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Central Nervous System Tumors

General

~1% of tumors in adults, but ~25% of malignancies in children (only 2nd to leukemia).
Significant increase in incidence in primary brain tumors in elderly.
Metastases to the brain far outnumber primary CNS tumors→ multiple cerebral tumors.

One can develop a very good DDX by just location, age, and imaging.

Differential Diagnosis by clinical information:

Location	Pediatric/Young Adult	Older Adult
Cerebral/ Supratentorial	Ganglioglioma, DNET, PXA, Ependymoma, AT/RT CNS Embryonal Neoplasms	Glioblastoma (GBM), Astrocytoma, Oligodendroglioma, Metastases, Lymphoma, Infection, Diffuse Hemispheric Glioma Histone-Altered
Cerebellar/ Infratentorial/ Fourth ventricle	PA, Medulloblastoma, Ependymoma, Choroid plexus papilloma, AT/RT Pediatric high-grade glioma	Metastases, Hemangioblastoma, Choroid plexus papilloma, Subependymoma
Brainstem	PA, Diffuse Midline Glioma (DMG)	Astrocytoma, Glioblastoma, DMG, Metastases
Spinal cord (intramedullary)	Ependymoma, PA, DMG, MPE, Drop metastases	Ependymoma, Astrocytoma, DMG, MPE (filum), NET/Paraganlgioma (filum),
Spinal cord (extramedullary)	Meningioma, Schwannoma, Metastases, Melanocytoma/melanoma	Schwannoma, Meningioma, Melanocytoma/melanoma, MPNST,
Spinal cord (extradural)	Bone tumor, Meningioma, Abscess, Vascular malformation,	Herniated disk, Lymphoma, Abscess, Metastases,
Extra-axial/Dural/ Leptomeningeal	Leukemia/lymphoma, Ewing Sarcoma, Rhabdomyosarcoma, Disseminated medulloblastoma, DLGNT,	Meningioma, SFT, Metastases, Lymphoma,
Sellar/infundibular	Pituitary adenoma, Craniopharyngioma, Rathke cleft cyst, Pituicytoma, LCH, Germ cell tumors	Pituitary adenoma, Craniopharyngioma, Rathke cleft cyst, Pituicytoma, Meningioma, Metastases, Chordoma
Suprasellar/ Hypothalamic/ Optic pathway/ Third ventricle	Germ cell tumors, Craniopharyngioma, PA/optic glioma, LCH	Colloid cyst, Craniopharyngioma, Chordoid glioma,
Pineal	Germ cell tumors, Pineocytoma, Pineoblastoma, Pineal cyst,	Pineocytoma, Pineal cyst, PPTID
Thalamus	PA, DMG,	DMG, GBM, Lymphoma,
Lateral ventricle	Central neurocytoma, SEGA, Choroid plexus papilloma/carcinoma, meningioma	Central neurocytoma, SEGA, Choroid plexus papilloma, Subependymoma, meningioma
Nerve root/ Paraspinal	Neurofibroma, Schwannoma, MPNST,	Neurofibroma, Schwannoma, MPNST, Lymphoma, Meningioma
Cerebellopontine angle	Schwannoma, Choroid plexus papilloma, AT/RT	Schwannoma, Meningioma, Epidermoid cyst, Choroid plexus papilloma, Endolymphatic sac tumor

Modified from: Practical Surgical Neuropathology: A Diagnostic Approach. Second Edition. 2018.

Common Abbreviations

PA→ Pilocytic Astrocytoma
PXA→ Pleomorphic Xanthoastroctyoma
DNET→ Dysembryoplastic Neuroepithelial Tumor
GBM→ Glioblastoma (Multiforme)
AT/RT→ Atypical Teratoid/Rhabdoid Tumor
DMG → Diffuse Midline Glioma (H3 K27M mutant)
SEGA → Subependymal Giant Cell Astrocytoma
MPE → Myxopapillary Ependymoma
DIPG → Diffuse Intrinsic Pontine Glioma
MPNST → Malignant Peripheral Nerve Sheath Tumor
SFT → Solitary Fibrous Tumor
LCH → Langerhans Cell Histiocytosis
PPTID → Pineal Parenchymal Tumor of Intermediate Differentiation
DLGNT→ Diffuse Leptomeningeal Glioneuronal Tumor

Classic Locations/Correlations

Imaging findings:
Metastases→ Multiple enhancing/rim-enhancing nodules at grey-white junctions in cerebrum
Lymphoma→ Periventricular enhancing lesion
Glioblastoma Multiforme→ Rim enhancing, "Butterfly" mass
Myxopapillary ependymoma→ Filium terminale mass
Meningioma→ Dural lesion with a "dural tail" (enhancing)
Pilocytic astrocytoma→ Circumscribed, cystic brain mass in the cerebellum of a child
Ganglioglioma→ Child with epilepsy and a temporal lobe cystic mass

Classic clinical associations:
Metastases→ Common sites of origin: lung, breast, and kidney
→ Strong prediction: melanoma and choriocarcinoma

A Note on CNS Tumor Grading

Grade is part of a **continuum** and **estimates malignancy/aggressiveness**.
Brain tumors are pathologically graded, but not staged (as often not resected en bloc).
Some tumors have inherent grades, while others have criteria for grading often depending on mitoses, necrosis/microvascular proliferation, and atypia. Some tumors also have molecular changes that impact grading (a recent addition).

Generally:
Grade 1 → Low proliferation potential and possibility of cure after surgical resection alone (typically well circumscribed).

Grade 2 → Usually infiltrative in nature and often recur, despite having low levels of proliferation. Some may progress to higher levels of malignancy. Often survive >5 years.

Grade 3 → Clear histologic evidence of malignancy, including nuclear atypia and sometimes brisk mitotic activity. Patients with these tumors often receive chemotherapy and/or radiation. Often survive 2-3 years.

Grade 4 → Cytologically malignant, mitotically active, necrosis-prone neoplasms that are often associated with rapid progression and fatal outcome. Includes GBM (survival < 1 year) and most embryonal neoplasms (survival depends on treatment and can be long).

Toward Molecular classification, and beyond!

Previously/originally, CNS tumors were categorized by strictly *morphology*.

However, there has been a revolution in CNS classification with the realization that many tumors have *unique molecular changes*, which are becoming increasingly *definitional*. Many of these definitional mutations (e.g., IDH in gliomas) have big implications for prognosis and therapy, while other mutations are for the time being mostly nosological (i.e., important for classification sake only, without current treatment implications).

The main types of changes/profiles that are currently utilized include: DNA mutations (detected by NGS), Gene fusions (fusion transcript detection), copy number variations, and methylation profile (genomic DNA methylation arrays).

For example, previously, all astrocytic tumors were diagnosed and graded primarily based on morphology: An astrocytic tumor with atypia, mitoses, and microvascular proliferation and/or necrosis would have been classified as "Glioblastoma."

However, now it is recognized that the presence of an IDH mutation greatly impacts behavior. Tumors with an IDH mutation are all designated astrocytomas. Only tumors with these morphologic findings and no IDH mutation are called glioblastomas.

How much testing really *needs* to be done (or *is* done)?

This really seems to depend on the institution.

At some institutions, pretty much *all* CNS tumors undergo comprehensive molecular profiling. This is particularly true of pediatric tumors in the United States.

Notably, in the United States, the NIH will perform free methylation profiling for tumors of the central nervous system (brain and spine) (link to form to submit tumor here).

In practicality though, such potentially expensive molecular testing is not always feasible.

Where able, immunohistochemical stains linked with specific molecular alterations are also helpful and can serve as surrogate makers in many cases. For example, the most common IDH mutation in Astrocytomas is IDH1 R132H, for which there is specific IHC stain. If positive, and in the context of other additional surrogate markers (like loss of ATRX IHC and strong nuclear p53 IHC staining), then further comprehensive molecular testing is likely of relatively low yield and can arguably be forgone.

Layered report structure and "Integrated diagnosis"

To present a large quantity of relevant information in an organized fashion, the WHO suggests a "layered report structure" that includes areas for a histological classification, CNS WHO grade, Molecular information and a summative, combined "Integrated diagnosis."

For example:

Integrated diagnosis: Oligodendroglioma, IDH-mutant and 1p/19q-codeleted
Histopathological classification: Oligodendroglioma
CNS WHO grade: 2
Molecular information: IDH mutation (IHC stain) and 1p/19q-codeleted (FISH)

What is the ideal testing to do (if you can do it)?

Many recommend a DNA/RNA Next-Generation Sequencing (NGS) panel plus genome-wide scan for copy number variations (CNVs) for the majority of gliomas and embryonal tumors.

DNA NGS can demonstrate mutations (e.g., IDH, BRAF, etc..), RNA NGS can detect fusions (e.g., NTRK), and the genome-wide scan can detect important CNVs like 1p/19q codeletion, thereby covering most of the abnormalities seen in brain tumors.

Soon, DNA methylation arrays and classifiers might replace genome-wide CNV platforms, as these arrays generate genomic CNV data plus epigenomic information on tumor subtype and tissue of origin.

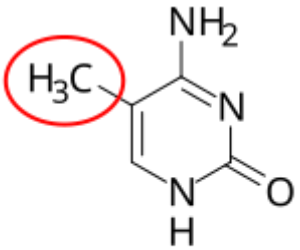
MGMT promoter methylation is still required for high-grade gliomas, but traditional MGMT-specific testing could be replaced with broader methylation profiling.

When tissue and tumor cellularity are sparse, single-target molecular testing like fluorescence in situ hybridization (FISH), Sanger sequencing, and pyrosequencing may be useful options.

While "expensive," comprehensive profiling is still currently cheaper than historical methods and the majority of treatments and radiology studies, so they therefore can "pay for themselves" in the long run.

DNA Methylation

Arguably the most impactful molecular tool in the recent years concerning the diagnostic classification of brain tumors. In fact, some WHO entities are *defined essentially by solely their methylation profile*!



Methylated Cytosine

Cancer cells show global hypomethylation and selective promoter-localized hypermethylation.

Genome-wide hypomethylation → chromosomal instability → Increased copy number of oncogenes and decreased copy of tumor suppressors → Carcinogenesis

Methylation of promoter DNA leads to decreased gene transcription and expression (attract proteins that cause chromatin condensation and block transcription).
Can block transcription of tumor suppressors→ cancer

Methylation of specific gene promoters has prognostic significance (e.g., promoter methylation of MGMT (DNA repair gene) in high-grade gliomas predicts response to alkylating agents).

Methylation profiling can be useful in classifying tumors and will likely be of increasing importance given its ability to identify new cancer classes and to consolidate histologically disparate cancers, particularly of the CNS and soft tissue.

The NIH has a large “Methylscape Analysis” project and will perform free analysis of any CNS or soft tissue tumors sent to them.

Gliomas

Tumors resemble **glial cells** that support neurons in the CNS, including **astrocytes** (form blood-bran barrier), **oligodendrocytes** (coat axons forming myelin sheath), and ependymal cells (that line ventricles).

General

Most common primary tumors of CNS parenchyma.

Diffuse gliomas ("infiltrative gliomas," including IDH-mutant astrocytomas) → widely invasive into brain parenchyma → often not resectable→ often naturally progress to higher grade lesions→ often resistant to therapy.

Circumscribed gliomas (like pilocytic astrocytoma, PXA, and SEGA) have a contained growth pattern and have different molecular pathways. Often easier to resect entirely.

Glioneuronal and neuronal tumors a diverse group with neurons as a component of the tumor.

Glial/Neuronal tumor diagnostic grouping	
Adult-type diffuse gliomas *(Most common group)*	Astrocytoma, IDH mutant Glioblastoma, IDH-wildtype Oligodendroglioma, IDH-mutant and 1p/19q deleted
Pediatric-type diffuse low-grade gliomas *(Generally favorable outcome)*	Angiocentric glioma Diffuse astrocytoma, MYB- or MYBL1-altered Polymorphous low-grade neuroepithelial tumor of the young Diffuse low-grade glioma, MAPK pathway-altered
Pediatric-type diffuse high-grade gliomas *(Generally aggressive)*	Diffuse midline glioma, H3K27-altered Diffuse midline glioma, H3-K27-altered, subgroup EGFR-altered Infant-type hemispheric glioma Diffuse hemispheric glioma, H3G34-altered Diffuse pediatric-type high-grade glioma, H3-wt and IDH-wt
Circumscribed astrocytic gliomas	Pilocytic astrocytoma Pleomorphic xanthoastrocytoma Subependymal giant cell astrocytoma Chordoid glioma Astroblastoma, MN1-altered High-grade astrocytoma with piloid features
Glioneuronal and neuronal tumors	Central neurocytoma Gangliglioma Desmoplastic infantile ganglioglioma/astrocytoma Rosette-forming glioneuronal tumor Dysembryoplastic neuroepithelial tumor Extraventicular neurocytoma Papillary glioneuronal tumor Rosette-forming glioneuronal tumor Myxoid glioneuronal tumor Multinodular and vacuolating glioneuronal tumor Cerebellar liponeurocytoma Diffuse leptomeningeal glioneuronal tumor Dysplastic cerebellar gangliocytoma DGONC
Ependymomas	Ependymoma *(further classified by site and molecular)*

Are these glial cells ***neoplastic***? *(or is it a mimic?!!)*

Gliosis = ***reactive*** **changes of glial cells in response to injury.** Includes both proliferation and hypertrophy.

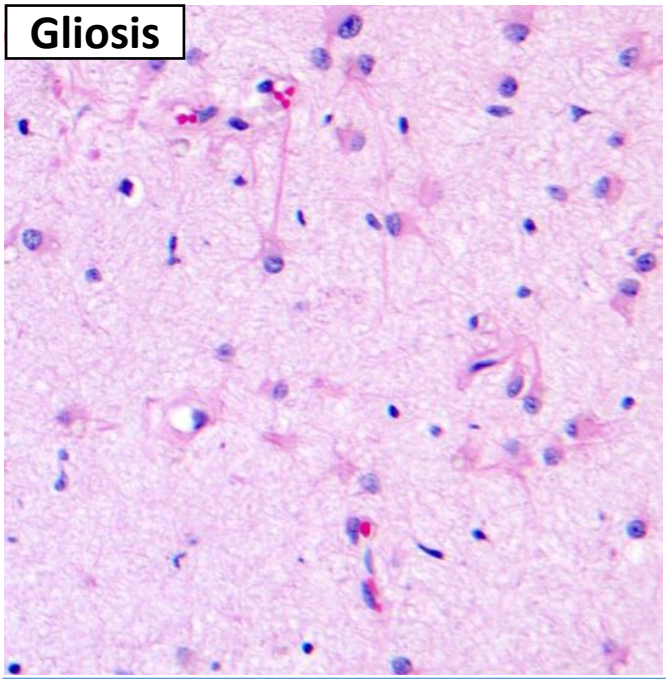
This can histologically mimic a tumor and pose a diagnostic dilemma, especially intraoperatively. This is particularly troublesome as gliosis can be found adjacent to tumors or as part of reactive process that can mimic tumors radiographically.

Early reactive astrocytosis→ hypertrophy with enlarged cytoplasm/processes and open chromatin with prominent nucleoli (abundant astrocyte cytoplasm is almost always pathologic!)

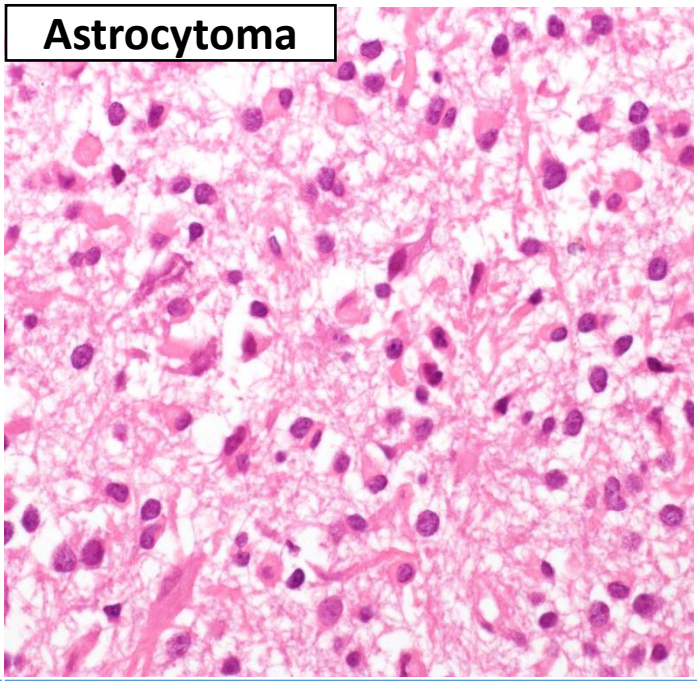
Longer term reactive astrocytosis → astrocytes become ***gemistocytic*** (large amounts of brightly eosinophilic eccentric cytoplasm) Warning: some tumors can appear gemistocytic too!!

Chronic reactive astrocytosis → often seen around slow-growing lesions → more fibrillar with long astrocytic processes and Rosenthal fibers → *"piloid gliosis" (as it resembles a pilocytic astrocytoma)*

Gliosis



Astrocytoma



Gliosis	Glioma
Euchromatic, round/ovoid nuclei Often single prominent nucleolus	Large, hyperchromatic, irregular (astrocytoma) to round nuclei (oligodendroglioma)
Evenly spaced astrocytes	Clustering of astrocytes, Hypercellular, Satellitosis
Abundant eosinophilic cytoplasm	"Naked" nuclei
Astrocytes with variable atypia	Uniform atypia (monomorphic)
No mitotic activity	Possible mitoses
Uncommon to see microcystic change	Microcystic changes more common
Radially oriented fibrillary processes	Necrosis and/or microvascular proliferation (usually in high grades)
Other reactive changes, such as inflammation, macrophages, etc…	Demonstratable mutation (e.g., IDH1, ATRX, etc…)

Common Diffuse Glioma Molecular Pathways

m = mutant
wt = wildtype

Preneoplastic Glial Cell

IDHm
TP53m
ATRXm

- **Astrocytoma**, IDHm, grade 2
  - **Astrocytoma**, IDHm, grade 3
    - 9p (CDKN2A/B) LOH
      - **Astrocytoma,** IDHm, grade 4

1p19q-codel
IDHm
TERTm

- **Oligodendroglioma**, grade 2
  - 9p (CDKN2A/B) LOH
    - **Anaplastic Oligodendroglioma**, grade 3

IDHwt
+7/-10
EGFR-amp
TERTm

- **Glioblastoma**, IDHwt, grade 4

H3 K27-altered

- **Diffuse midline glioma**, H3 K27M, grade 4

H3 G34-mutant

- **Diffuse hemispheric glioma**, H3 G34-m, grade 4

Modified from a talk by Dr. Arie Perry, University of California, San Francisco

Is this tumor ***Glial***?

