic, abnormally-clustered, binucleated). Features of malignancy should be lacking. Consider it a ganglioglioma without the atypical glial component.

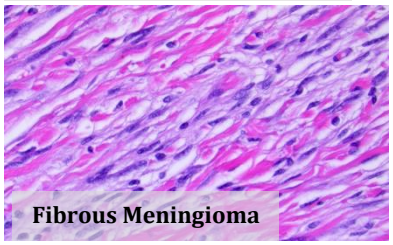
Dural-based Tumors – Meningioma

General Concepts: Tumors arising from "meningothelial rests" – small nodules of meningothelial tissue that are present throughout the leptomeninges, pachymeninges, and in the choroid plexus. Although there are many different subtypes of meningioma with varying histologic appearance, several key diagnostic features are nearly constantly seen, and can help one to arrive at the correct diagnosis.

- **Intranuclear pseudoinclusions** – obviously not exclusive to meningioma, but are the single most helpful feature, particularly during intraoperative consultation.
- **Intralesional collagen deposition** – Not many primary CNS tumors produce collagen. Meningiomas are the most common.
- **Localization** – When evaluating a dural-based mass, meningioma is the diagnosis that should be considered first.
- Meningiomas are one of the tumors that women beat men. The majority (~ 2/3) of intracranial tumors are seen in females. In the spinal cord, the female predominance is much higher (~ 9:1). No one is sure why.
- There is no single specific and sensitive immunostain that is reliably positive in meningioma. Epithelial membrane antigen (EMA) is the best we have, and it is often patchy and unreliable.

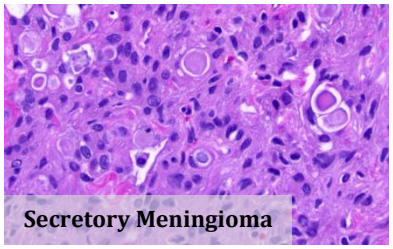

Meningothelial Meningioma

Meningothelial Meningioma (WHO I): The most common subtype. Characterized by the presence of meningothelial whorls and Psammoma bodies (Psammoma bodies are the calcified corpses of dead meningothelial whorls). Features of atypia should not be seen (see discussion below).


Fibrous Meningioma

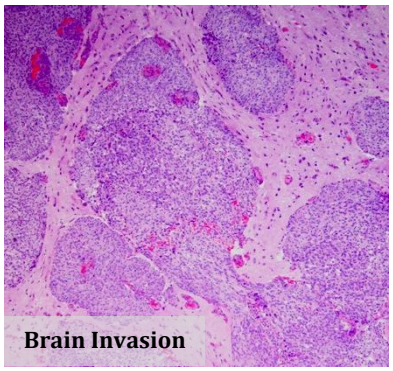
Fibrous Meningioma (WHO I): Collagen-rich, spindled tumor. Whorls and Psammoma bodies are helpful when they are present, but are not required for the diagnosis.

Psammomatous Meningioma (WHO I): A type of meningothelial meningioma in which Psammoma bodies predominate. Otherwise nothing distinctive about this tumor.


Secretory Meningioma

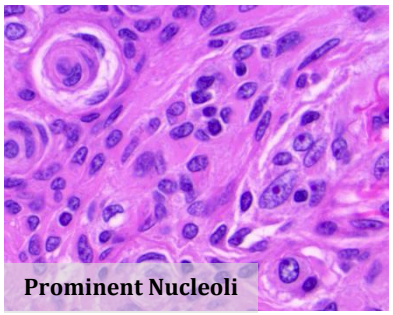
Secretory Meningioma (WHO I): An interesting subtype of meningioma in which "**pseudopsammoma bodies**" are present. Instead of rounded basophilic Psammoma bodies, there are scattered, round eosinophilic concretions not associated with whorls. These bodies are highlighted with PAS special stains and carcinoembryonic antigen (CEA). Unlike other subtypes of meningiomas, secretory-type tumors are often focally cytokeratin positive.

Atypical Meningioma (WHO II): Finding sufficient features for a diagnosis of "atypical meningioma" signifies a more aggressive clinical course, warranting a higher WHO grade (II). In most cases, it takes a constellation of findings to arrive at a diagnosis of atypical meningioma. Below are the criteria that one must evaluate for…

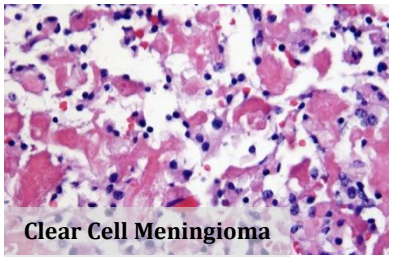

Brain Invasion

- Brain invasion: If you find brain invasion, you have met the criteria for an atypical meningioma. While it seems unnecessary to define brain invasion, here it is: "Meningioma surrounded on at least three sides by brain". Extension of meningioma down the Virchow-Robin perivascular space does not count for brain invasion, nor does adherent brain not invaded by meningioma.
- Mitoses: Four or more mitotic figures per 10 HPF are sufficient for a diagnosis of atypia. No other features needed.

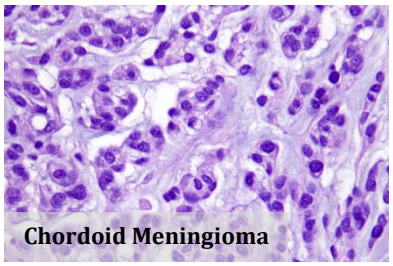
- Other findings: Finding *three or more* of the following criteria allows for the diagnosis of atypia.
    - **Prominent nucleoli**: Many meningiomas have small, indistinct nucleoli. The nucleoli need to be prominent to count.
    - **Sheet-like growth pattern**: Loss of the normal meningothelial growth pattern.
    - **High nucleus to cytoplasmic** (N:C) ratio – "small cell change".
    - **Increased cellularity**: Judgment call…
    - **Spontaneous necrosis**: Note the term spontaneous. *Necrosis in an emboli zed tumor does not count!* In many cases, you'll have to talk to the surgeon to find out if the tumor has been embolized.


Prominent Nucleoli

Clear Cell Meningioma (WHO II): By definition, is WHO grade II (don't need to look for features of atypia).
Pathology: Round cells with **clear cytoplasm** amongst thick, ropey bundles of **eosinophilic collagen**. Extracellular tyrosine crystals have been reported in clear cell meningioma. Classic features of meningothelial differentiation are often lacking. Needs to be differentiated from metastatic clear-cell renal cell carcinoma.