As opposed to a metastases, and other non-glial tumors, glial tumors often have:

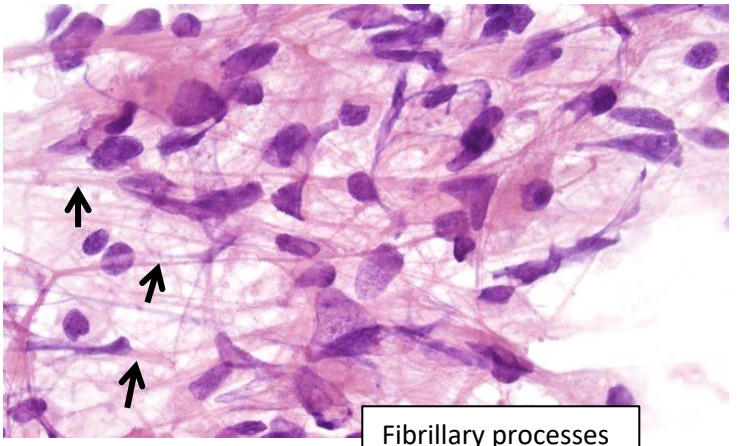
Fibrillary processes (→), often also naked nuclei. Best appreciated on cytology like squash prep.

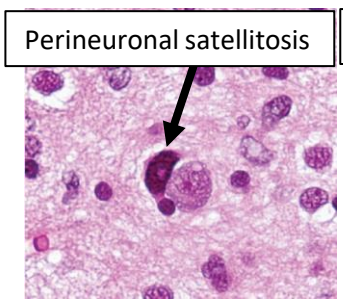
Infiltrative growth into brain parenchyma with intra tumoral axons (neurofilament +; primarily seen with astrocytoma and oligodendroglioma). (vs non-glial tumors, which are usually well-demarcated)

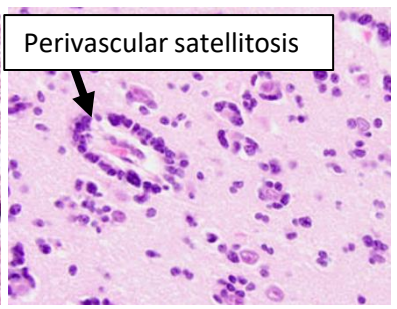
Secondary structures, such as **perineuronal satellitosis,** subpial density, perivascular collections.

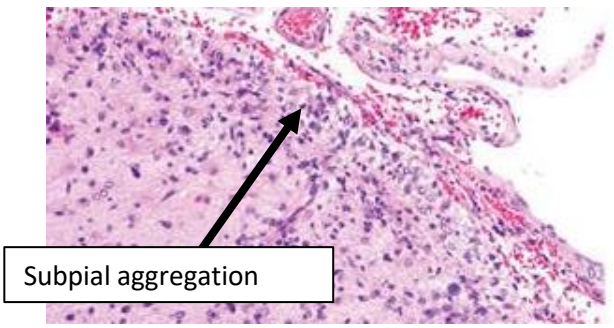
Eosinophilic cytoplasm with nuclear hyperchromasia/pleomorphism

IHC: GFAP and/or OLIG2 positive (Warning: broad spectrum cytokeratins may stain glial filaments as they are both intermediate filaments!).









Adult Diffuse Gliomas

Astrocytoma Organization/Grading

WHO Grade	Tumor	Histologic criteria	Prognosis
1	None		
2	Astrocytoma, IDHm, grade 2 *(previously Diffuse astrocytoma)*	One: Nuclear atypia *(but lacks anaplasia)*	>5 years
3	Astrocytoma, IDHm, grade 3 *(previously Anaplastic astrocytoma)*	Two: Atypia + Mitoses *Focal or dispersed anaplasia*	2-5 years
4	Astrocytoma, IDHm, grade 4 *(previously Glioblastoma)*	Three: Above + Vascular proliferation, Necrosis, and/or homozygous deletion of CDKN2A/B	1 year

Modified from a presentation by Dr. Hannes Vogel, Stanford University Medical Center.

Atypia → Variation in nuclear size and shape with hyperchromasia
Mitoses → Must be unequivocal. No strict cut-offs, but a single mitotic figure in a large specimen is insufficient to upgrade to Grade III.
Microvascular proliferation → Apparent multilayering of endothelium or glomeruloid microvasculature.
Necrosis → Can be any type (does *not* need to be pseudopalisading).

Order of appearance: Atypia→ Mitoses→ Increased cellularity→ Necrosis and/or microvascular proliferation.

Astrocytoma, IDH-mutant

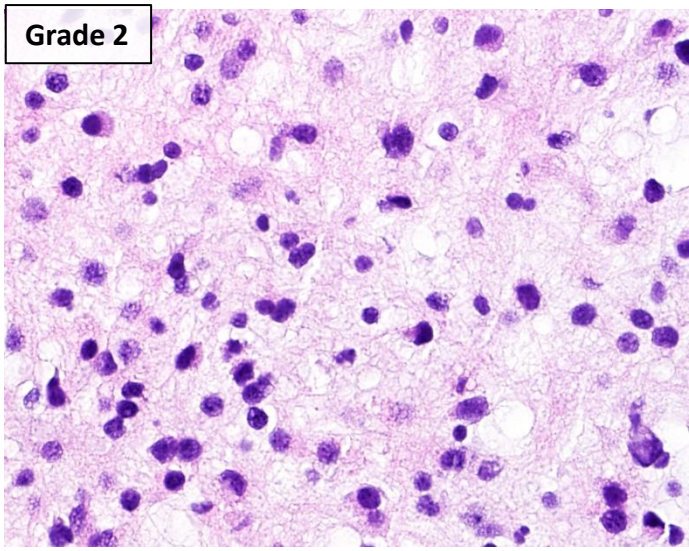
A diffusely infiltrating glioma with a mutation in either the IDH1 or IDH2 gene
Can be CNS WHO grades 2, 3, or 4 (see next page)
Grade depends on histology and predicts behavior.

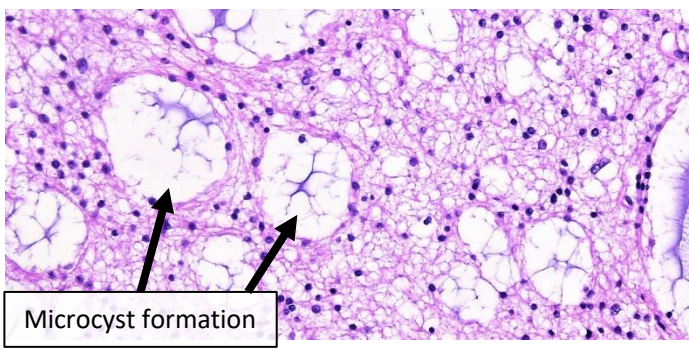
Intrinsic capacity for slow progression, with prolonged survival (>10 yrs sometimes!) for low-grade tumors.

Most common in **young adults** (30s), most commonly in **frontal lobes** (but can get anywhere in CNS).
Commonly present with seizures.

Molecular/IHC: IDH1 or IDH2 mutations
Most common mutation (~90%) is **IDH1 R132H**
→ can detect with mutation-specific IHC
If negative→ proceed to IDH1&2 sequencing to exclude other mutation
Also, class-defining loss of function in p53 and ATRX
ATRX mutation → loss of ATRX IHC staining
TP53 mutation→ strong nuclear p53 IHC staining.
Absent 1p/19q codeletion.
Tumor progression → Homozygous deletion of CDKN2A/B → shorter survival → grade 4

IHC: Express GFAP. Usually also OLIG2





Virtual slide 1 2

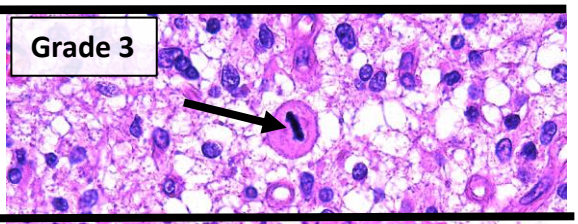
Gemistocytic Astrocytoma: A variant of IDH-mutated astrocytoma with prominent gemistocytic neoplastic astrocytes (>20%). No definite clinical association.

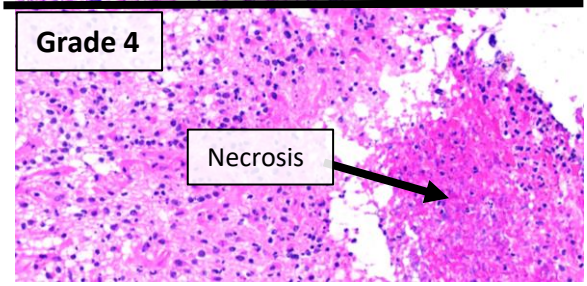
Astrocytoma, IDH-mutant (continued)

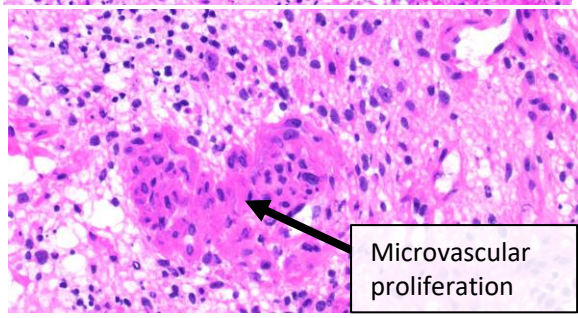
Grade 2: *(formerly "Diffuse astrocytoma")*
Well-differentiated fibrillary astrocytes.
Cellularity is moderately increased.
Moderate nuclear atypia.
Often loose microcystic background.
Mitotic activity is generally absent (A single mitotic figure in a large specimen is forgiveable, but not in a Bx)
Ki67 usually <4%.

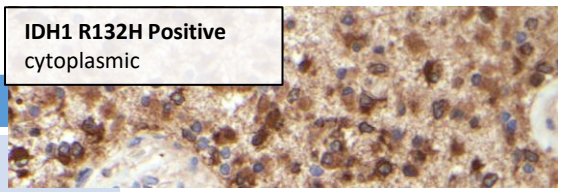
Grade 3: *(formerly "Anaplastic astrocytoma")*
Above, plus:
Focal or diffuse **anaplasia** (increased cell density and atypia)
Increased mitotic activity → must evaluate in context of sample size. A single mitotic figure on a biopsy is enough. In resections, need to see "significant" mitotic activity (often ≥2).
By definition: NO necrosis and NO microvascular proliferation.
Ki67 usually 5-10% Virtual slide

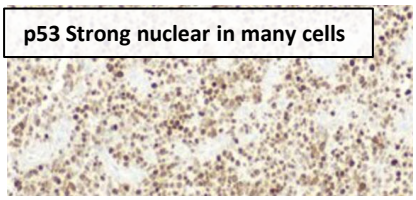
Grade 4: *(formerly "Glioblastoma")*
Above, plus: Necrosis and/or microvascular proliferation.
OR CDKN2A/B homozygous deletions

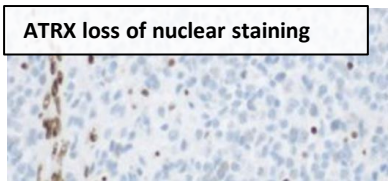












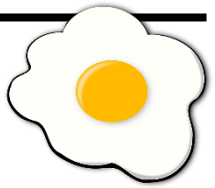
WHO Diagnostic Criteria: Astrocytoma, IDH-mutant

Essential:
A diffusely infiltrating glioma
AND
IDH1 codon 132 or IDH2 codon 172 missense mutation
AND
Los of nuclear ATRX expression or ATRX mutation
OR
Exclusion of 1p/19q codeletion

Desirable:
TP53 mutation or strong nuclear expression of p53 in >10% of tumor cells
Methylation profile of astrocytoma, IDH-mutant
Astrocytic differentiation by morphology

Grade	Criteria
CNS WHO grade 2	1) A diffusely infiltrative astrocytic glioma with an *IDH1* or *IDH2* mutation that is well differentiated and lacks histological features of anaplasia 2) Mitotic activity is not detected or very low 3) Microvascular proliferation, necrosis, and homozygous deletions of *CDKN2A* and/or *CDKN2B* are absent
CNS WHO grade 3	1) A diffusely infiltrative astrocytic glioma with an *IDH1* or *IDH2* mutation that exhibits focal or dispersed anaplasia and displays significant mitotic activity 2) Microvascular proliferation, necrosis, and homozygous deletions of *CDKN2A* and/or *CDKN2B* are absent
CNS WHO grade 4	A diffusely infiltrative astrocytic glioma with an *IDH1* or *IDH2* mutation that exhibits microvascular proliferation or necrosis or homozygous deletion of *CDKN2A* and/or *CDKN2B*, or any combination of these features

Oligodendroglioma, IDH-mutant and 1p/19q-codeleted



Diffusely infiltrating gliomas morphologically resembling ***oligodendrocytes***.

******Defining genetics:* IDH1 or IDH2 mutations AND 1p/19q-codeletions.*****

→ An unbalanced translocation between chromosomes 1 and 19 results in loss of the der(1;19) chromosome, causing codeletion of whole arms of 1p and 19q

→ it's acceptable if some cells show astrocytic differentiation if these genetic changes are present.

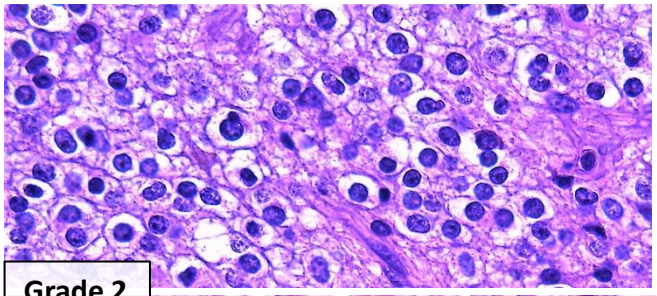
→ IDH1 R132H mutations (present in >90%) can be detected by IHC.
1p/19q-codeletions are usually identified by FISH.

→ Frequent TERT promoter mutations. Unlike in astrocytomas, there is no ATRX loss or p53 mutations

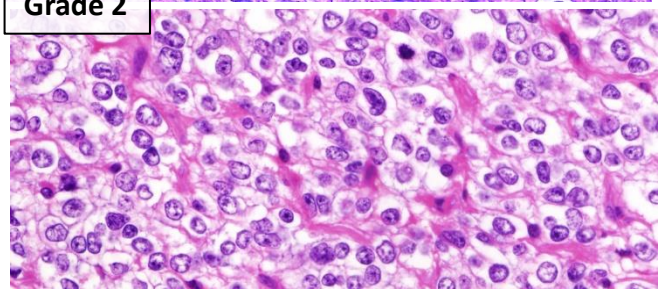
Usually adult patients (mean 40s) in the cerebral hemispheres (esp. frontal lobe). Rare in children. Often present with seizures.

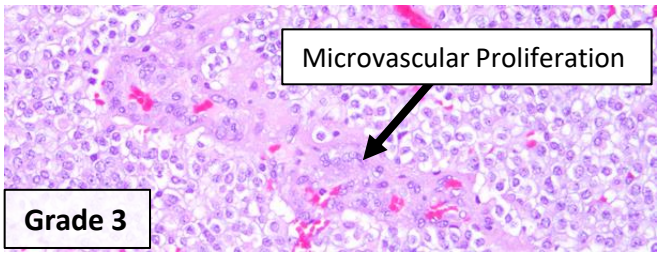
IHC: (+)MAP2, S100, SOX10, OLIG2, ; Usually (+) IDH1 R132H, Intact ATRX, wild-type p53.

General morphology:
Moderately cellular, diffusely infiltrating.
Monomorphic round nuclei with artifactual perinuclear halos→ "***fried egg***" or "honeycomb" appearance (only seen on formalin-fixed sections)
"Salt and pepper" chromatin
Well-defined cell borders. Clear cytoplasm.
Microcalcifications and cystic degeneration common.
Delicate branching capillary network (resemble "chicken wire")



Grade 2





Grade 3

Grade 2:
Low mitotic activity (rare mitoses acceptable)
Ki67 proliferation index usually < 5%
Prolonged survival→ Often >10 years!
Generally recur. Progression common (but much slower than astrocytomas).

Grade 3: *(formerly Anaplastic oligodendroglioma)*
Distinction is not well defined. Tumors often show:
- **High cellularity and marked atypia** (anaplasia)
- **Brisk mitotic activity** (often >6 per 10HPF)
- **Microvascular proliferation**
- **Necrosis**
- **CDKN2A homozygous deletion**

(Although some of these findings are also seen in GBM's, as long as the defining genetic alterations are present, you can still make this Dx).

Ki67 often >10%

Shorter survival, but still prolonged.

Virtual slide 1 2 3

WHO Diagnostic Criteria: Oligodendroglioma, IDH-mutatnt and 1p/19q-codeleted

Essential:
A diffusely infiltrating glioma
AND
IDH1 codon 132 or IDH2 codon 172 missense mutation
AND
Combined whole-arm deletions of 1p and 19q

Desirable:
Methylation profile of Oligodendroglioma
Retained nuclear expression of ATRX
TERT promoter mutation

Glioblastoma, IDH-wildtype

CNS WHO grade 4

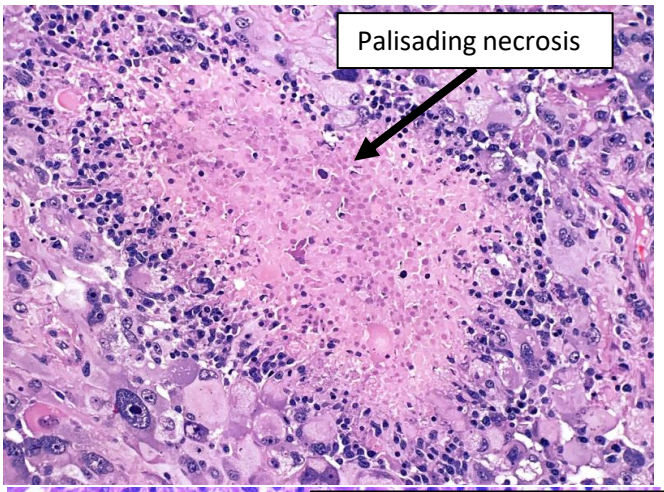
Old name: Glioblastoma Multiforme ("GBM")

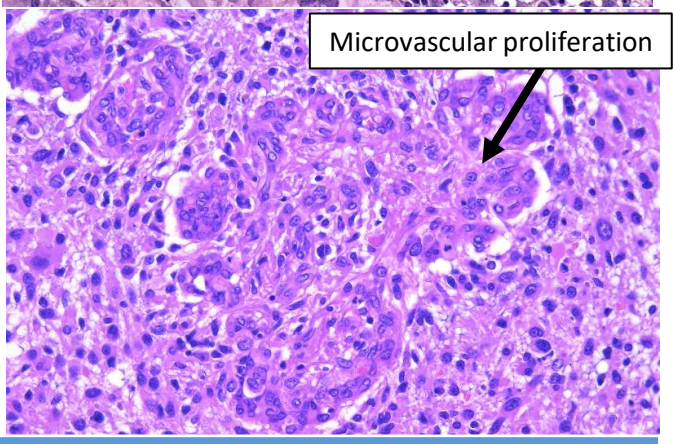
A **high-grade diffuse glioma** with astrocytic differentiation that is IDH-wildtype and H3-wildtype and has one or more of the following: 1) Microvascular proliferation, 2)Necrosis, 3) TERT promoter mutation, 4) EGFR gene amplification, or 5) +7/-10 chromosome copy number changes.

Most common malignant *primary* brain tumor in adults. Usually older (>60rs).
Often **diffusely infiltrates** adjacent and distant brain structures.
Usually in **cerebral hemispheres**. Present with seizure or neurological deficits, depending on location.
Very aggressive! **Rapid progression and death,** often within 1 year.

On imaging→ **irregularly shaped with ring-shaped enhancement** around central dark necrosis.
→ Can grow along corpus callosum into other hemisphere→ "butterfly glioma."

Variable histology (hence "*multiforme*"):
Highly cellular with poorly differentiated, sometimes very pleomorphic tumor cells.
Brisk mitotic activity.
Necrosis, classically, with palisading
Microvascular proliferation → glomeruloid tufts of multilayered mitotically active endothelium with smooth muscle and pericytes. Often near necrosis.
Often **regional heterogeneity**.





Tumor cells will often migrate/invade around existing structures, e.g., around neurons (satellitosis), in subpial zone, etc..

IHC: Typically (+) GFAP, S100, OLIG2
Ki67 typically ~15-20%, but can be much more

Can extensively grow into multiple lobes/hemispheres → "gliomatosis cerebri"
Metastases are very uncommon.

There is tremendous morphologic variability and heterogeneity, including many recognized patterns (see later), which are reserved for tumors that show a "predominance" of one appearance.
Virtual slide 1 2 3

Common changes/metaplasias include:
Gemistocytic change (copious, glassy, cytoplasm that displaces the nucleus of the cell to the side)
Mesenchymal metaplasia (spindled cells)
Epithelial metaplasia (squamous or adenomatous differentiation)
Oligodendrocyte-like cells (Clear cells with round nuclei)
Lipidized cells (foamy cytoplasm)
Granular cells (abundant pink granular cytoplasm)

WHO Diagnostic Criteria: Glioblastoma, IDH-wildtype

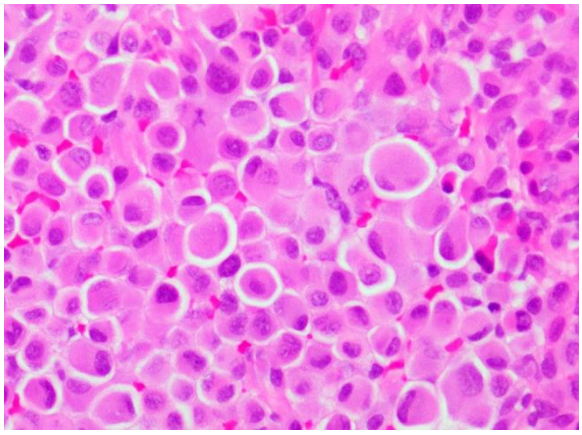
Essential:
An IDH-wildtype, H3-wildtype, diffuse astrocytic glioma
AND
One or more of the following
- Microvascular proliferation
- Necrosis
- TERT promoter mutation
- EGFR gene amplification
- +7/-10 chromosome copy-number alterations

Desirable:
Methylation profile of Glioblastoma, IDH-wildtype

Glioblastoma Patterns

True to the outdated term "Glioblastoma *Multiforme*," there is tremendous histologic variability. Some Glioblastomas have well-recognized patterns that are characterized by the predominance of a particular cell type. Below are some relatively common patterns.

Epithelioid Glioblastoma

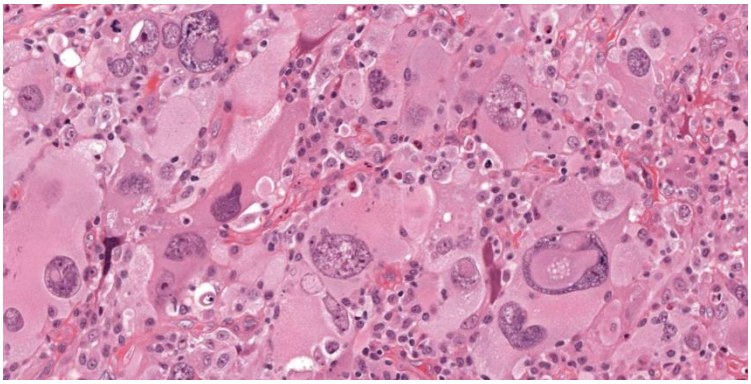


Dominant population of sharply demarcated, loosely cohesive, **large epithelioid to rhabdoid cells with abundant cytoplasm, large vesicular nuclei, and prominent micronucleoli**. *(Mimics metastatic carcinoma/melanoma!)*

Predominantly in **young adults and children** (emerging molecular subclassification though, stay tuned)

IHC/Molecular: (+)GFAP, S100, OLIG2
Frequent expression of CK AE1/AE3 or EMA
Frequent **BRAF V600E mutations**

Giant Cell Glioblastoma

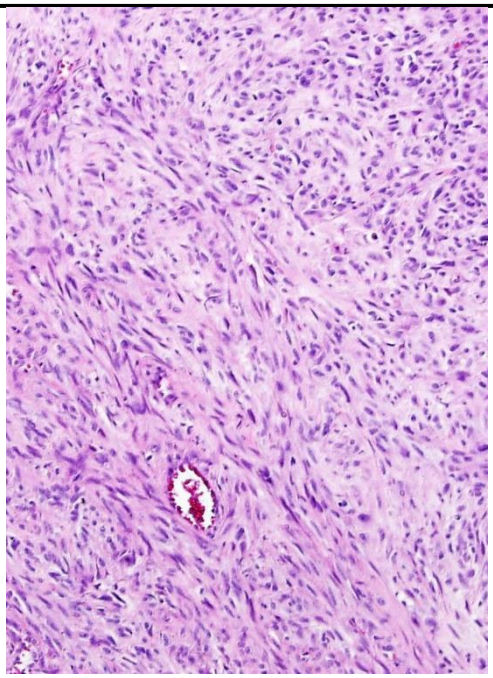


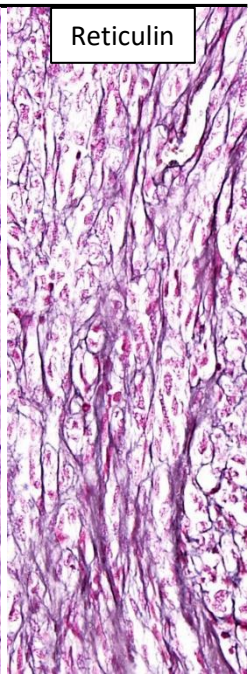
Dominant population of bizarre, multinucleated giant cells.
Occasionally abundant reticulin network.

Often more **circumscribed** (mimic metasases)→ Slightly **better prognosis.**

High rate of genomic instability, often with superimposed **TP53 mutations** and/or MMR defects.
Consider PXA in differential diagnosis

Gliosarcoma





biphasic growth displaying glial and prominent mesenchymal differentiation
→ analogous to epithelial-to-mesenchymal transition in carcinomas

Sarcomatous component often has a **spindle cell pattern** with densely packed long bundles of spindle cells with **abundant reticulin** framework. Also mitoses, necrosis, and atypia.

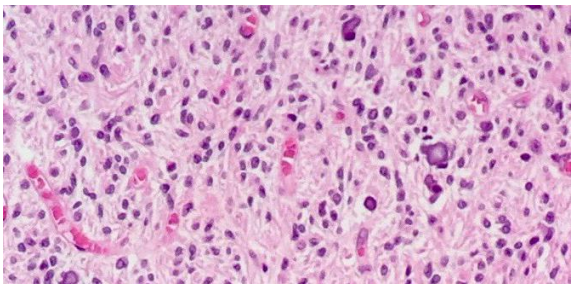
IHC: Sarcoma component often *lacks* GFAP

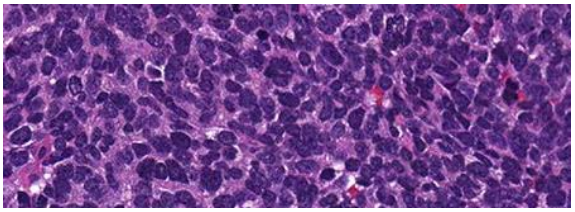
Can have heterologous differentiation (e.g, cartilage, rhabdomyoblasts, etc…).

Similar prognosis and clinical characteristics to glioblastoma Virtual slide 2

Glioblastoma Patterns (continued)

Small cell Glioblastoma



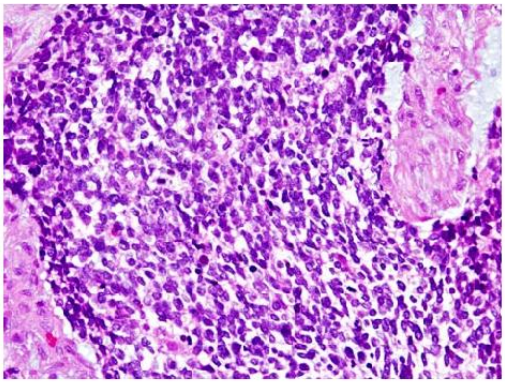


Predominance of **highly monomorphic, small, round to slightly elongated, hyperchromatic nuclei, and minimal discernible cytoplasm,** little nuclear atypia, and (often) brisk mitotic activity. Chicken-wire vasculature and calcifications can make it resemble Oligodendroglioma.

IHC: GFAP highlights process (supports glial differentiation)
Frequent **EGFR amplification** and chromosome 10 loss.
High Ki67.

Similar behavior

Glioblastoma with a primitive neuronal component



Solid nodules of immature cells with variable neuronal differentiation. High cellularity. Lots of mitoses and apoptoses. (Resemble medulloblastoma, can see rosettes)
High rate of MYC or MYCN gene amplification

IHC: (+) Synaptophysin; Markedly elevated Ki67; (-/+) GFAP

High rate of **CSF dissemination**.

Although they were ***both*** previously called "*Glioblastoma*" due to their sometimes identical morphology, Grade 4 IDH-mutant astrocytomas are now separated out due to their distinct molecular and clinical characteristics (see below). This is a big change from prior classification and is emblematic of the shift of classification toward meaningful molecular underpinnings.

	Glioblastoma, IDH-wildtype	**Astrocytoma, IDH-mutant, grade 4** *(old name: IDH-mutant Glioblastoma)*
Old alternative name	Primary glioblastoma	Secondary glioblastoma
Precursor lesion	None	Astrocytoma, IDH-mutant, grade 2/3
Relative incidence ratio	~90%	~10%
Mean age at Dx	~60 years (Older)	~45 years (younger)
Mean length of clinical Hx	4 months (short)	15 months (long)
Survival with treatment	< 1 year (short)	2 years (long)
Location	Supratentorial	Frontal lobe specifically
Necrosis	Extensive	Limited
TERT promoter mutations	70%	25%
ATRX mutations	Rare	70%
EGFR amplifications	35%	Rare
PTEN mutations	25%	Rare

Modified from: WHO Classification of Tumors of the Central Nervous System. 4th Edition. 2016.

Glioblastoma molecular testing:

For use in Diagnosis

Glioblastomas lack IDH mutations. Absence of immunoreactivity for IDH1 R123H is sufficient (no further sequencing is necessary) to diagnose IDH-wildtype glioblastoma in a patient who meets the following criteria:
1) aged > 55 years,
2) who has a histologically classic glioblastoma,
3) not located in a midline structures, and
4) no history of a pre-existing lower-grade glioma.
(As there is a <1% chance of a different IDH mutation in this context)

Otherwise, especially if there is loss of ATRX by IHC (which is lost in IDH-mutant tumors), negative IDH1 R132H staining should be followed by DNA sequencing for less common IDH mutations→ only when this is negative can tumors be classified as "IDH-wildtype."

Tumors in midline structures should additionally be evaluated for H3 mutations, including H3 K27M and H3 G34 by IHC and/or sequencing.

What if there isn't necrosis or microvascular proliferation?
Frequent additional alterations include TERT promoter mutations, EGFR amplification, and +7/-10 genotype. The presence of at least one of these aberration in an IDH- and H3-wildtype diffuse glioma allows for the diagnosis of IDH-wild type glioblastoma.

For use in Management

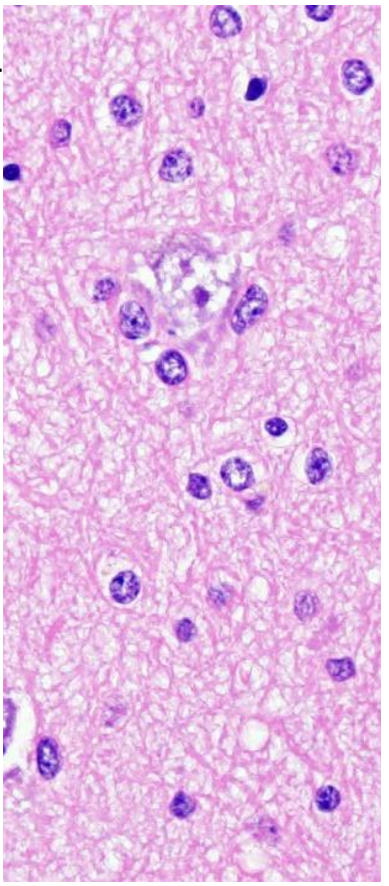
MGMT promoter methylation status is commonly determined because it provides clinically relevant information on response to chemotherapy and survival of patients treated with temoszolomide. (Promoter methylation → longer survival and treatment response).

Otherwise, molecularly targeted therapies have not yielded major success.
Possible exceptions include BRAF V600E mutations and NTRK mutations.

Pediatric-type diffuse low-grade gliomas

Diffuse Astrocytoma, MYB- or MYBL1-altered

CNS WHO grade 1



Diffusely infiltrative astroglial neoplasm composed of monomorphic cells with genetic alterations in MYB or MYBL1 (fused with a variable partner gene).

Consider when you have an IDH and H3 alteration negative astrocytoma!

Rare. Usually in cerebral hemispheres.
Present with drug resistant **seizures**, often since childhood (Long-term epilepsy-associated tumor).
Often diagnosed in early adulthood (20s).

Monomorphic glial cells with bland, round to spindled nuclei. Fibrillary matrix.
Tumor cells can be so scarce as to almost resemble normal brain!

Limited outcome data, but appears to follow a benign course.

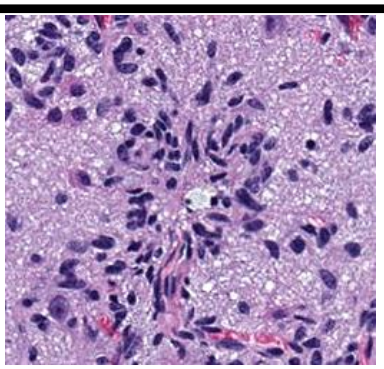
***WHO Diagnostic Criteria*: Diffuse Astrocytoma, MYB- or MYBL1-altered**

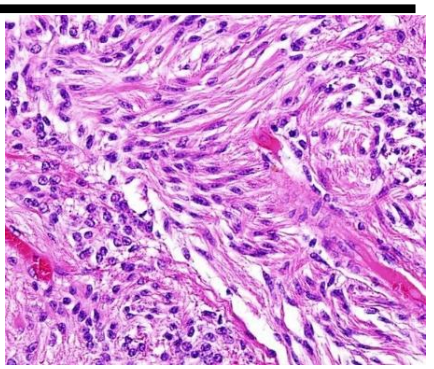
Essential:
Diffuse astrocytoma without histological features of anaplasia
AND
No mutations in IDH or H3 genes
AND
Structural variant of MYB or MYBL1
OR
Corresponding DNA methylation

Desirable:
Absence of OLIG2 or MAP2 expression

Angiocentric Glioma

WHO grade 1





Stable or **slow-growing**. **Well-circumscribed.**

Primarily impacts **children** and young adults.
Presents with **epilepsy**.
Cerebral location, usually.