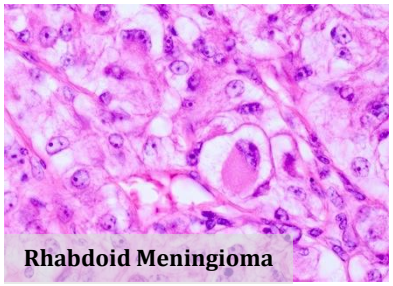

Clear Cell Meningioma

Chordoid Meningioma (WHO II): Also WHO grade II, regardless of presence of absence of atypical features.
Pathology: Nests and chords of epithelioid cells with cytoplasmic vacuolization ("**physaliferous cells**" - resembling chordoma of clivus/sacrum) in a **myxoid background**. The presence of focal meningothelial features (whorls, Psammoma bodies) confirms meningothelial differentiation. Immunohistochemical stains will easily differentiate (Chordoid meningioma = EMA +/S-100 -/CK - ; Chordoma = S-100 +/CK +/EMA -).


Chordoid Meningioma

Papillary Meningioma (WHO III): A more aggressive variant of meningioma, seen most often in children
Pathology: Cellular discohesion results in a papillary appearance, in which atypical meningothelial cells surround vascular cores. **Not a true papillary neoplasm**. Small foci of papillary architecture in an otherwise typical meningioma are not sufficient for a papillary designation, often resulting from physical manipulation of surgical resection. Classic meningothelial features should be present yet focal. Mitoses are frequent.

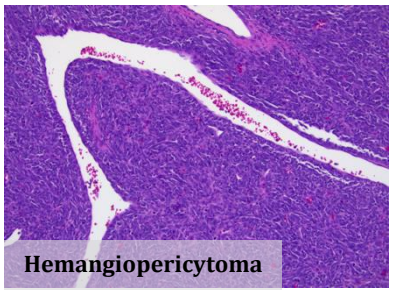
Rhabdoid Meningioma (WHO III): Continuing the theme of aggressive meningiomas, the rhabdoid. Anything bearing the adjective "rhabdoid" is going to be more aggressive.
Pathology: A significant portion of the tumor (i.e. the majority) shows cytologic atypia, hypercellularity, and tumor cells with **rhabdoid features** (eccentric nucleus, voluminous eosinophilic cytoplasmic, oft with eosinophilic, fibrillar cytoplasmic inclusions. Small foci of apparent rhabdoid features are not sufficient, but should be noted as worrisome features.


Rhabdoid Meningioma

Anaplastic Meningioma (WHO III): An atypical meningioma taken to the next level…
Two ways to arrive at the diagnosis:

1) Find **20 more mitotic figures per 10 HPF**
2) "**Anaplastic cytology**" – a higher degree of cellularity, nuclear atypia, and abundant necrosis than one would be expected in an atypical meningioma. In other words, a judgment call.

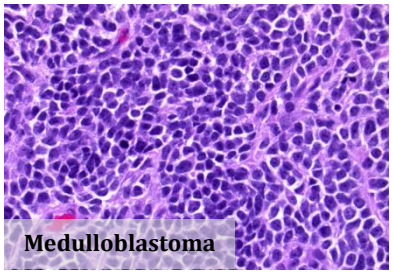
Dural-based Tumors - Not Meningioma


Hemangiopericytoma

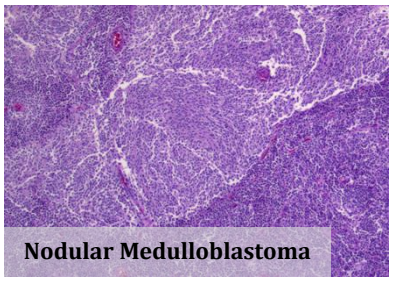
Hemangiopericytoma (WHO II-III): Often mistaken for meningiomas (overlapping clinical and radiologic features)
Pathology: No different from Hemangiopericytoma elsewhere. Abundantly cellular, ovoid cellular proliferation with scattered irregularly branching, "staghorn" vessels. Graded as anaplastic if there is elevated mitotic activity (5 or more mitoses per 10 HPF) and/or necrosis. In addition, two of the following must be seen: hemorrhage, moderate to high-grade nuclear atypia, and/or high cellularity.
Stains: Reticulin staining will highlight the well-developed pericellular reticulin network. Most tumors will show patchy CD34 immunoreactivity. Beware that hemangiopericytoma can be focally positive for EMA, just like meningiomas.

Metastatic Carcinoma: We'll delve more into this later. Suffice it to say that it is not uncommon for breast and prostate carcinomas to metastasize to the dura mater and clinically and grossly mimic a meningioma. The best minds have been fooled by this phenomenon.

Primitive Tumors – "Small Round Blue Cells"


Medulloblastoma

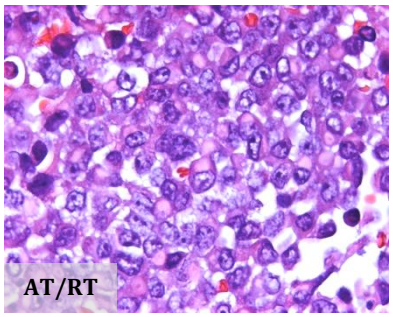
Medulloblastoma/Primitive Neuroectodermal Tumor (PNET; WHO IV): Malignant, common, posterior fossa, kids
Clinical: Peak age is 7 years old. Extremely rare in adults. Slight predilection for males. Often seeds CSF.
Radiology: Some tumors enhance, some don't. Often project into the fourth ventricle.
Pathology: **Small round blue cell tumor** of frankly-malignant cells (frequent mitoses, apoptotic bodies). The characteristic immunophenotype is that of overlap between neuronal and glial differentiation. Thus, the tumor cells should express **both GFAP and synaptophysin**.


Nodular Medulloblastoma

- *Desmoplastic/nodular variant*: Tumors with desmoplasia and/or nodularity are often present in the lateral cerebral hemispheres (typical tumors involve the vermis). The nodular appearance is imparted by nodules of tumor cells with ganglionic differentiation and background neuropil.
- *Anaplastic variant*: Defined by numerous apoptotic bodies and nucleomegaly. Various grading systems have been proposed, in which the size of nuclei has to be measured. I prefer the gestalt method.
- *Large cell variant*: Defined by large cells. Considerable overlap with anaplastic variant.
- Others: Medullomyoblastoma (myogenic differentiation), melanotic Medulloblastoma.