Diffuse glioma. **Angiocentric growth pattern.**
Monomorphous, thin, bland bipolar cells, oriented around cortical blood vessels.
Can resemble pseudorosettes of ependymomas. Other areas can resemble schwannoma with fibrillary areas.

IHC: (+) GFAP, dot-like EMA (like ependymoma)
Molecular: **MYB fusions** (usually **MYB-QKI**)

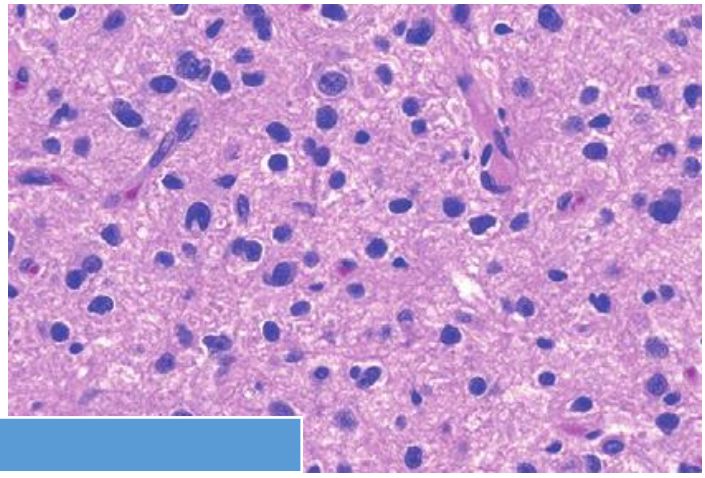
Excellent prognosis → usually cured by excision

***WHO Diagnostic Criteria*: Angiocentric glioma**

Essential:
Glioma with diffuse growth architecture and a focal angiocentric pattern
AND
Monomorphic spindled cells with immunophenotypic and/or ultrastructural evidence of astrocytic and ependymal differentiation

Desirable:
Lack of anaplastic features
Alteration of MYB
Corresponding DNA methylation profile

Polymorphous Low-grade Neuroepithelial tumor of the Young *(PLNTY)*



CNS WHO Grade 1

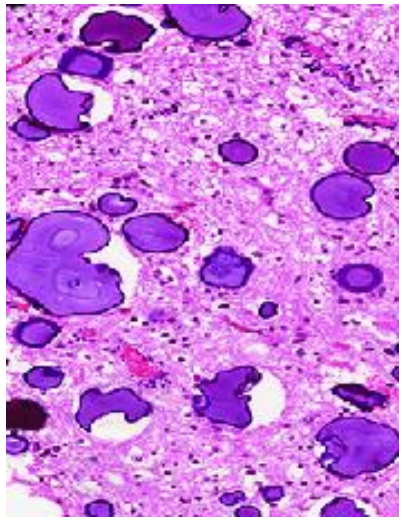
Rare. Mainly children and adolescents.
Indolent **cerebral** neoplasm.
Present with **seizures** in young individuals.

Diffuse growth with oligodendroglioma-like areas.
Frequent **calcifications**.
IHC: **(+) CD34**, GFAP, OLIG2
Molecular: MAPK pathway-activating mutations, usually **BRAF V600E mutations**

WHO Diagnostic Criteria: PLNTY

Essential:
Diffuse growth pattern (at least regionally)
AND
Oligodendroglioma-like component (can be focal)
AND
Few (if any) mitoses
AND
Regional expression of CD34 by tumor cells and by ramified neural cells in associated cerebral cortex
AND
IDH-wild type status
AND
Unequivocal expression of BRAF p.V600E by IHC
OR
Molecular evidence of a BRAF V600E mutation, FGFR2 or FGFR3 fusions, or potentially other MAPK-pathway-driving genetic abnormalities

Desirable:
Conspicuous calcification (characteristic, but not constant)
Absence of 1p/19q codeletion



Similar morphology, molecular, and setting.
Consider in kids with IDH and H3 wild type diffuse gliomas

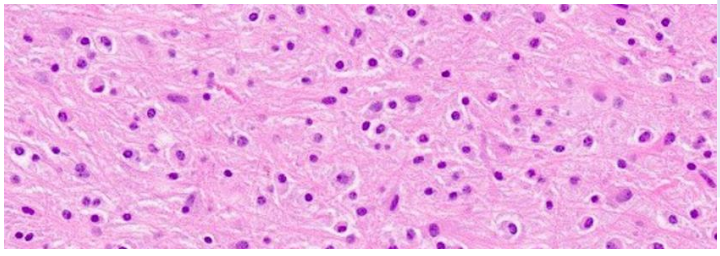
Diffuse low-grade glioma, MAPK pathway-altered

Rare. No current CNS WHO grade (pending).

Low-grade glioma with diffuse astrocytic or oligodendroglial morphology. Bland appearance.

Generally, presents in childhood.
Variable location and symptoms.

Pathogenic alterations in MAPK pathway: usually FGFR1 or BRAF V600E



WHO Diagnostic Criteria: Diffuse low-grade glioma, MAPK pathway-altered

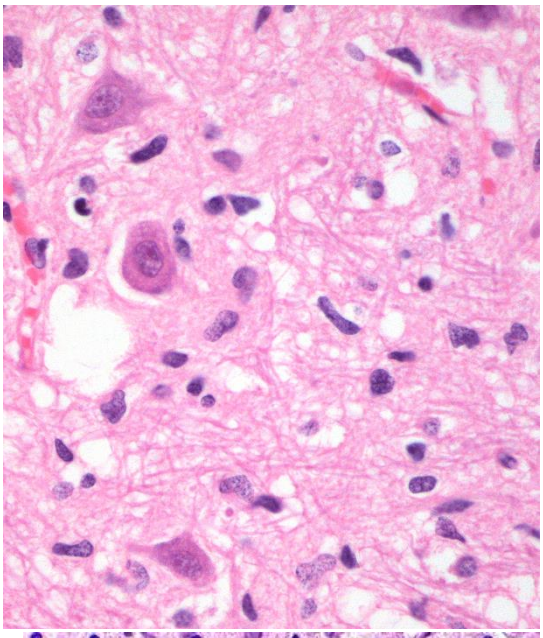
Essential:
Diffuse glioma with absent or minimal mitotic activity and neither microvascular proliferation nor necrosis
AND
Genetic alteration in the MAPK pathway
AND
IDH and H3 wildtype
AND
Absence of homozygous deletion of CDKN2A

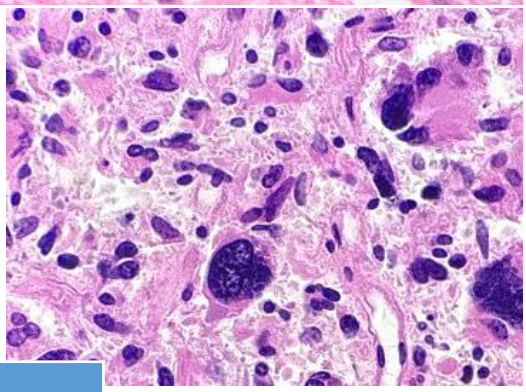
Desirable:
Onset in childhood, adolescence, or early adulthood
Corresponding DNA methylation profile

Pediatric-type diffuse high-grade gliomas

Diffuse Midline Glioma, H3 K27-altered — CNS WHO grade 4

Older name: ***Diffuse Intrinsic Pontine Glioma (DIPG)***





An **infiltrative high-grade midline glioma** with predominantly astrocytic differentiation
Predominates in children, but can see in adults.
Common locations: **Brainstem/Pons**, Thalamus, spinal cord.
→ Cranial nerve palsy, ataxia, long tract signs
Poor prognosis (<2 years)

Defined by loss of H3 p.K28me3 (K27me3), usually with one of the following: 1) H3 pK28M substitution in one of the histone H3 isoforms, 2) aberrant overexpression of EZHIP, or 3) EGFR mutation.

Tumor cells usually small and monomorphic,
sometimes can be pleomorphic
Diffusely infiltrates adjacent and distant brain structures.
Mitotic activity is often present.
Necrosis and microvascular proliferation may be present, but are not necessary for Dx.

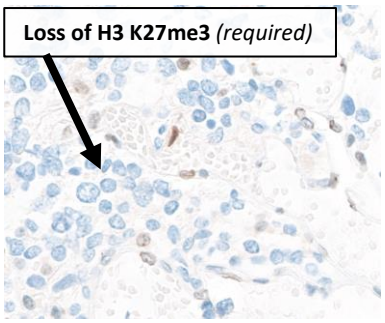
IHC: (+) S100, OLIG2, MAP2; (+/-) GFAP,
Loss of expression of H3 pK28me3 (K27me3)
(+) Mutation-specific antibody for H3 K27M in most cases

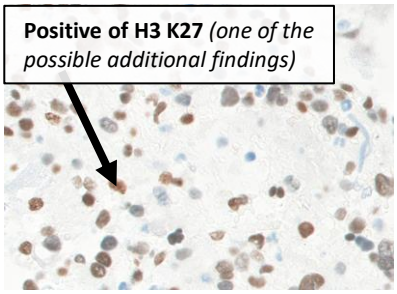
Virtual slide 2

WHO Diagnostic Criteria: Diffuse midline glioma, G3 K27-altered

Essential:
A diffuse glioma
AND
Loss of H3 p.K28me3 (K27me3) (Immunohistochemistry)
AND
Midline location
AND
Presence of an H3 p.K28M (K27M) or pK28I mutation (IHC or molecular)
OR
Presence of a pathogenic mutation or amplification of EGFR
OR
Overexpression of EZHIP
OR
Corresponding methylation profile

Desirable:
Results from molecular analysis that enable discrimination of the H3.1 or H3.2 p.K28 (K27)-mutant subtype from the H3.3 p.K28 (K27)-mutant subtype.





Diffuse hemispheric glioma, H3 G34-altered

CNS WHO grade 4

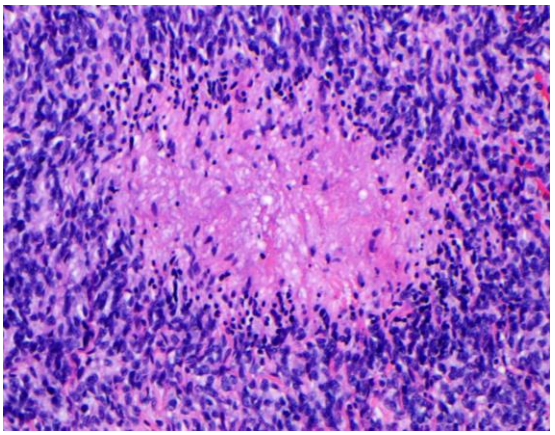
A **diffuse infiltrative glioma** of the **cerebral hemispheres** with a **missense mutation of the H3-3A gene** resulting in a H3 G34R or G34V substitution.

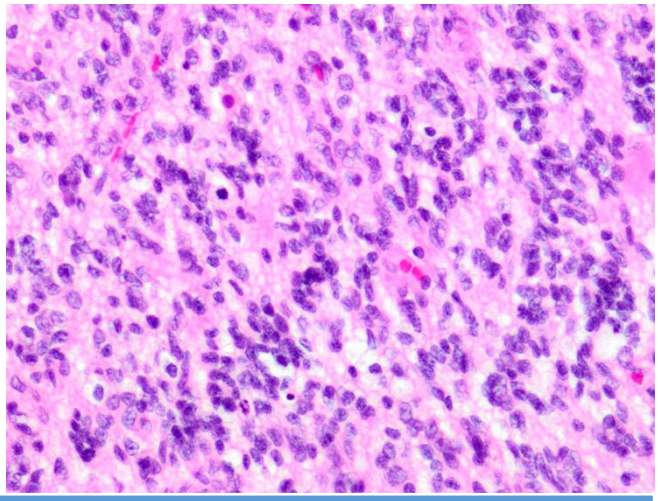
Usually presents in adolescents (teens).

Diffusely infiltrating atypical astrocytes in a GBM-like pattern with high cellularity, brisk mitotic rate, microvascular proliferation, and/or necrosis. Sometimes may resemble Embryonal tumor (high N:C ratio).

Molecular/IHC: **(+) H3.3 G34-mutant specific IHC,** MAP2. p53 overexpression. Loss of ATRX.
(-) IDH, OLIG2.

Poor prognosis.





***WHO Diagnostic Criteria*: Diffuse hemispheric glioma, H3 G34-altered**

Essential:
Cellular, infiltrative glioma with mitotic activity
AND
H3.3 p.G35R (G34R) or p.G35V (G34V) mutation
AND
Hemispheric location
AND (for unresolved lesions)
Corresponding methylation profile

Desirable:
OLIG2 immunonegativity
Loss of ATRX expression
Diffuse p53 expression

Diffuse pediatric-type high-grade glioma (pHGG), H3-wildtype and IDH-wildtype

CNS WHO grade 4

A diffuse glioma with histologic features of malignancy. **Aggressive**.

Diverse location.
GBM-like or primitive, undifferentiated morphology.

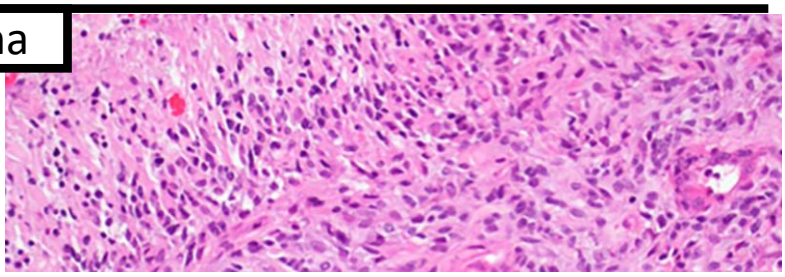
Three molecular subgroups based on methylation and other alterations:
1) RTK1, enriched for PDGFRA alterations
2) RTK 2, enriched for EGFR & TERT alterations
3) MYCN amplification

***WHO Diagnostic Criteria*: Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype**

Essential:
A diffuse glioma with mitotic activity occurring in a child or young adult
AND
Absence of mutations in IDH1 or IDH2
AND
Absence of mutations in H3 genes
AND
Corresponding methylation profile
OR
Key molecular features: PDGFRA alteration, EGFR alteration, or MYCN amplification

Desirable:
Microvascular proliferation
Necrosis, typically palisading
H3 K27me3 retained

Infant-type hemispheric glioma



Rare. Not currently graded (pending data)

Cellular hemispheric, high-grade cellular astrocytoma that arises in early childhood.

Typically have Receptor Tyrosine Kinase (RTK) fusions
→ *can potentially therapeutically target!*

Typically, cellular and well-demarcated from the adjacent brain and involve the leptomeninges.
Astrocytic, often spindled, cells with mild to moderate pleomorphism.
Frequent palisading necrosis, mitoses, and microvascular proliferation.

***WHO Diagnostic Criteria*:**
Infant-type hemispheric glioma

Essential:
Cellular astrocytoma
AND
Presentation in early childhood
AND
Cerebral hemispheric location
AND
Presence of typical receptor tyrosine kinase abnormality (e.g., fusion in NTRK family, ROS1, MET1, or ALK)
OR
Corresponding methylation profile

Circumscribed astrocytic gliomas

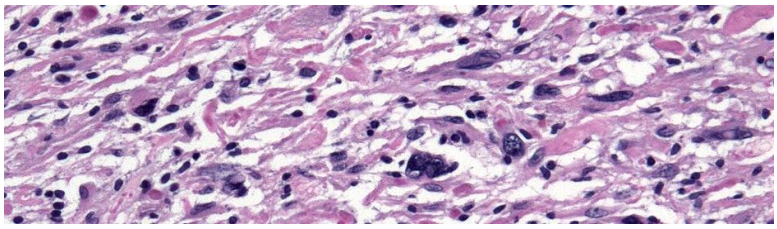
High-grade astrocytoma with Piloid features (HGAP)

New entity, not currently graded.

High-grade piloid and/or glioblastoma-like morphology.
<u>Distinct DNA methylation profile</u> (required!)

Alterations of MAPK pathway genes, often combined with homozygous deletion involving CDKN2A/B and/or ATRX mutation/loss.

Usually **adults** in the **cerebellum**.



***WHO Diagnostic Criteria*:**
High-grade astrocytoma with Piloid features

Essential:
An astrocytic glioma
AND
A compatible DNA methylation profile

Desirable:
MAPK pathway gene alteration
Homozygous deletion or mutation of CDKN2A/B or amplification of CDK4
Mutation of ATRX or loss of nuclear ATRX
Anaplastic histological features

Pilocytic astrocytoma ("*PA*")

CNS WHO grade 1

An **astrocytoma** with a biphasic pattern with varying proportions of 1) **compact bipolar "hair-like" cells with Rosenthal fibers** and 2) **loose, microcystic regions with oligodendroglioma-like cells and eosinophilic granular bodies** (EGBs).

Nuclei are relatively bland.

Still allowed: Rare mitoses, Hyperchromatic pleomorphic nuclei, microvascular proliferation, necrosis, and infiltration of meninges

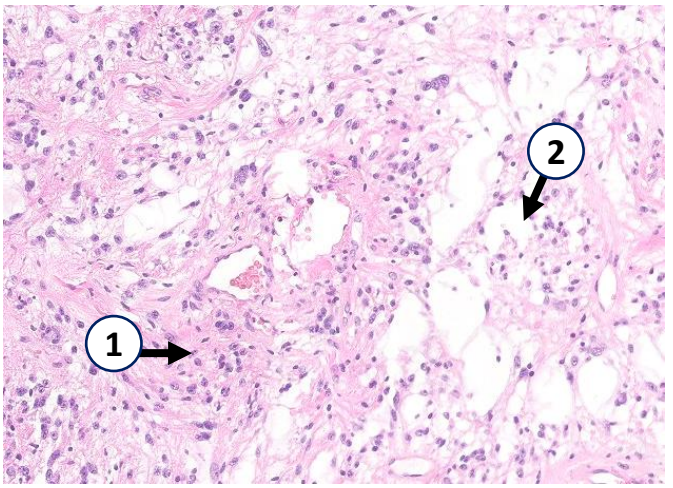
Most common glioma in <u>children</u> and adolescents. Preferentially infratentorial, located in the **<u>cerebellum</u>** and cerebral **midline structures** (e.g., optic pathways, brainstem, etc..).
Can present with ventricular obstruction→ macrocephaly, endocrinopathy, headache, etc..