Misc: One issue that needs to be clarified… Medulloblastoma is the same thing as a **CNS primitive neuroectodermal tumor (PNET)**. If supratentorial, call it a PNET, if posterior fossa, call it a medulloblastoma. That being said, A CNS PNET and a soft tissue PNET/Ewing's sarcoma are **absolutely unrelated** tumors. The t(11;22) translocation and CD99/FLI-1 immunoreactivity typical of PNET/Ewing's sarcoma are not seen in CNS PNETs. The person responsible for this irresponsible nosologic overlap should be punished mercilessly…

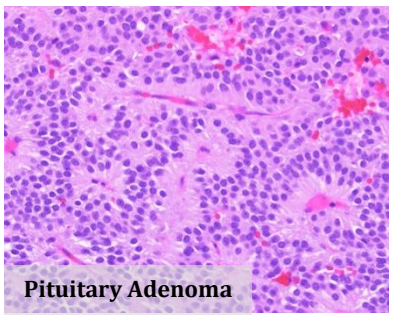
Atypical Teratoid Rhabdoid Tumor (AT/RT; WHO IV): Extremely aggressive brain tumor of young children.
Clinical: Can be both supratentorial and infratentorial. When infratentorial, clinically mimics medulloblastoma.
Pathology: Primitive embryonal neoplasm that takes cytologic atypia to the next level. Highly atypical small cells with frankly malignant nuclear features. The finding of **rhabdoid morphology** (eccentric eosinophilic cytoplasm distended by homogenous, eosinophilic cytoplasmic inclusion) is characteristic. Other examples are primarily epithelioid or medulloblastoma-like. By immunohistochemistry, a wide range of markers can be positive (cytokeratin, GFAP, synaptophysin, EMA, SMA, myogenin, vimentin, etc…). Only one stain is really helpful… The characteristic mutation of AT/RT is **loss of the INI1 gene** on 22q11.2, the gene product of which is responsible for maintaining and remodeling the chromatin structure. One can utilize FISH for the 22q11.2, but a more straightforward approach is to do am immunostain for the INI1 gene product, **BAF47**. A positive BAF47 indicates no deletion of the INI1 gene; absent BAF47 reactivity indicates mutation. If you haven't figured it out already, this was my area of research during my neuropathology fellowship, so I find it particularly interesting...


AT/RT

Pineoblastoma (see "pineal region tumors")

Sellar Region Tumors

Pituitary Adenoma: Most common tumor of the sellar region.
Clinical: Tumor of young adults and the elderly. < 1 cm = microadenoma; > 1 cm = macroadenoma. Macroadenomas typically do not secrete, so they don't come to attention until large enough to become symptomatic (**headache, bitemporal hemianopsia**)
Pathology: Monotonous proliferation of round epithelioid cells with variable nuclear atypia (depends on subtype). The key features that distinguish between normal adenohypophysis and tumor are:


Pituitary Adenoma

- Sheet-like growth pattern
- Loss of normal small-nest architecture
- Monotonous cells (no mixture of eosinophilic, basophilic, and/or clear cells)
- Expansion/effacement of the normal reticulin network of the adenohypophysis (seen on reticulin stain)

Features of an atypical pituitary adenoma are increased nuclear pleomorphism, frequent mitoses, and elevated Ki-67 labeling index (normally quite low, <2%). By immunohistochemistry, the finding of diffuse, strong CAM5.2 and synaptophysin staining is characteristic. Application of hormone specific immunostains (FSH, LH, ACTH, TSH, Prolactin, GH) may help in subtyping. Pituitary adenomas can also be subtyped by expression of nuclear transcription factors (nuclear stains show less artefactual staining).

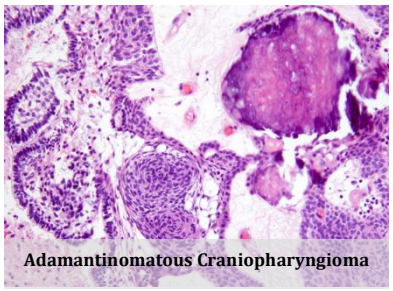
- **SF1**: Gonadotroph adenomas (FSH, LH)
- **Pit1**: Prolactinomas, somatotroph, and thyrotroph adenomas
- **Tpit**: Corticotroph adenomas

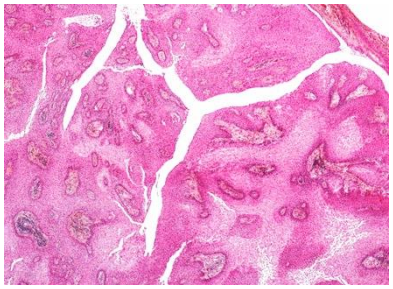
Misc: Correlation with serum hormone levels may be insightful. However, one must be aware of "**stalk effect**" – the physical effect of a large pituitary mass impinging on the pituitary stalk interrupts the normal flow of dopamine ("prolactin inhibitory factor") to the adenohypophysis, thus resulting in mild elevations of dopamine. Thus, a low-level elevation of serum prolactin does necessarily indicate a prolactinoma.
Aggressive subtypes of adenomas:

- Acidophil stem cell in men
- Crooke cell adenoma
- Lactotroph adenoma in men
- Pit-1 positive pleurihormonal adenoma
- Sparsely-granulated GH adenoma
- Silent cortitroph adenoma

Craniopharyngioma: Two distinct histologic patterns and ages of presentation:

- *Adamantinomatous*: Tumor of younger adults, sellar region, often cystic (contains "motor-oil")
  - **Ameloblastic-like epithelium** (peripheral palisading, stellate reticulum)
  - **Wet keratinization** (clumps of anuclear, "ghost" keratinocytes)
  - **Dystrophic calcification** (seen on CT scan)
  - **Finger-like extension into adjacent brain parenchyma** (responsible for high incidence of tumor recurrence following resection)
  - Positive for **beta-catenin** (CTNNB1) mutations
- *Papillary craniopharyngioma*: Older patients, more posterior (often within third ventricle), non-cystic
  - **Bland squamous proliferation** with focally papillary architecture
  - **No keratinization**
  - **No calcification**
  - Positive for **BRAF V600E** mutations


Adamantinomatous Craniopharyngioma

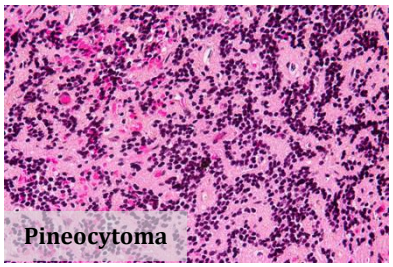

Papillary Craniopharyngioma

Others: Many other neoplastic and non-neoplastic conditions can cause a mass in the sellar region

- *Langerhan's cell histiocytosis* (LCH): S-100+, CD1a+, frequent eosinophils and coffee beans.
- *Germinoma*: Beware – may be granulomatous, with paucity of tumor cells. Seen in children and adolescents.
- *Metastatic carcinoma*: Breast and cervical carcinoma are notorious for metastasizing to the sellar region.
- *Lymphocytic hypophysitis*: Inflammatory tumor of sella. Etiology unknown. Diagnosis of exclusion.
- *Neurohypophyseal tumors* (pituicytoma, granular cell tumor, etc…)

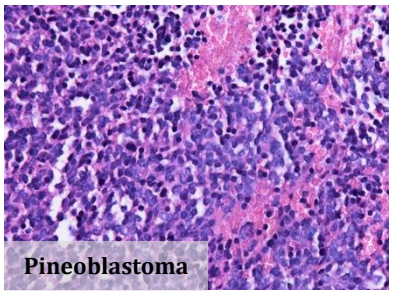
Pineal Region Tumors – Parinaud's Syndrome!

Pineocytoma (WHO I): Rare tumor, affects most often in adults
Radiology: Most tumors are homogenously contrast enhancing. May be solid or cystic.
Pathology: Sheets of small, monotonous cells that resemble normal pineocytes. Large "**pineocytomatous" rosettes** are often seen. Mitoses are rare or absent. Degenerative atypia may be prominent, yet tumor is still benign. Tumor cells are synaptophysin and neurofilament positive.

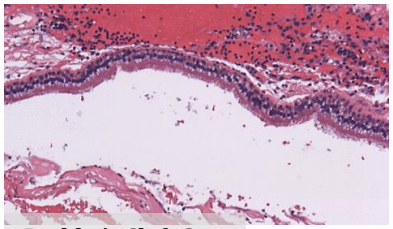

Pineocytoma

Pineal Parenchymal Neoplasm of Intermediate Differentiation (WHO II-III): Intermediate between pineocytoma and pineoblastoma. Cellularity is higher, atypia is more pronounced, mitotic indices higher, and Ki-67 labeling index higher > 3%. However, accepted criteria for this diagnosis have not been agreed upon, leaving a great degree of subjectivity in the diagnosis. Seek help with this one.

Pineoblastoma (WHO IV): Highly malignant, seen most often in children. Seeds CSF.
Pathology: Pineoblastoma is the most primitive end of the pineal neoplastic spectrum, comprising a **small-round blue cell tumor** with small rosettes (not the large "pineocytomatous" of benign tumors). Mitotic activity should be high. Synaptophysin and NFP immunoreactivity is maintained, and the Ki-67 labeling index is high.

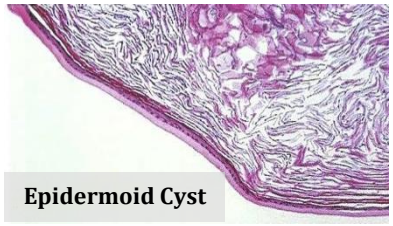

Pineoblastoma

Cysts in the Brain


Rathke's Cleft Cyst

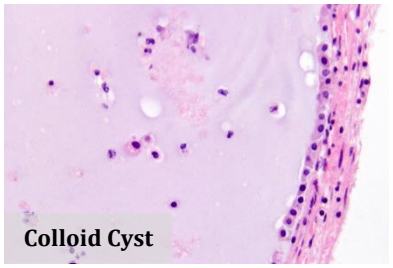
Rathke's Cleft Cyst: Sellar region cyst. Lined by respiratory-type epithelium. (CK8, CK20 positive)

Epidermoid Cyst: Most often in cerebellopontine angle. Squamous epithelium without pilosebaceous structures.


Epidermoid Cyst

Dermoid Cyst: Most often in Sylvian fissure region. Squamous epithelium with pilosebaceous structures.

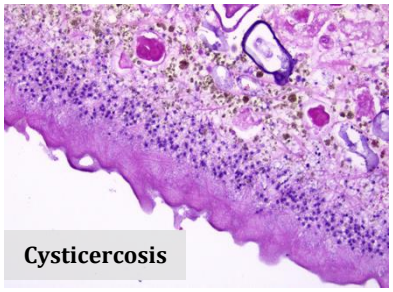
Colloid Cyst: Attenuated, focally respiratory-type epithelium with central homogenous eosinophilic contents. Located adjacent to the foramen of Monro.


Colloid Cyst

Enterogenous Cyst: Most often seen in brainstem or spinal cord region. Developmental abnormality. Lined by columnar, often mucinous epithelium. May be ciliated (i.e. just like bronchial epithelium). Benign.

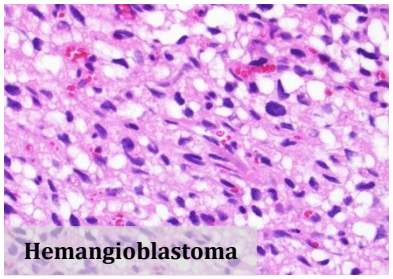
Arachnoid Cyst: Occur in association with the leptomeninges. Lined by thin, loose fibroblastic stroma with variable meningothelial rests.

Cysticercosis: CNS infection by the pork tapeworm ***Taenia solium***. Forms well-circumscribed cysts in the brain. While parenchymal cysts may be seen, **intraventricular lesions are the most common** (and may cause hydrocephalus). One may see various body parts (scolices, gut, gonads), often all one sees in the resected specimen is a degenerating cystic structure with the three following layers (from outer to inner): 1) Undulating eosinophilic "waxy" **cuticle**, 2) **Germinal layer** (immature, small-round blue cells), and inner 3) inner**, loose "myxoid" layer**. Calcifications are commonly seen.