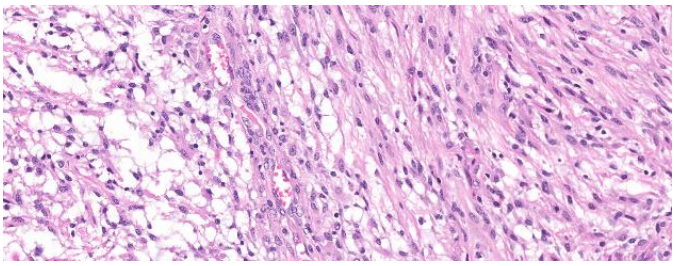
Generally **<u>circumscribed</u>** and **slow growing.** Sometimes **cystic**.

Mutations in MAPK pathway, most commonly KIAA1549::**<u>BRAF</u>** fusion protein (detect with BRAF FISH)
IHC: (+)GFAP, S100, OLIG2

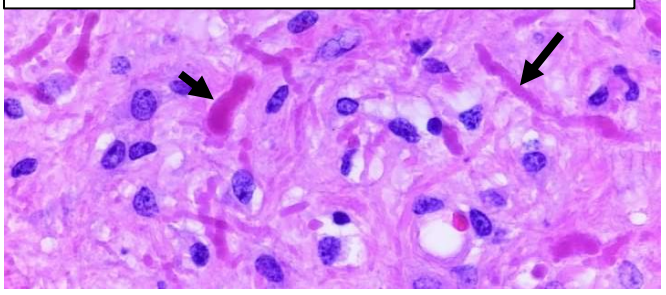
Slow-growing, low-grade with **favorable prognosis.** Can be **<u>cured</u>** <u>with surgical excision</u> (if possible).

Optic nerve tumors are a hallmark of NF1.
Virtual slide 1 2 3

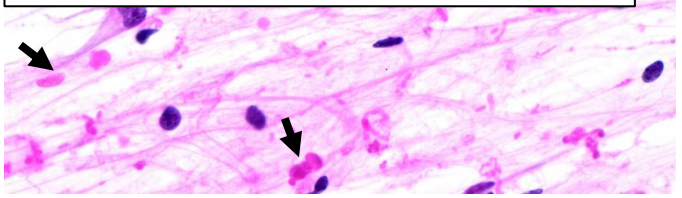




Rosenthal Fibers: Corkscrew-like pink inclusions



EGBs (round/globular pink inclusions) on a smear



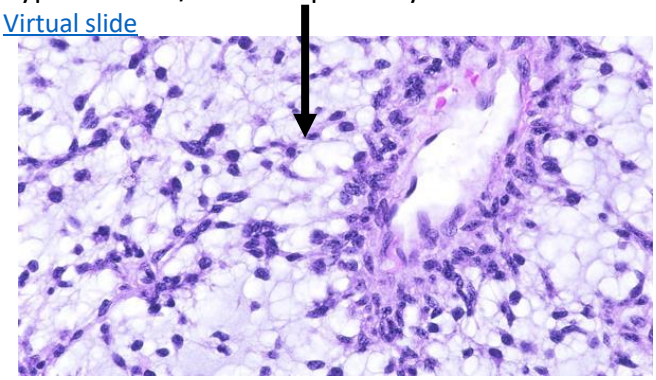
Pilocytic astrocytoma (Classic)

Essential:
Classic histologic features, such as biphasic compact and loose growth patterns, piloid cytology, and low proliferative activity, with or without Rosenthal fibers and/or Eosinophilic granular bodies
OR
Low-grade piloid astrocytic neoplasm with solitary MAPK alteration, such as BRAF fusion.

Pilomyxoid astrocytoma

Essential:
A monomorphic, loose, myxoid neoplasm with piloid cytology and prominent angiocentric pattern, often without Rosenthal fibers an Eosinophilic granular bodies.
OR
Low-grade astrocytic neoplasm with pilomyxoid features and a solitary MAPK alteration, such as a BRAF fusion

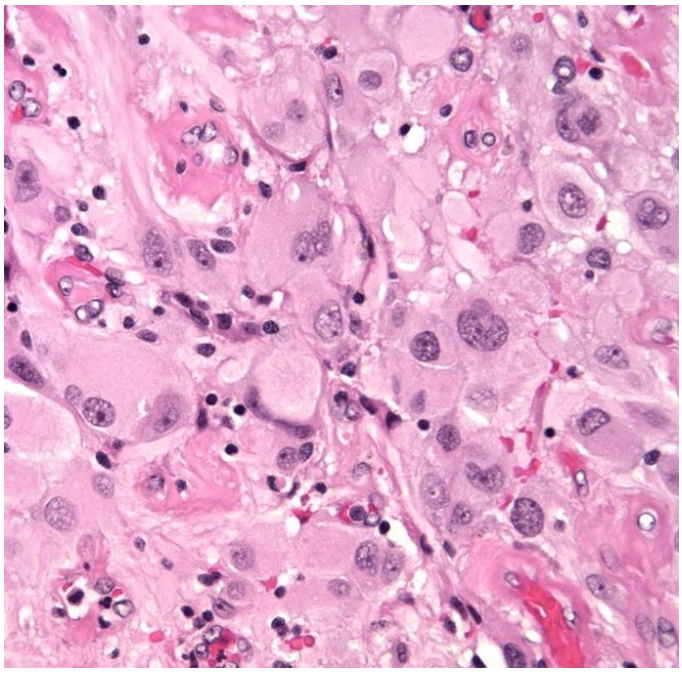
Pilomyxoid astrocytoma—variant with angiocentric arrangement of monomorphous, bipolar cells in a prominent myxoid background. Tumor of infancy in hypothalamic/chiasmic pathway. Worse outcomes.
Virtual slide



Subependymal Giant Cell Astrocytoma (SEGA) **WHO grade 1**

Benign, slow-growing tumor

Well-circumscribed. Often calcifications



Composed of a spectrum of glial phenotypes with **polygonal cells with abundant glassy cytoplasm to smaller spindle cells** and gemistocyte-like cells arranged in sweeping fascicles, sheets, or nests. Giant **ganglion-like cells** are common.

Considerable nuclear pleomorphism.
Mitoses and necrosis do not impact grade.

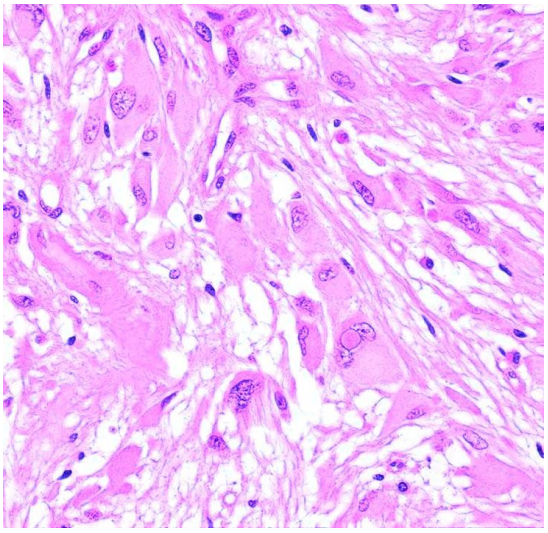
Typically arises in the **wall of the lateral ventricles** near the Foramen of Monro.
Usually present before age 20, often with increased intracranial pressure (close foramen of Monro)

Very strong association with **Tuberous sclerosis**.
→ One of the major diagnostic criteria
→ Frequent TSC1 or TSC2 biallelic th inactivation

IHC: (+) S100, TTF1; (+/-) GFAP, Synaptophysin, NeuN

Good prognosis when totally resected.

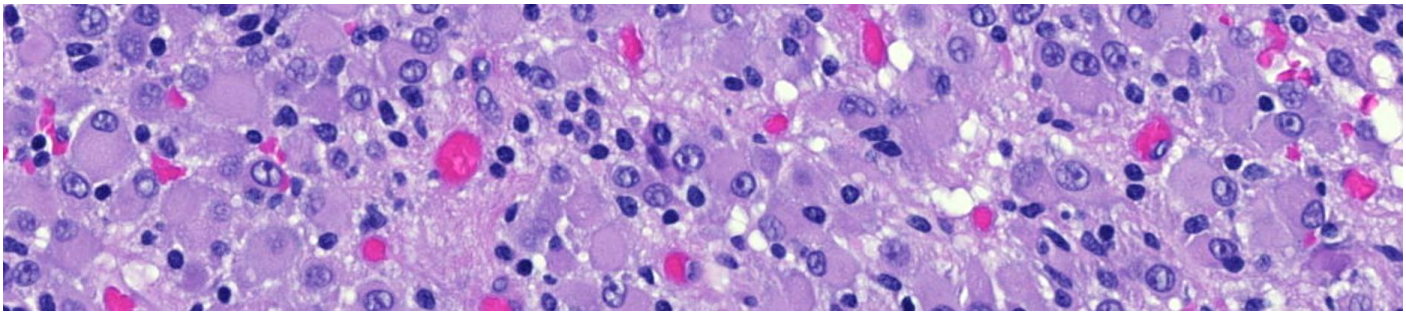
Virtual slide 1 2 3



***WHO Diagnostic Criteria*:**
SEGA

Essential:
Characteristic histological features, with multiple glial phenotypes including polygonal cells, gemistocytic-like cells, spindle cells, and ganglionic-like cells
AND
Immunoreactivity for glial markers (GFAP, S100)
AND
Variable expression of neuronal markers (NF, Synaptophysin, NeuN)

Desirable:
Nuclear expression of TTF1
Lost or reduced expression of tuberin and hamartin
Immunoexpression of phosphorylated S6
History of Tuberous sclerosis
TSC1 or TSC2 mutation
Compatible DNA methylation profile



Pleomorphic Xanthoastrocytoma ("*PXA*")

Astrocytic tumor with **large, pleomorphic, and frequently multinucleated spindled and lipidized cells**.

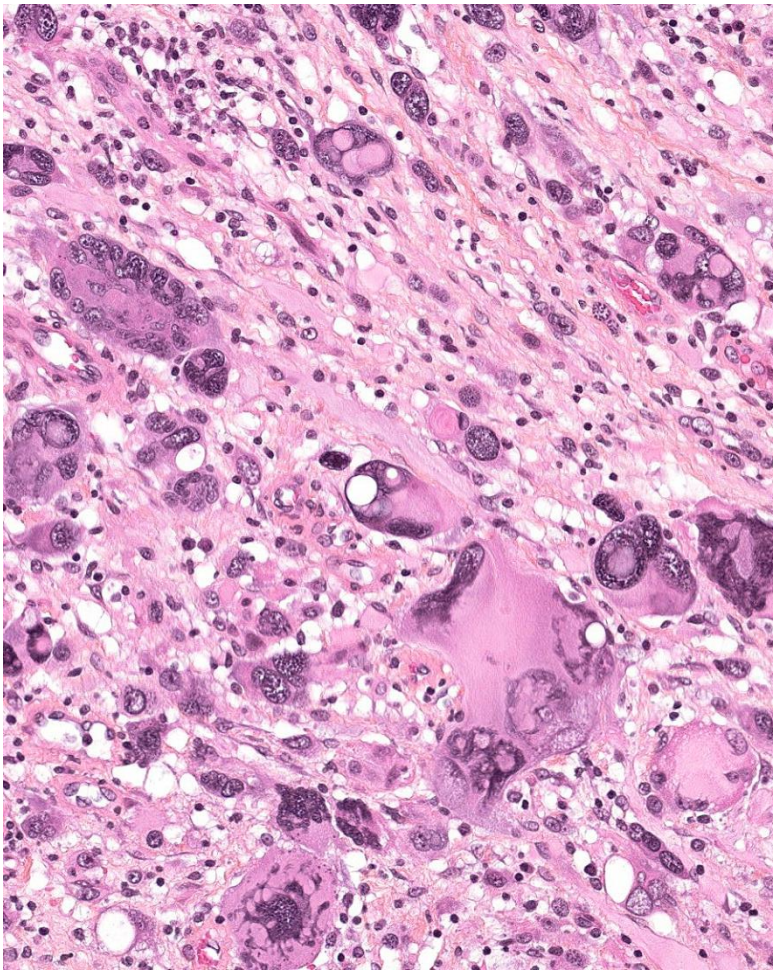
Frequent intranuclear inclusions and prominent nucleoli.

Dense reticulin network.
Numerous eosinophilic granular bodies.
Often neuronal differentiation.

IHC/Molecular: Frequent **BRAF V600E**
(No IDH mutations!)
Majority have combo of BRAFV600E *AND* CDKN2A/B homozygous deletion
(+) GFAP, S100
(+/-) CD34, Neuronal markers (e.g., MAP2), BRAF V600E

Virtual slide

Relatively rare.
Most common in **children and young adults.**
Often superficially located in cerebral hemispheres (esp. temporal lobe) with involvement of leptomeninges.
Good prognosis with long survival.



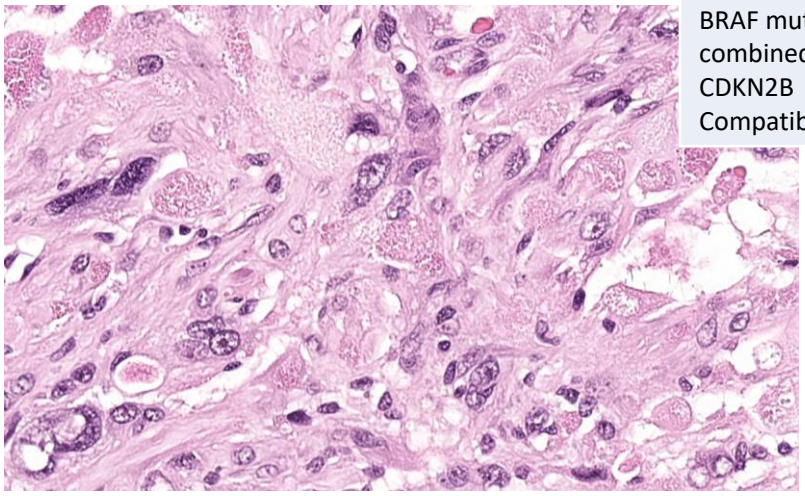
CNS WHO grade 2:
Low mitotic activity: <5 mitoses/10 HPF (<2.5 mitoses/mm^2); Ki67 usually <1%

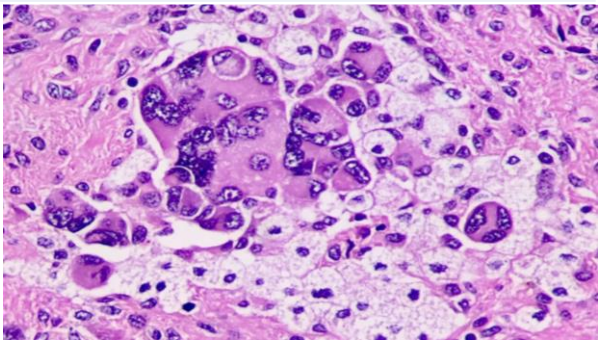
CNS WHO grade 3:
≥5 mitoses/10 HPF (≥2.5 mitoses/mm^2)
May have necrosis, but not necessary for Dx.
Ki67 usually ~15%

***WHO Diagnostic Criteria*: Pleomorphic Xanthoastrocytoma**

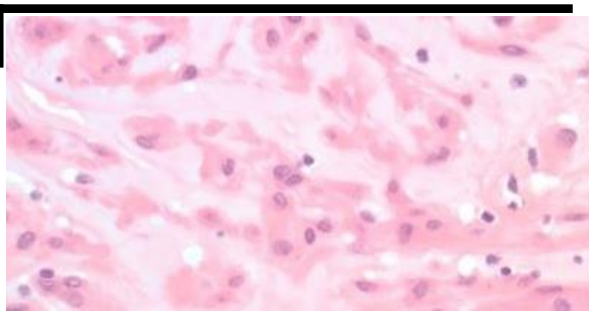
Essential:
An astrocytoma with pleomorphic tumor cells, including large multinucleated cells, spindled cells, xanthomatous (lipidized) cells, and eosinophilic granular bodies.

Desirable:
Reticulin deposition
BRAF mutation or other MAPK pathway gene alteration, combined with homozygous deletion of CDKN2A and or CDKN2B
Compatible DNA methylation profile





Chordoid Glioma (of the Third Ventricle)



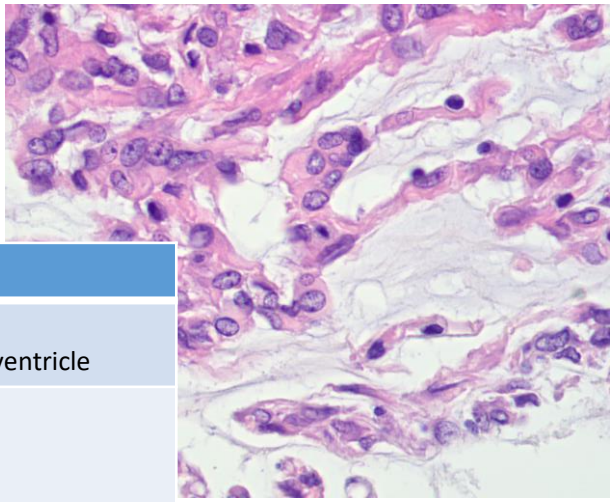
Very rare. CNS WHO grade 2

Well-circumscribed glial neoplasm in the anterior 3rd ventricle→ obstructive hydrocephalus

Clusters and cords of GFAP-expressing epithelioid cells within variably **mucinous stroma.**
PRKCA p.D463H missense mutation.
Typically has associated lymphoplasmacytic infiltrate.

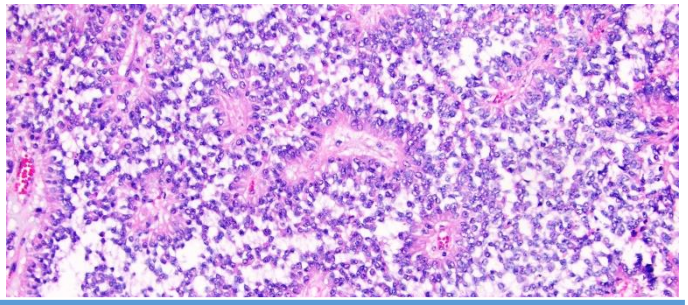
IHC: **(+) GFAP** (strong, diffuse), TTF-1, CD34; (+/-) S100, CK

Usually Adults.
Good prognosis if resected.



***WHO Diagnostic Criteria*: Chordoid Glioma**
Essential: A glial neoplasm with chordoid features located in the anterior third ventricle
Desirable: Nuclear TTF1 IHC PRKCA pD4683H mutation or Corresponding DNA methylation profile

Astroblastoma, MN1-altered



Rare. Mainly children and adolescents.
Well-demarcated. Within cerebral hemispheres.

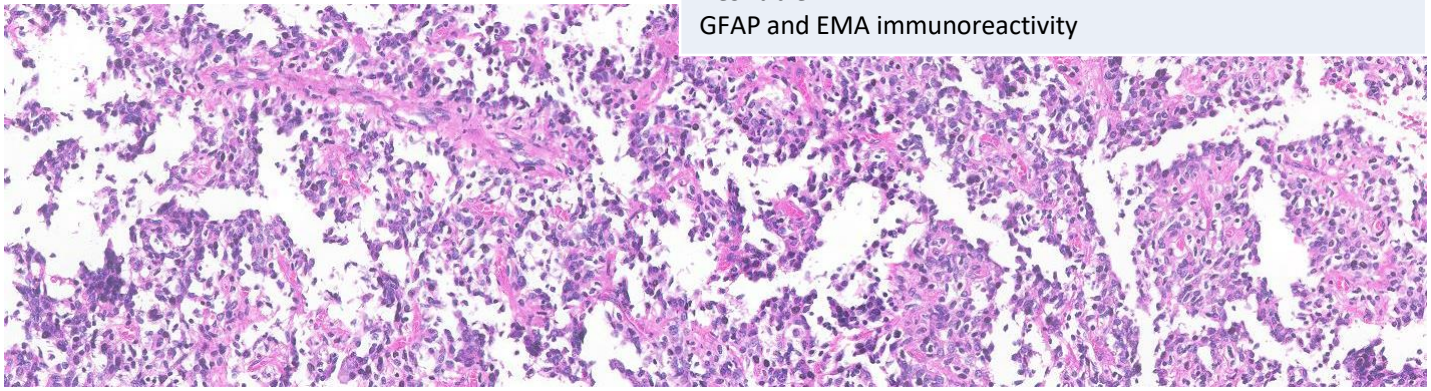
Inverted to columnar cells with eosinophilic processes radiating towards central blood vessels (astroblastic pseudorosettes)
Pseudopapillary/pseudovascular growth.
Can have round cell component.
Frequent vascular hyalinization.

IHC: (+) GFAP, S100, EMA
Molecular: **MN1-alterations**

Biologic behavior varies→ not currently graded.

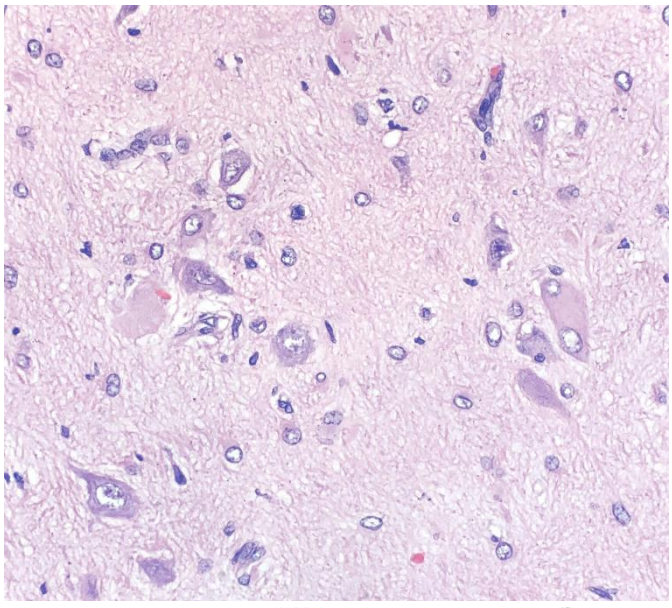
Virtual slide

***WHO Diagnostic Criteria*: Astroblastoma, MN1-altered**
Essential: A glial neoplasm with astroblastic perivascular pseudorosettes **AND** MN1-alteration **AND (for unresolved cases)** Compatible DNA methylation profiling
Desirable: GFAP and EMA immunoreactivity



Neuronal and Mixed Neuronal-Glial Tumors

Ganglioglioma — WHO grade 1



Well-differentiated, slow-growing.
Often in the **temporal lobe** of **children**.
Intracortical, circumscribed, and **cystic**
Frequently present with early-onset focal **epilepsy**.

Dysplastic ganglion cells (binucleate, dysmorphic neuronal features, without the architectural arrangement or cytological characteristics of cortical neurons) with **neoplastic glial cells** (may resemble astrocytoma, oligodendroglioma, or pilocytic astrocytoma) Virtual slide 2
Can be **heterogenous** within tumor.

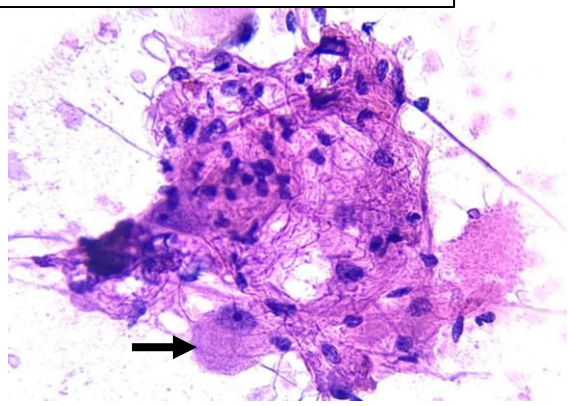
Molecular/IHC: BRAF V600E mutation in ~1/3.
Presence of an IDH mutation *excludes* this Dx.

WHO Diagnostic Criteria: Ganglioglioma

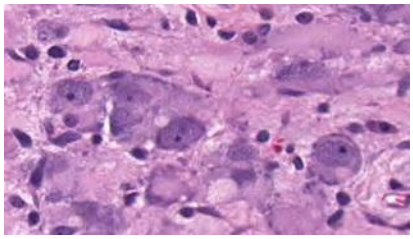
Essential:
Intra-axial low-grade glioneuronal tumor
AND
Combination of neoplastic ganglion and glial cells
AND (for unresolved lesions)
BRAF V600E mutation or other MAPK pathway alteration
OR
Compatible DNA Methylation profile

Desirable:
Absence of IDH mutation

Intraop smear with a ganglion cell!



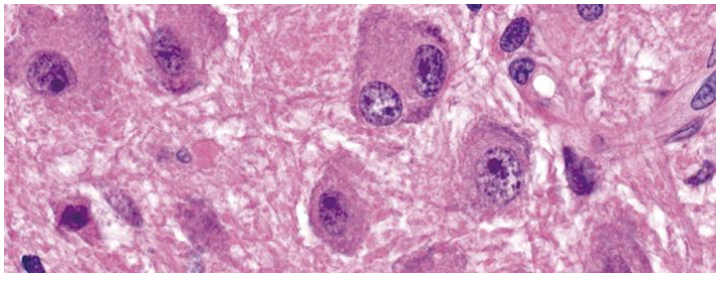
Gangliocytoma — WHO grade 1



Rare. Slow-growing.
Usually in temporal lobe of **Children** with **epilepsy**

Composed of **irregular clusters of mature neoplastic ganglion cells**, often with dysplastic features (binucleation, cytoplasmic ballooning).
Sparse stroma of non-neoplastic glial elements.

May be hard to distinguish from Ganglioglioma in some cases (spectrum).



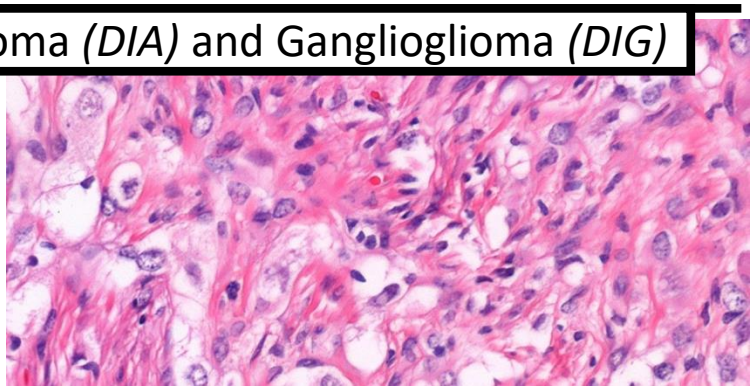
WHO Diagnostic Criteria: Gangliocytoma

Essential:
A tumefactive lesion with presence of irregular groups of large, mature ganglion cells
AND
Matrix resembling normal neuropil, sometimes more coarsely fibrillar or vacuolated

Desirable:
Atypical and binucleated ganglion cells
Cytoplasmic ballooning or vacuolization

Desmoplastic Infantile Astrocytoma *(DIA)* and Ganglioglioma *(DIG)*

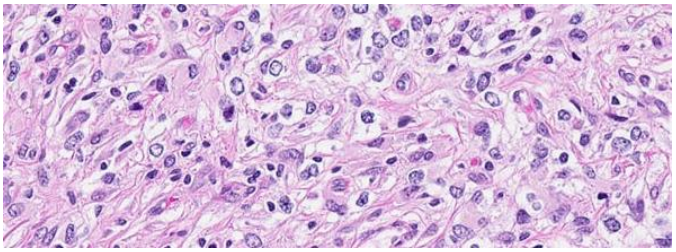
WHO grade 1



Rare neoplasms of **early childhood**.
Cerebral hemispheres. Often large and cystic.
Leptomeningeal component.

Biphasic: **1) Prominent desmoplastic leptomeningeal stroma** with**, 2) a variable neuroepithelial population of astrocytes** (DIA) possibly with a mature **neuronal component** (DIG).
Abundant connective tissue→ Prominent reticulin surrounding most cells → may mimic a mesenchymal tumor! Virtual slide

Molecular: MAPK pathway activation, usually via BRAF or RAF1 mutations



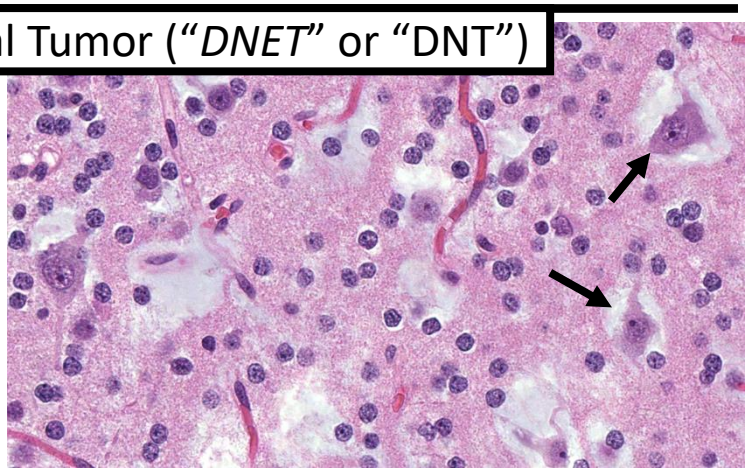
WHO Diagnostic Criteria: DIG/DIA

Essential:
Biphasic morphology with a dominant desmoplastic leptomeningeal component admixed with a neuroepithelial component containing astrocytic cells only (DIA) or astrocytes and neuronal cells (DIG)
AND (for unresolved lesions)
Methylation profile of DIG/DIA
OR
BRAF or RAF1 mutation or fusion, occurring in the absence of homozygous deletion of CDKN2A/B

Desirable:
Tumor with a cystic component and a solid portion, with leptomeningeal involvement, usually attached to the dura
Infantile onset (typically <24 months)

Dysembryoplastic Neuroepithelial Tumor ("*DNET*" or "DNT")

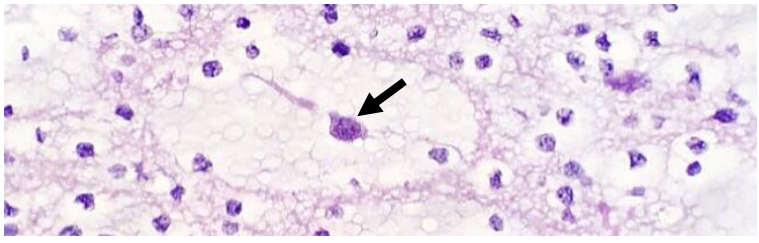
WHO grade 1



Usually **Children** or young adults.
Typically cortex of **temporal lobe**.
"Soap bubble" appearance on MRI.
Present with early onset **epilepsy**.

Columns of **small round monotonous cells** (oligodendroglioma-like) oriented perpendicular to the cortical surface formed by axon bundles.
Normal **neurons "floating" in mucin pools (→).**
Multinodular architecture.
May be associated with cortical dysplasia.

Molecular: FGFR1 activating mutations.
Presence of an IDH mutation or Codeletion of 1p/19q *excludes* this Dx. Virtual slide



WHO Diagnostic Criteria: DNET

Essential:
Cortical ganglioneuronal tumor
AND
Presence of the specific ganglioneuronal component
AND (for unresolved cases)
FGFR1 gene alteration
OR
Compatible DNA methylation profile

Desirable:
Early-onset focal epilepsy

Papillary Glioneuronal Tumor

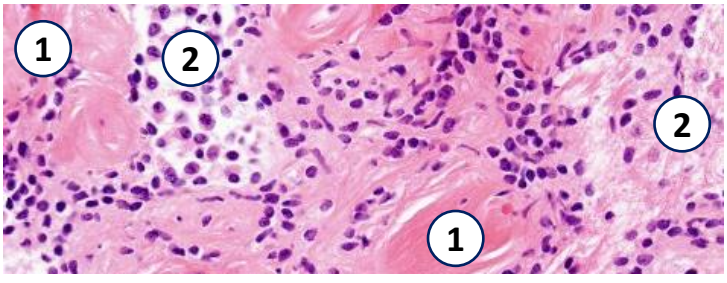
WHO grade 1

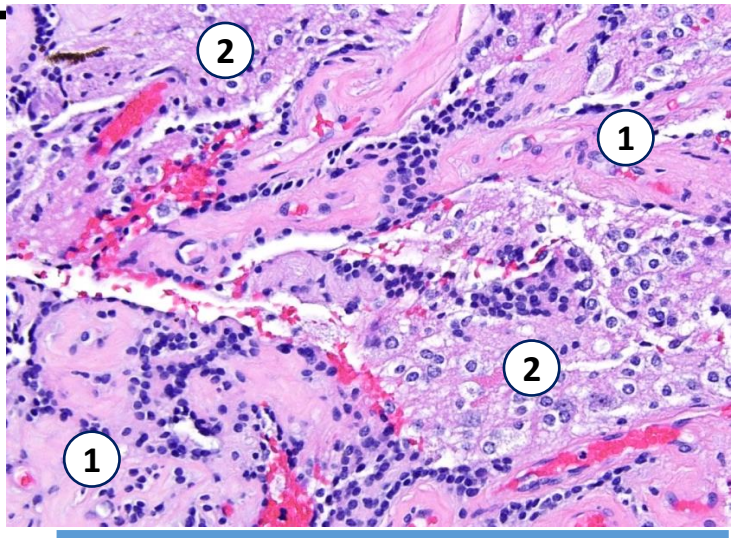
Low-grade biphasic neoplasm with:
1) Prominent pseudopapillary architecture with a cuboidal glial cells with round nuclear and scant cytoplasm around hyalinized blood vessels.
(+)GFAP

2) Intervening collections of neurocytes with medium-sized **ganglion cells** with neuropil.
(+) Synaptophysin

Often in the **cerebral hemispheres near the ventricles**.
Often **young adults**. **Circumscribed**.

Molecular: Frequent **SLC44A1-PRKCA fusions**





WHO Diagnostic Criteria: PGNT

Essential:
Biphasic histologic and immunophenotypic pattern with pseudopapillary glial lining and interpapillary neuronal components
AND
PRKCA gene fusion (mostly SLC33A1::PRKCA)
AND (for unresolved lesions)
Compatible DNA methylation profile

Desirable:
Well-delineated, solid and cystic tumor

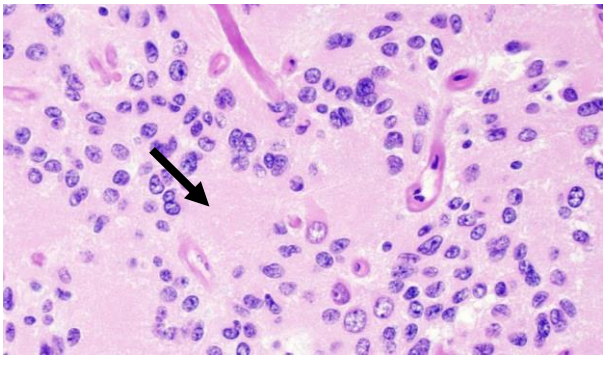
Rosette-forming Glioneuronal Tumor

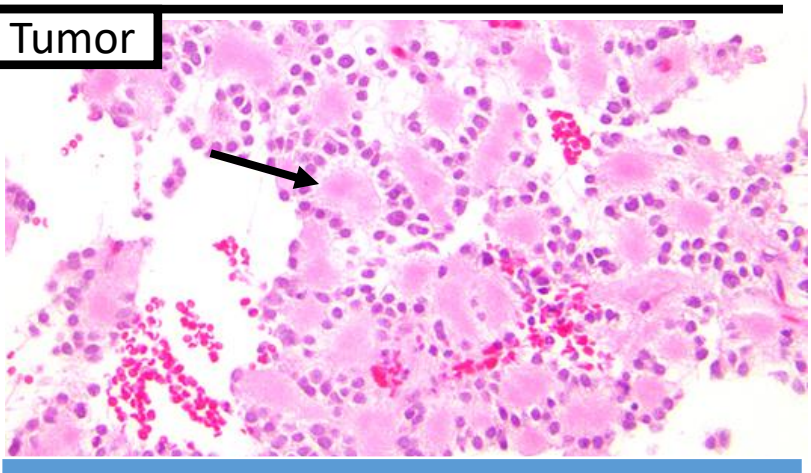
WHO grade 1

Two distinct components:
1) **Uniform neurocytes forming rosettes** (→) and/or perivascular pseudorosettes
2) An **astrocytic component** resembling pilocytic astrocytoma.