Cysticercosis

Unusual Tumors

Hemangioblastoma (WHO I): Adolescents and adults. Tumor of uncertain histiogenesis.
Radiology: **Cyst with enhancing mural nodule**. Often cerebellar, also may be cerebellar and retinal.
Pathology: Two components. The neoplastic component comprises nondescript, ovoid "**stromal cells**" with foamy, clear cytoplasm. The non-neoplastic component comprises a delicate capillary network. The stromal cells may show a significant degree of "degenerative" nuclear atypia, without corresponding mitotic activity. Non-infiltrative.
Miscellaneous:


Hemangioblastoma

- While most tumors are sporadic, a minority are seen in association with **von Hippel Lindau syndrome**, due to VHL gene mutations on chromosome 3p.
- **Must be distinguished from metastatic renal cell carcinoma**. IP stains will help (hemangioblastoma = inhibin+, EMA -; RCC = EMA +, inhibin -).

Chordoid Glioma of the Third Ventricle (WHO II): Rare tumor of adults and elderly, most often females.
Radiology: Solid, well-circumscribed contrast-enhancing mass in the third ventricle.
Pathology: **Looks just like a chordoma** (epithelioid cells lying in chords, mucinous background). However, occurs in third ventricle, and cells strongly express GFAP, CD3, TTF-1 (CK, S-100 negative or weak). Not aggressive, but location in third ventricle location prevents complete excision, and many patients eventually die from tumor progression.
Miscellaneous: Must be distinguished from chordoma (S-100/CK+, GFAP-) and chordoid meningioma (EMA+, GFAP-)

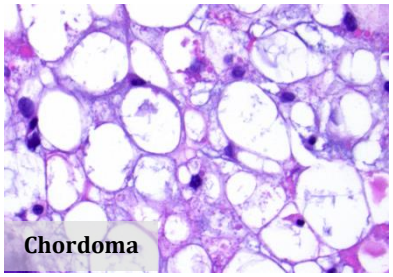
Paraganglioma: Occurs in the cauda equina region of the spinal cord. By histology, indistinguishable from paragangliomas elsewhere. Characterized by nests/trabeculae of epithelioid "chief" cells with "salt and pepper" chromatin and encircling spindled sustentacular cells. Blood vessels are often prominent, and presence of rosettes may cause confusion with ependymoma. Interestingly, are often cytokeratin positive (non-CNS paragangliomas are cytokeratin negative).

Metastatic Tumors: Support Organ Neoplasia

Site of origin of brain metastases – Lung (50%), Breast (15%), Skin/melanoma (11%), Unknown (11%) (WHO data)
Metastatic tumors that are most often **hemorrhagic** – choriocarcinoma, melanoma, renal cell carcinoma
Metastatic tumors that preferentially affect the **dura mater** – Breast, prostate, lymphoma
Metastatic tumors that tend to involve the **sellar region** – Breast, cervix
Radiology: Often present at the gray-white junction (embolic in origin), may be solitary or multifocal. Heterogeneous **ring-enhancing mass** is often seen by radiology.

Clival Tumors

Chordoma: Low-grade yet aggressive tumor of notochordal remnants.
Radiology: Expansile, destructive lesion, most often in clivus and sacral region.
Pathology: Epithelioid neoplasm comprising chords of "**physaliferous cells**" with vacuolated cytoplasm. Background myxoid stroma. May have well-developed chondroid features. Infiltrates bone.
Misc: Must be distinguished from low-grade chondrosarcomas. IP stains are helpful (chordoma = cytokeratin +, chondrosarcomas = cytokeratin -.


Chordoma

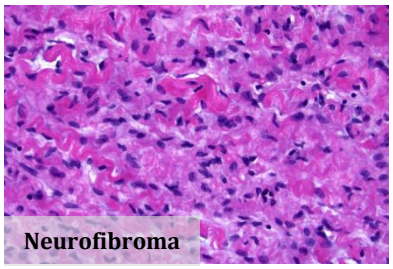
Chondrosarcomas: Low-grade examples may share similar histologic features with chordoma, as well as occurring in similar locations. See chordoma discussion above.

Giant Notochordal Hamartoma: Intra-osseous lesions of the clivus. Developmental in origin. Non-aggressive radiologic features. Histology shows bland chords of physaliferous cells amongst trabeculae of bone.

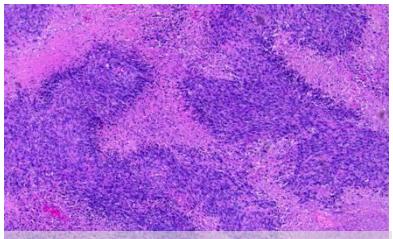
Ecchordosis Physaliphora: Presents as a nodule of firm tissue adherent to the basal artery. Histologically indistinguishable from chordoma. Distinction from chordoma/notochordal hamartoma is based on clinical/radiologic features.

Peripheral Nerve Sheath Tumors

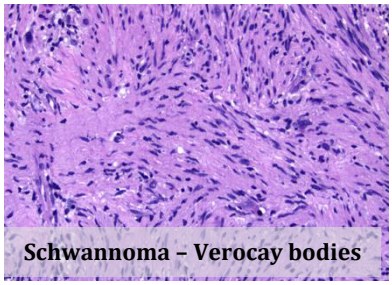
Neurofibroma: Nerve sheath tumor comprising all of the expected nerve constituents.
Pathology: Polymorphous proliferation that enlarges nerve segment. Termed "plexiform" if involves significant length of nerve. Tumor comprises spindled Schwann cells, fibroblasts, capillaries, "shaved-carrot"-like wavy, fibrillary collagen, **intermixed axons**, and mast cells. May be difficult to distinguish cellular neurofibromas from low-grade MPNST (see below).


Neurofibroma

Malignant Peripheral Nerve Sheath Tumor: Malignant tumor arising in association with peripheral nerve
Pathology: Call MPNST if: 1) Arises in association with peripheral nerve, 2) Patchy S-100 positive, and/or 3) History of previously-excised nerve tumor in same area. Often has "dumb-bell" morphology in spinal region. Malignant mesenchymal neoplasm with varied, often "marbled" low-power appearance. Patchy S-100 immunoreactivity is characteristic (neurofibroma should be diffusely positive).

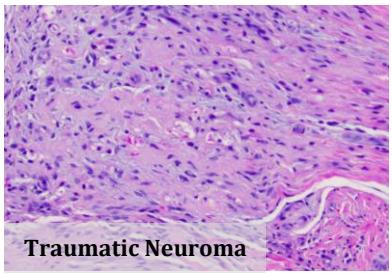

MPNST – "marbled appearance"

Schwannoma: Nerve sheath tumor consisting solely of Schwann cells
Pathology: Well-circumscribed mass, often peripherally attached to peripheral nerve (i.e. separable from affected nerve segment). Spindled proliferation with 1) **Verocay bodies** (linear arrays of nuclei and intervening eosinophilic anuclear stroma), 2) biphasic low-power architecture with hypercellular (**Antoni A**) and hypocellular (**Antoni B**) areas, 3) hyalinized blood vessels, and 4) thin fibrous capsule. As entire tumor comprises Schwann cells, S-100 should be diffuse and strong (all cells labeling). *If axons are present, should be displaced to periphery of lesion*.


Schwannoma – Verocay bodies

Traumatic Neuroma: Non-neoplastic, painful mass at sites of previous trauma.
Pathology: **Disorganized** proliferation of maloriented bundles of axons, may see nerve bundle from which mass is arising.
Misc:

- Occurs due to distal axonal outgrowth and sprouting in an attempt to bridge injured segment and reestablish the axonal connection. If unable to reestablish the connection, a traumatic neuroma results.
- A "**Morton's neuroma**" is **not a traumatic neuroma**. It is an irritated peripheral nerve segment in the second and third intermetatarsal space of the foot. Histologic examination reveals perineurial fibrosis, but no disorganized axonal proliferation.


Traumatic Neuroma

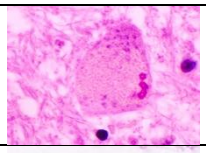
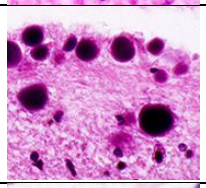
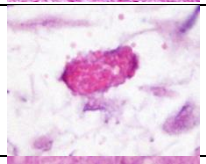
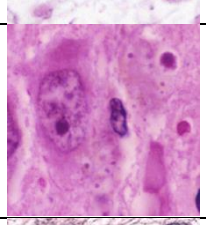
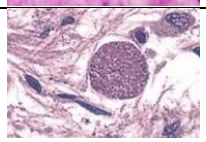
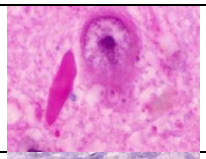
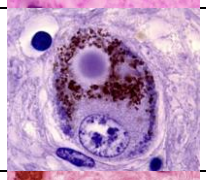
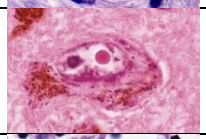
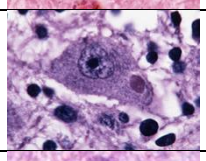
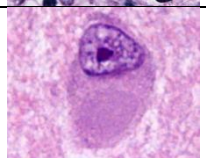
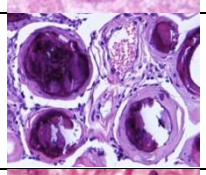
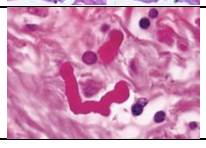
Perineuroma: Rare nerve sheath tumor arising from perineurial cells (fibroblast-like cells in the perineurium).
Pathology: Well-circumscribed, un-encapsulated proliferation of spindled cells, focally with nuclear palisading and perivascular accumulations. Immunohistochemistry is characteristic (EMA+, S-100/NFP negative)

Appendix I: Immunohistochemistry and the CNS

Tumor	GFAP	NFP	EMA	Synapt	CAM5.2	S-100	Ki-67	Misc
Pilocytic astrocytoma	+	Few/no axons	-	-	-	-	< 2.5%	
SEGA	+	Few/no axons	-	-	_	+/-	Low	
Angiocentric glioma	+	+ many axons	DLP +	-	-	+	< 1%	
Infiltrating astrocytoma	+	+ many axons	-	-	-	-	2-4%	p53 +
PXA	+	Few / no axons	-	-/+	-	+	< 1%	CD34+
Anaplastic astrocytoma	+	+ many axons	-	-	-	-	5-10%	p53 +
Glioblastoma	+	+ many axons	-	-	-	-	> 10%	EGFR + (primary) p53 + (secondary)
Oligodendroglioma	+	+ many axons	-	-	-	+	< 5%	1p/19q LOH- molecular
Ependymoma	+	No axons	DLP +	-	-	-	Varies	
Choroid plexus	+	-	-	-	+	-	Varies	
Ganglioglioma	+	+ few /many axons	-	+	-	-	Varies	Neu-N / CD34 + ganglion cells
Central neurocytoma	-	+ (neuropil)	-	+	-	-	Low	Neu-N +
Meningioma	-	No axons	+	-	-	-	Varies	
Hemangio-pericytoma	-	-	-	-	-	-	Varies	CD34 patchy/ reticulin +
Metastatic carcinoma	-	-	+	+/-	+	+/-	N/A	Immunoprofile varies with site of origin
Medullo-blastoma	+	Many axons	-	+	-	-	High	
AT/RT	+/-	Many axons	+/-	+/-	+/-	+/-	High	**INI1 (BAF47) negative**
Pituitary adenoma	_	_	_	+	+	_	< 2%	May be pituitary hormone marker +
Pineocytoma	-	+	-	+	-	-	Low	Retinal S antigen +
Hemangio-blastoma	-	-	-	-	-	-	Low	**Inhibin +**
Paraganglioma	-	-	-	+	+	+	Low	
Chordoma	-	-	-	-	+	+	N/A	
Neurofibroma	-	Few/many axons	+ patchy	-	-	+	N/A	Intralesional axons are characteristic
MPNST	-	+/-	-	-	-	+ patchy	N/A	Patchy S-100 loss is characteristic
Schwannoma	-	Few/no axons	-	-	-	+	N/A	Diffuse, strong S-100 is characteristic
Perineuroma	-	-	+	-	-	-	N/A	

DLP = “dot-like perinuclear” – characteristic finding in EMA immunostains of ependymoma

Appendix II: Brain Bodies – "Eponymous Inclusions"