Slow-growing. Relatively well-circumscribed.
Midline: Most common in the **4th ventricle.**
Typically **children or young adults.**

Molecular: FGFR1 mutations with frequent co-occurring PIK3CA and/or NF1 mutations.



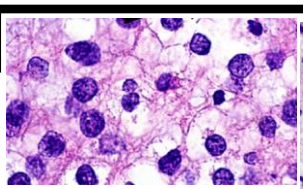


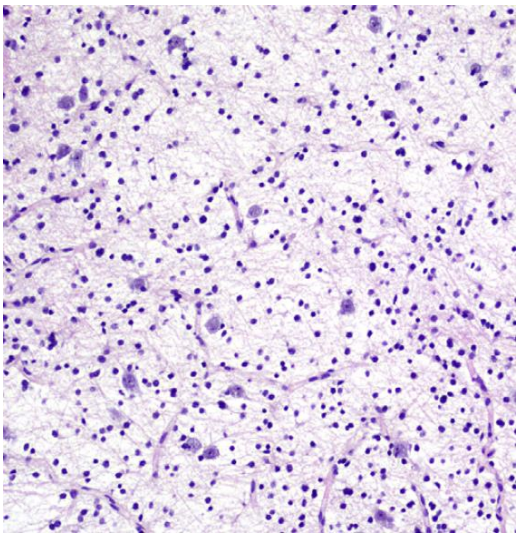
WHO Diagnostic Criteria: RGNT

Essential:
Biphasic histomorphology with a neurocytic component and a glial component
AND
Uniform neurocytes forming rosettes and/or perivascular pseudorosettes associated with synaptophysin expression
AND (for unresolved lesions)
Small biopsies showing only one component and a compatible DNA methylation profile

Desirable:
FGFR1 mutation with co-occurring PIK3CA and/or NF1 mutation

Myxoid Glioneuronal Tumor





CNS WHO grade 1

Very rare. Children and young adults.

***WHO Diagnostic Criteria*: Myxoid glioneuronal tumor**

Essential:
Oligodendrocyte-like tumor cells embedded in a prominent myxoid stroma
AND
Location in septal nuclei, septum pellucidum, corpus callosum, or periventricular white matter

Desirable:
PDGFRA p.K385L/I dinucleotide mutation (or other PDGFRA mutation)
Compatible DNA Methylation profile

Diffuse Leptomeningeal Glioneuronal Tumor

Rare. Usually young children. Spine or Intracranial.

Predominant and Widespread leptomeningeal growth.
Oligodendroglioma-like morphology,
Neuronal differentiation in a *subset* of cases.
Usually low-grade appearing. Occasional anaplasia.

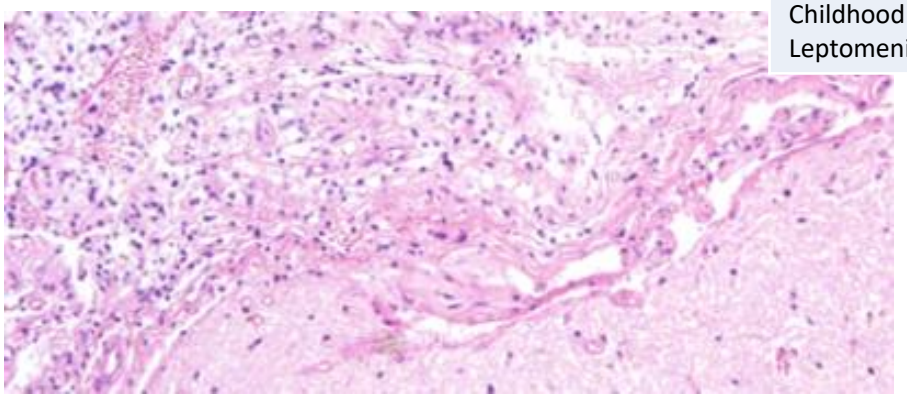
Molecular: **MAPK pathway activation** (Frequent KIAA1549-BRAF fusions) ***and*** **1p deletion** (can have 19q codeletion in a subset)

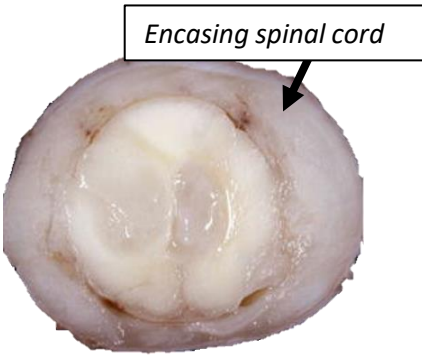
Not currently graded (too rare).
Slow progression over many years.

***WHO Diagnostic Criteria*: DLGNT**

Essential:
Oligodendrocyte-like morphology
AND
OLIG2 and Synaptophysin immunoreactivity
AND
Chromosome arm 1p deletion
AND
MAPK pathway alteration (mostly KIAA1549::BRAF)
AND (for unresolved lesions)
Compatible DNA methylation profile

Desirable:
Childhood onset
Leptomeningeal dissemination



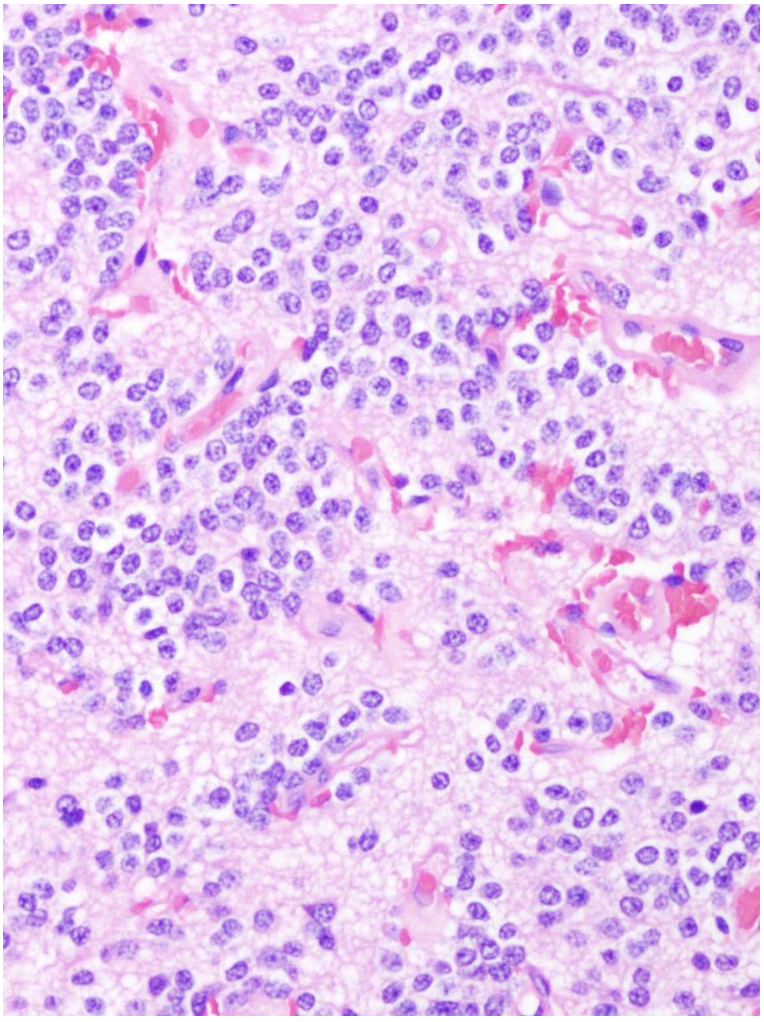


Central Neurocytoma

CNS WHO grade 2

Uncommon. **Intraventricular**, often lateral.
Usually young adults.

Uniform round cells with speckled chromatin and a neuronal immunophenotype
(+Synaptophysin, - GFAP)
Fibrillary areas may mimic neuropil or ependymal pseudorosettes.
Arborizing capillaries and calcifications.
Virtual slide



***WHO Diagnostic Criteria*: Central neurocytoma**

Essential:
Intraventricular localization
AND
Oligodendroglioma-like monomorphic cells
AND
Synaptophysin expression
AND (for unresolved lesions)
Compatible DNA methylation profile

Desirable:
Young adult patient
In most cases, no sign of malignancy

Extraventricular Neurocytoma

CNS WHO grade 2

Present throughout CNS, often cerebrum, *without* ventricular association.
Well-circumscribed. Slow-growing.

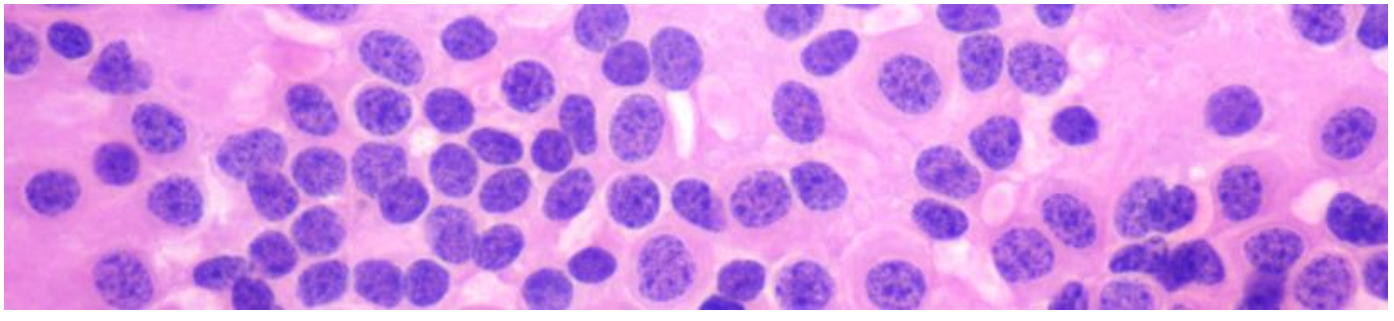
Histologically similar to central neurocytoma, but more varied in appearance.

Wide age range, often middle-age.
Must rule out a diffuse glioma→ make sure *no* IDH mutations.
Frequent FGFR1::TACC1 fusions

***WHO Diagnostic Criteria*: Extraventricular neurocytoma**

Essential:
Extraventricular neurocytic neoplasm without IDH mutation
AND
Synaptophysin expression
AND (for unresolved lesions)
Compatible DNA methylation profile

Desirable:
FGFR1 alteration (mostly FGFR1::TACC1 fusion)

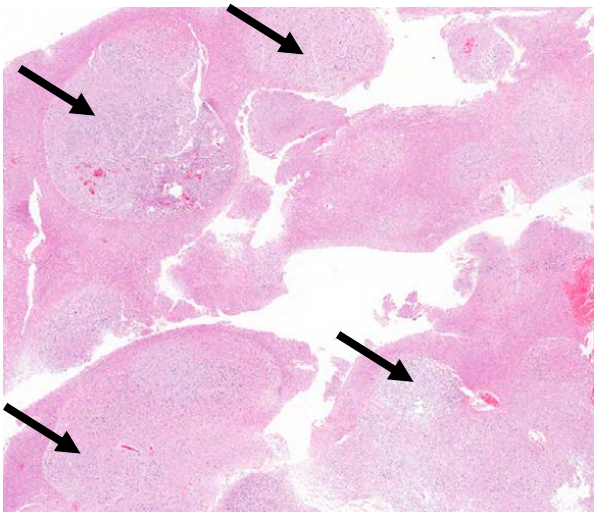


Multinodular and vacuolating neuronal tumor

CNS WHO grade 1

Cortex Temporal lobe. Adults.

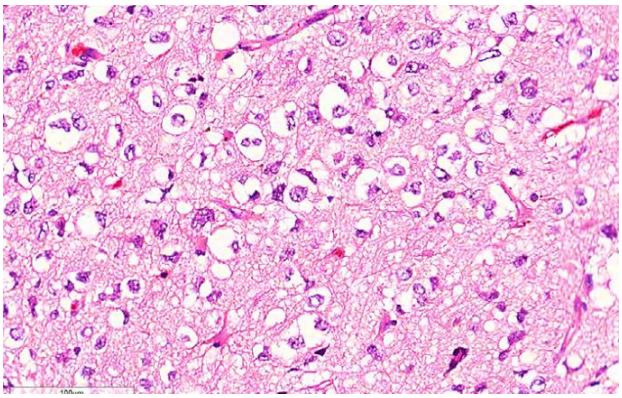
Multinodular!
Monomorphic neuronal elements with round, vesicular nuclei, and distinct nucleoli, distributed in discrete and coalescent pale, hypomyelinated nodules with vacuolar changes in tumor cells and matrix.



***WHO Diagnostic Criteria*:**

Essential:
Multinodularity
AND
Neuronal cytological features or tumor cell immunoreactivity for synaptophysin, HUC/HUD, or non-phosphorylated 200-kDA NFP
AND
Absence of mitotic activity
AND
Tumor cell/matrix vacuolation (but may be minimal)

Desirable:
Immunoreactivity for OLIG2 and Internexin A
Absence of NeuN or chormogranin expression
MAPK pathway-activating abnormalities



Other Glioneuronal tumors

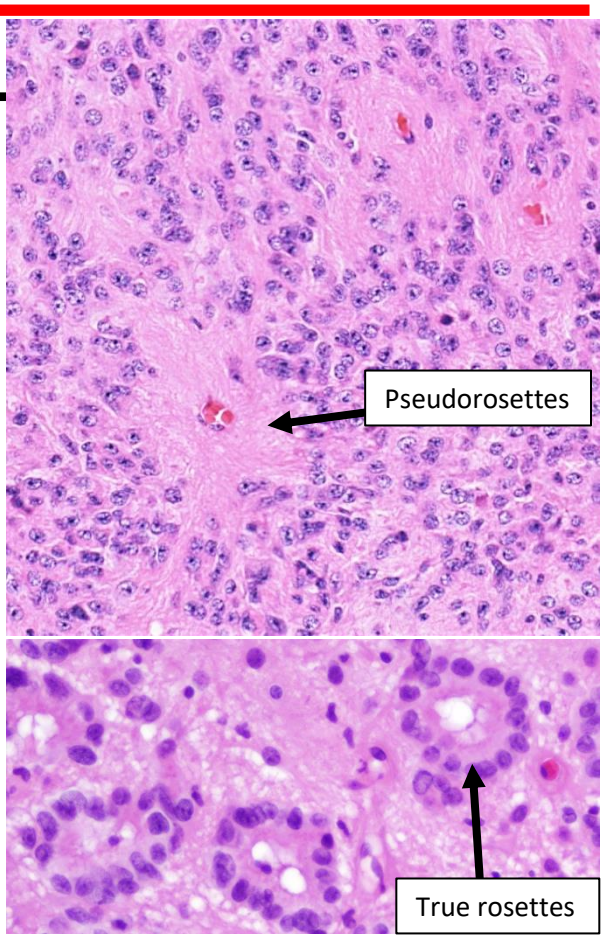
Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters (DGONC): A provisional tumor proposed as a neuroepithelial tumor characterized by variably differentiated cells frequently showing perinuclear haloes, scattered multinucleated cells, and nuclear clusters, with a distinct DNA methylation profile and frequent monosomy of chromosome 14.

Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease) (WHO grade 1): Cerebellar mass composed of dysplastic ganglion cells of various sizes that conform to the existing cortical architecture and thicken the cerebellar folia. Calcifications and ectatic vessels. PTEN mutation/deletion or loss (primarily seen in Cowden syndrome). Usually adults. Unclear if hamartomatous vs neoplastic.

Cerebellar Liponeurocytoma (WHO grade 2)—a rare **cerebellar** tumor with a mixture of small, monomorphic, oligodendroglioma-like **neurocytic cells with regular round nuclei and focal lipoma-like changes** (just lipid in tumor cells, not actual adipocytes). (+) Synaptophysin, Focal GFAP. Adults.

Ependymal Tumors

Ependymoma



Circumscribed glioma, composed of **uniform small cells with round nuclei and speckled chromatin in a fibrillary matrix**

Characteristic: **pseudorosettes** (perivascular anucleate zones) found in practically every case.
True ependymal **rosettes** (bland cuboidal cells arranged around a central lumen) found in ~1/3 of cases.

Variable cellularity. Can hyalinize or have "canals."

Mainly **intracranial, can get in spinal cord**.
Can occur in both children and adults.
In children→ usually posterior fossa (often 4th ventricle)

Generally low cell density and mitotic index.
Electron microscopy: shows cilia and microvilli.