Bunina body		Eosinophilic intranuclear inclusions, often beaded in appearance. Seen in anterior horn cells (motor neurons) in the spinal cord in patients with amyotrophic lateral sclerosis (ALS).
Corpora amylacea		Rounded eosinophilic inclusions in the brain neuropil, found in greatest density in the subpial and perivascular space. Be aware that corpora amylacea will stain for everything. Increase in density with age.
Eosinophilic granular bodies (EGB)		Well-circumscribed aggregate of round, granular eosinophilic bodies. Characteristic finding of pilocytic astrocytoma. Also may be seen in ganglioglioma.
Granulovacuolar degeneration		Round, clear vacuoles containing central basophilic inclusion. Occurs in hippocampal pyramidal neurons. The greatest densities occur in the setting of Alzheimer disease. May also be seen in non-demented aged individuals.
Herring bodies		Round, faintly eosinophilic well-circumscribed granular bodies. Dilated synaptic terminals containing oxytocin and arginine vasopressin (AVP), found in normal posterior hypothalamus (neurohypophysis). Helpful to recognize location in neurohypophysis.
Hirano bodies		Rod-like eosinophilic inclusions associated with hippocampal pyramidal neurons. Interestingly, often seem to lie both within the neuronal cytoplasm and adjacent neuropil. Similar to granulovacuolar degeneration, seen most often in patients with Alzheimer disease and non-demented aged individuals.
Lewy bodies		Dense, eosinophilic cytoplasmic inclusions seen in the cytoplasm of pigmented neurons (substantia nigra, locus coeruleus, dorsal vagal motor nucleus). Sine qua non of idiopathic Lewy body disease. May stain with **alpha-synuclein** by IHC.
Marinesco bodies		Eosinophilic **intranuclear** inclusions in substantia nigral neurons. Of no pathologic significance, except for occasional misdiagnosis as Lewy bodies (should be cytoplasmic)
Negri bodies		Well-circumscribed eosinophilic cytoplasmic inclusions comprising **rabies virions**. Seen in **hippocampal pyramidal neurons** and **Purkinje cells**. If poorly-circumscribed, are called "Lyssa bodies".
Pick bodies		Well-circumscribed, lightly basophilic cytoplasmic neuronal inclusions composed of hyperphosphorylated tau. Seen in Pick's disease. Neurons throughout the cerebral hemispheres and hippocampi are typically affected. The inclusions are most prominent in the hippocampal dentate gyrus.
Psammoma bodies		Rounded, basophilic lamellated calcifications. Seen in meningiomas. Form when the cells in the center of a meningothelial whorl die, degenerate, and calcify. May also be seen in papillary neoplasms outside the brain (i.e. serous carcinoma of ovary, papillary thyroid carcinoma, mesothelioma)
Rosenthal fibers		Serpentine, often tapered eosinophilic inclusions. Consist of protein aggregates in astrocytic processes. By immunohistochemistry, stain with alpha-B Crystallin. Seen in both Pilocytic astrocytomas and piloid gliosis.

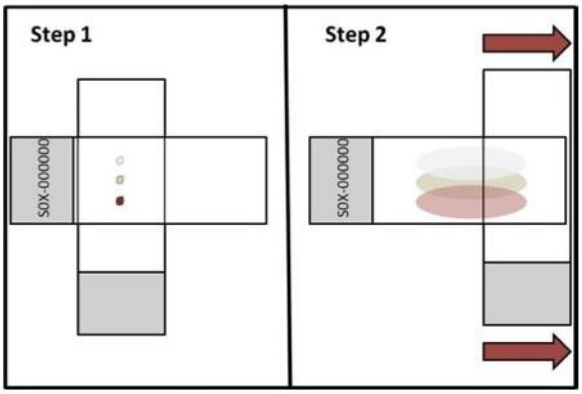
Appendix III: Guidelines for Grossing Neuropathology Specimens

GUIDELINES FOR GROSSING NEUROPATHOLOGY SPECIMENS

* Remember to always place the specimen on a smooth, non-porous surface (e.g. specimen container lid), as nervous tissue is inherently "sticky", and will adhere to paper towels and gauze, never to be returned.

* Keep specimen moistened. This is easily accomplished by placing a small amount of saline on the specimen. Nervous tissue will dry out quickly while the smear and frozen section are being prepared.

* Make the **smear preparation**. First, remove and inspect all fragments from the specimen container. Serially section any larger fragments. Select the tissue to be crushed. White matter is white, cortex is a light-tan, and neoplastic tissue is frequently dusky, gray to yellow, friable, or hemorrhagic. Up to three small (**< 1mm**) fragments from areas with varying gross appearance should be selected.



* Place specimen on labeled slide approximately 1 cm from the labeled end. With a second slide (held perpendicularly to labeled slide), apply **sufficient pressure** to crush the specimen. Move unlabeled slide across length of lower slide to smear the crushed tissue. Place labeled slide (with smeared specimen) immediately (**within 2 seconds**) in alcohol fixative. Any delay in fixation will introduce air-drying artifact. Stain with hematoxylin and eosin.

* Next, on to the frozen section. **Note: Avoid freezing the entire specimen!!** If freezing an adequate amount of tissue requires freezing the entire specimen, wait until the pathology staff arrive to determine if the diagnosis can be made solely on the smear. This is because sections from specimens which have been frozen and subsequently formalin fixed and paraffin embedded show poor histology, with significant distortion of nuclear and cytoplasmic details. Additionally, freezing may interfere with subsequent immunohistochemistry. If adequate tissue is present, freeze approximately half of the tissue (unless the specimen is large). Remember to sample areas with varying gross appearance. One exception to the rule of not freezing the entire specimen is in the case of ACTH secreting microadenomas, in which no smear should be performed, and all tissue is frozen to look for the adenoma.

* Now, specimen submission for processing. In most cases, the entire tissue will most likely be submitted for permanent sections. Rare instances require submitting a small portion for electron microscopy or flow cytometry. In **large meningioma resections**, submit up to 8 cassettes. If tissues remain, submit one cassette per cm of the remaining tissue. In cases where large amounts of tissue is submitted for glioma, and the grading is uncertain on the smear and frozen section, submit up to 20 blocks of tissue. This is because grading will depend on the identification of areas of necrosis and/or microvascular proliferation, among other features. In temporal lobe resections, the entire hippocampus (typically submitted separately) should be sectioned in the coronal plane and entirely submitted. If the remaining brain tissue is grossly unremarkable, submit one cassette per cm.

* Wrap small specimens (e.g. stereotactic biopsies, spinal cord lesions) in formalin-moistened **lens paper** helps to avoid tissue loss. Larger specimens go in regular cassettes. Specimens are dictated as usual, keeping in mind that all issue is not just tan and pink. In neuropathology, descriptive terms, especially terms descibing consistency (firm, friable, gelatinous, etc) are particularly important.

* To avoid specimen handling errors and their subsequent impact on diagnosis, query the pathology attending prior to handling the specimen. This is particularly important in stereotactic brain biopsies, as a repeat biopsy may require a subsequent visit to the operating room.

Prepared by Jeremy Deisch, MD (2012)

Appendix IV: Template for Autopsy Brain Gross Description

Below is a "template" for gross descriptions of autopsy brains. While the template is somewhat nonspecific (and most appropriate for an adult brain), most pertinent details are addressed. Remember, when dealing with templates, one must be careful that inaccurate statements are not mistakenly left in the report. You have to read your report before you consider them "done". Also, the following are features of developmental features that should be addressed in pediatric brains, particularly in neonatal/infantile examples (see Appendix VI for photographs of developing brains):

- **Gyral pattern**: As the brain develops, gyri develop in a predictable fashion. You must ensure that the gyri are not too wide (pachy gyri), too small (microgyria), or absent (lissencephaly). Keep in mind that early in development, the brain completely lacks gyri, mimicking lissencephaly ("physiologic lissencephaly").
- **Opercular development**: As the brain develops, the edges of the Sylvian fissure ("operculum") progressively approximate, gradually closing the Sylvian fissure and covering the insular cortex. The degree of closure of the operculum is the single best method of assessing developmental age by gross means.

Forebrain/Hindbrain weight ratio: Early in development, the hindbrain (cerebellum + brainstem) is much smaller than the forebrain (cerebrum). As brain development ensues, the hindbrain grows relative to the hindbrain. These issues should be addressed in pediatric autopsy brains.

Age (EGA)	20 weeks	30 weeks	Term	3 months	9 months	1 year	2 years
Hindbrain weight (% of total brain wt)	~ 5%	~ 5%	~ 6%	~ 8%	~ 10%	~ 11%	~ 12%

Adapted from Ellison and Love's Neuropathology Textbook,

Template for gross description of a "*normalis totalis*" autopsy brain…

"Available for review are the _____-gram formalin-fixed brain and dural fragment. Examination of the dura shows no adherent blood, exudate, or dural defects. Examination of the formalin-fixed brain demonstrates an unremarkable gyral pattern. The gyri are neither edematous nor atrophic, and the sulci are not effaced. The cerebral hemispheres are symmetric. The overlying leptomeninges are thin and transparent. No subfalcine, transtorial, or cerebellar tonsillar herniations are seen. The blood vessels and cranial nerves at the base of the brain are unremarkable. Cross sections of the cerebrum demonstrate an intact cortical ribbon, distinct gray-white junction, and homogeneous subcortical white matter. The thalami, basal ganglia, and hippocampi are symmetric and unremarkable. The ventricles are neither slit-like nor dilated. There is no shift of midline structures. Cross sections of the brainstem show no abnormalities. The substantia nigra and locus coerulei are adequately pigmented. Parasagittal sections of the cerebellum reveal no abnormalities."

Appendix V: Histologic Assessment of Developmental Age

External granular layer (EGL): thickness equal to underlying molecular layer	24 wks EGA to 2nd to 4th postnatal month
EGL: two cells thick	4-6 months
EGL: continuous single layer	9 months
EGL: isolated single cells	12 months (complete disappearance is highly variable)
EGL: vermis	May disappear completely by 4-12 months.
Internal granular layer (IGL): sparsely populated with indistinct grey/white junction	< 30 weeks EGA (vermis), < 32 weeks EGA (hemisphere)
Lamina dissecans (pentalaminar cerebellar cortex)	21-32 weeks EGA
Purkinje cells: indistinct from granule neurons	< 25 weeks EGA (vermis), < 33 weeks EGA (hemisphere)
Neuroepithelial cell rests, white matter of cerebellar vermis	< 28 weeks EGA
Subpial cortical granular layer	Maximal thickness at 22 weeks EGA, disappears at term (remnants may be seen in inferior orbital/temporal lobes).
Neocortex: solid band of indistinct cells, no lamination	20 weeks EGA
Neocortex: lamination	Progressively more distinct between 24-32 weeks.
Cajal-Retzius cells	Identifiable throughout gestation, only few persist at term.
Neuronal maturation: globus pallidus	Matures by 24 weeks EGA.
Neuronal maturation: striatum	Matures by 33-36 weeks, adult cytomorphology at 38 weeks.
Germinal matrix	At term, only scattered islands of periventricular germinal matrix. Thicker cushion between thalamus and head of caudate persists for 12 months.
Ependyma	Temporal and occipital horns are last to be lined by ependyma, which occurs as late as 22 weeks EGA.

External granular layer: outer layer of post-mitotic premigratory granule neurons in the cerebellum. Migrate down the perpendicular processes of **Bergmann glia** to reside in the internal granular layer.
Lamina dessicans: transitory fetal zone, consists of amorphous eosinophilic lamina between the Purkinje cells and internal granular layer. Temporarily results in a **pentalaminar** cerebellar cortex.
Subpial granular layer of cerebellar cortex: neuroectodermal cells which mature into astrocytes (unlike cerebellar EGL).
Cajal-Retzius cells: earliest neurons of the cerebral cortex, bipolar neurons lying in the fetal molecular zone. Both axons and dendrites extend parallel to the cortical surface.
Subventricular germinal matrix: postmitotic premigratory cells which migrate outward to the cortical plate and deep gray matter. Early in gestation (8-16 weeks), form neurons. Later (>24 weeks), the great majority form glial cells. Remember that the most superficial cells of the cortex are the most recent immigrants.
Ependyma: the development of the fetal ependyma signals the cessation of mitotic activity in that region.

Compiled from *Neuropathology; the Diagnostic Approach*, J.H. Garcia ed, Mosby, 1997, by Jeremy Deisch, MD (2009)

Appendix VI: Gross Photographs of Developing Brains