IHC: **(+) EMA** (along lumina surface of rosettes or dot-like perinuclear), GFAP in pseudorosettes, S100.
(- or sparse) OLIG2

Variable outcome depending on resection, therapy, and molecular group. Virtual slide 1 2 3 Virtual Smear

Current recommendation is to classify based on Location *and* molecular changes (e.g., "*Supratentorial ependymoma, YAP1 fusion-positive*" or "*Supratentorial ependymoma, Not elsewhere classified*")

If molecular analysis shows a not listed change, say "*Not Elsewhere Classified*" (NEC).
If molecular testing is not feasible, say "*Not Otherwise Specified*" (NOS)

Beyond this molecular classification, grading is of uncertain prognostic significance. Historically, we would grade as 2 or 3 morphologically (default = 2; brisk mitotic activity and dese cellularity → grade 3)

Morphologic subtypes of ependymoma exist (tanycytic, clear cell, papillary), but do not impact prognosis. Subependymoma and myxopapillary ependymoma are identified morphologically.

Unique Molecular Subgroups by Location:

Location	Molecular Subgroup	Age	Prognosis	Comments
Supratentorial (ST)	YAP1-fusion	Infants and kids	Good	
	ZFTA-fusion (*c11orf95*)	Infants to adults	Intermediate	IHC: (+) p65 and L1CAM
Posterior Fossa (PF)	Methylation group A (PFA)	Infants	Poor	IHC: Loss of H3K27me3
	Methylation group B (PFB)	Older children and adults	Good	IHC: Retained H3K27me3
Spinal Cord (SC)	MYCN amplified	Older children and adults	Poor	Frequent dissemination

Ependymoma Subtype Diagnostic Criteria

Supratentorial Ependymoma

WHO Diagnostic Criteria: Supratentorial Ependymoma, ZFTA fusion-positive

Essential:
Supratentorial tumor with morphological and immunohistochemical features of ependymoma
AND
Gene fusion involving ZFTA (C11orf95)

Desirable:
Compatible DNA methylation profile
Immunoreactivity for p65 (RELA) or L1CAM

WHO Diagnostic Criteria: Supratentorial Ependymoma, YAP1 fusion-positive

Essential:
Supratentorial tumor with morphological and immunohistochemical features of ependymoma
AND
Gene fusion involving YAP1

Desirable:
Compatible DNA methylation profile
No immunoreactivity for p65 (RELA) or L1CAM
PAS-positive eosinophilic granular bodies

Posterior Fossa Ependymoma

WHO Diagnostic Criteria: Posterior Fossa group A Ependymoma

Essential:
Posterior fossa tumor with morphological and immunohistochemical features of ependymoma
AND
Global reduction of H3 K27me3 in tumor cell nuclei
OR
Compatible DNA methylation profile

Desirable:
Stable genome on genome-wide copy number analysis

WHO Diagnostic Criteria: Posterior Fossa group B Ependymoma

Essential:
Posterior fossa tumor with morphological and immunohistochemical features of ependymoma
AND
Compatible DNA methylation profile

Desirable:
Chromosomal instability and aneuploidy on genome-wide copy number analysis
Retained nuclear expression of H3 K27me3

Spinal Ependymoma

WHO Diagnostic Criteria: Spinal Ependymoma

Essential:
Spinal tumor with morphological and immunohistochemical features of ependymoma
AND
Absence of morphologic features of myxopapillary ependymoma or subependymoma

Desirable:
Compatible DNA methylation profile
Loss of chromosome 22q
No MYCN amplification

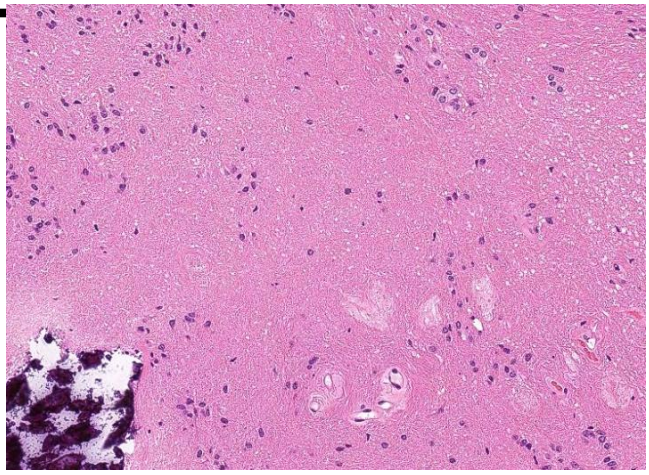
WHO Diagnostic Criteria: Spinal Ependymoma, MYCN-amplified

Essential:
Spinal tumor with morphological and immunohistochemical features of ependymoma
AND
MYCN amplification

Desirable:
Compatible DNA methylation profile
High-grade histopathological features
(High mitotic count, necrosis, microvascular proliferation, etc…)

Subependymoma

CNS WHO grade 1



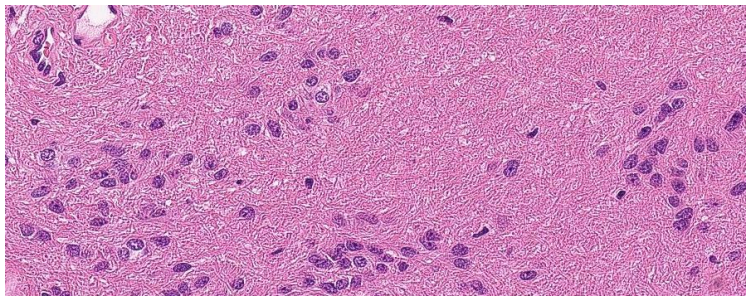
Slow-growing, exophytic, and intraventricular.

Clusters of mostly bland cells embedded in abundant fibrillary matrix.
No significant mitotic activity.
Frequent microcystic change. Sometimes calcified.
Rare pseudorosettes. Virtual slide 1 2

Often detected incidentally→ often asymptomatic.
All ages. Sharply demarcated grossly.

IHC: (+) GFAP; Usually only focal EMA (unlike ependymoma); Ki67 <1%

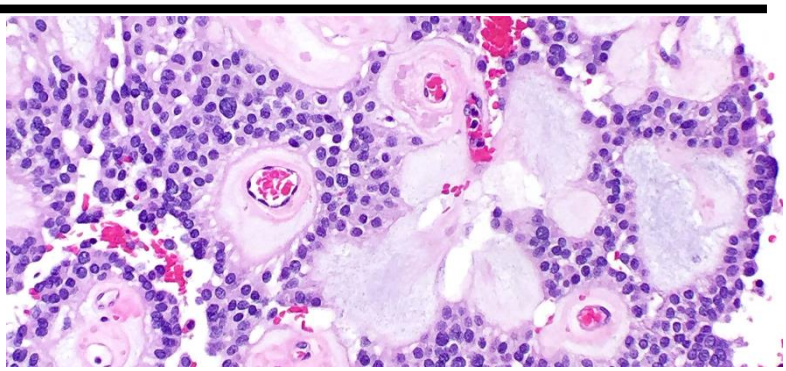
Excellent prognosis



***WHO Diagnostic Criteria*: Subependymoma**

Essential:
Circumscribed glioma with cluster of tumor cell nuclei within expansive, focally microcystic fibrillary matrix
AND
Lack of conspicuous nuclear activity
AND
Absent or minimal mitotic activity
AND (for unresolved lesions)
Compatible DNA methylation profile

Myxopapillary Ependymoma



CNS WHO grade 2

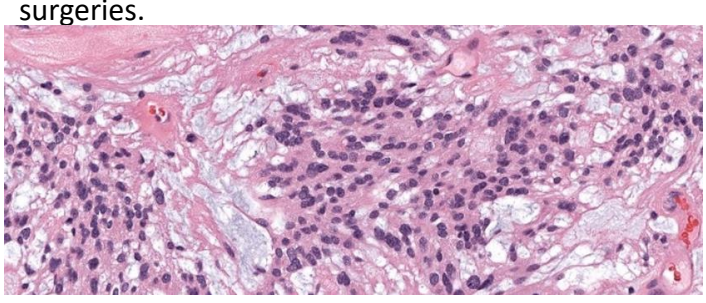
Arises almost exclusively in region of conus medullaris, **cauda equina**, and filum terminale.

Elongated to cuboidal cells arranged in radial patterns around vascularized, mucoid, fibrovascular cores
Basophilic, myxoid material around vessels with microcysts is highlighted by Alcian blue and PAS

Slow-growing. Typically occurs in young adults.

IHC: (+) GFAP, S100, CD99, CD56, CK AE1/AE3
Ki67 less than 2-3% usually.

High survival rates, but many patients have persistent/recurrent disease requiring multiple surgeries.



***WHO Diagnostic Criteria*: Myxopapillary Ependymoma**

Essential:
Glioma with papillary structures and perivascular change or at least focal myxoid microcysts
AND
Immunoreactivity for GFAP
AND (for unresolved lesions)
Compatible DNA methylation profile

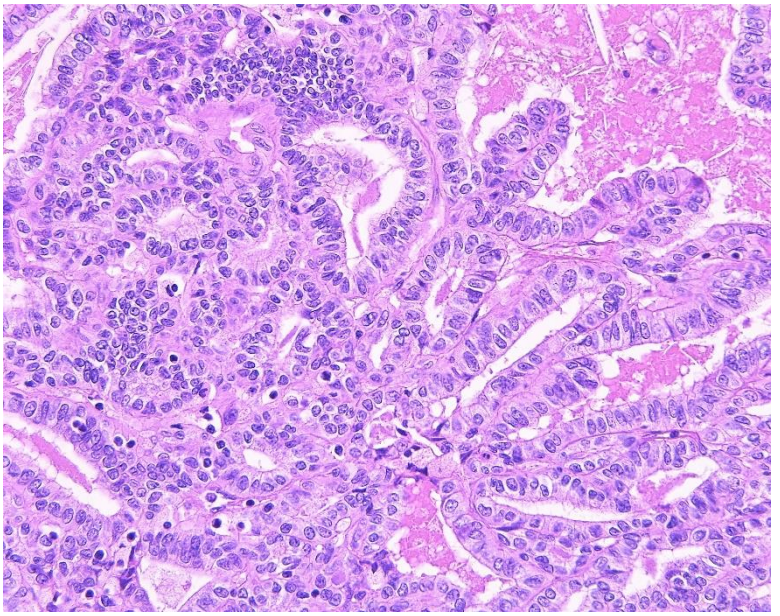
Desirable:
Papillary arrangement of tumor cells around vascularized fibromyxoid cores
Location in the filum terminale of the conus medullaris

Virtual slide 1 2 3 Smear

Choroid Plexus Tumors

Derived from choroid plexus epithelium; Found in **Ventricles**.
IHC: (+) KIR7.1, CK AE1/AE3, Vimentin, CK7, S100. (-) EMA,

Choroid Plexus Papilloma



CNS WHO grade 1

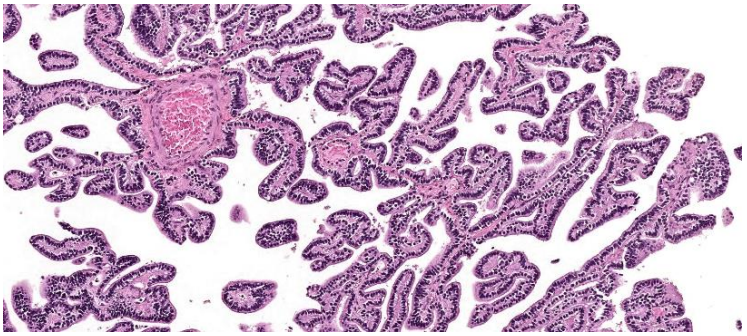
Ventricular papillary neoplasm.
Most common in lateral ventricle
~2/3 of choroid plexus tumors.
All ages, but more common in kids.
Can present with hydrocephalus.

Delicate fibrovascular fronds covered by a single layer of cuboidal to columnar epithelium.
Round to oval, basal, **monomorphic nuclei**.
Very low/absent mitotic activity (<2/10 HPF)
Ki67 usually <2%

Patients usually cured by surgical resection.

Atypical Choroid Plexus Papilloma

WHO grade 2



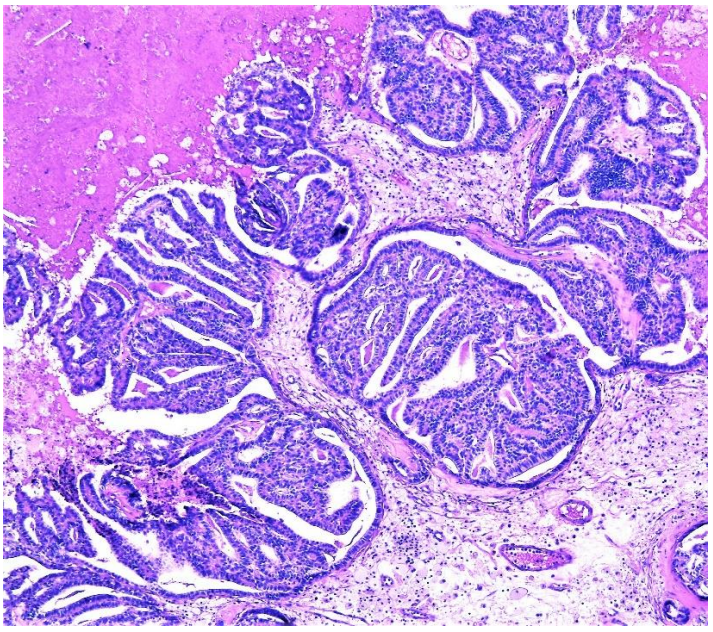
A choroid plexus papilloma that has increased mitotic activity (≥2 mitoses/10 HPF), but does not fulfill the criteria of choroid plexus carcinoma.

Often present, but not required: increased cellularity, nuclear pleomorphism, solid growth, necrosis. Ki67 ~10% often.

More likely to recur, but still relatively good prognosis.

Choroid Plexus Carcinoma

WHO grade 3



Frankly malignant epithelial neoplasm.
Most commonly in the **lateral ventricles** of **children**

At least 4 of the following:
1) Frequent mitoses (>5/10 HPF)
2) Increased cellular density
3) Nuclear pleomorphism
4) Blurring of the papillary pattern with poorly-formed sheets of tumor cells
5) Necrosis

Frequently invades neighboring brain and metastasizes via CSF.

Ki67 often >10%
~1/2 have TP53 mutations

Intermediate prognosis/survival

Choroid Plexus Tumor Diagnostic Criteria

WHO Diagnostic Criteria: Choroid Plexus Papilloma

Essential:
Demonstration of choroid plexus differentiation by histopathological and immunophenotypic features
AND
Absent or low mitotic index
AND
Intraventricular or cerebellopontine angle location

Virtual slide 2

WHO Diagnostic Criteria: Atypical Choroid Plexus Papilloma

Essential:
Intraventricular or cerebellopontine angle location
AND
Demonstration of choroid plexus differentiation by histopathological and immunophenotypic features
AND
Demonstration of ≥1 mitoses/mm^2 in a minimum of 2.3 mm^2 (equating to ≥2 mitoses/10 HPF)
AND
Absence of criteria qualifying the diagnosis of choroid plexus carcinoma

Desirable:
In select cases: demonstration of hyperploid by genome-wide chromosomal copy-number analysis

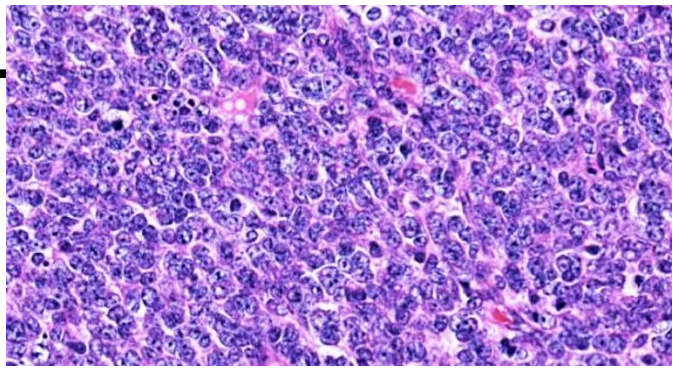
WHO Diagnostic Criteria: Choroid Plexus Carcinoma

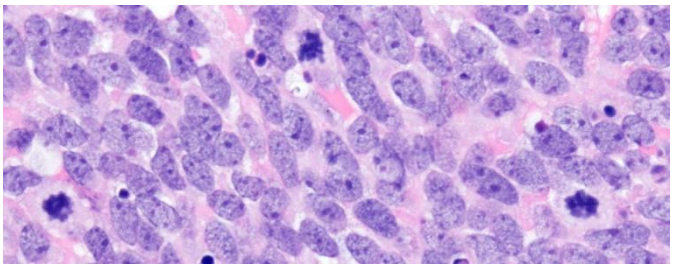
Essential:
Demonstration of choroid plexus differentiation by histopathological and immunophenotypic features
AND
Presence of at least 4 of the following 5 features
1)Increased cellular density
2)Nuclear pleomorphism
3)Blurring the papillary pattern with poorly-formed sheets of tumor cells
4)Necrotic areas
5)Frequent mitoses, usually >2.5 mitoses/mm^2 in a minimum of 2.3 mm^2 (equating to >5 mitoses/10 HPF)
AND
Intraventricular location

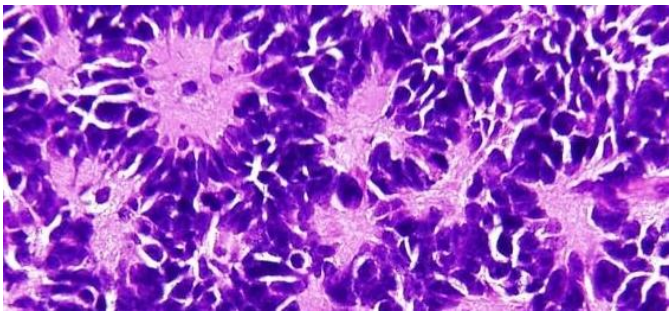
Desirable:
TP53 mutation analysis
Methylation profile of choroid plexus carcinoma
In select cases: demonstration of hypoploidy by genome-wide chromosomal copy-number analysis

Embryonal Tumors

Medulloblastoma — WHO grade 4







Second most common *malignant* brain tumor of **childhood** (after high-grade glioma). Average age 9.
Arise in **cerebellum** or dorsal brainstem/4th ventricle.
Block CSF flow→ increased ICP→ short history of headaches, nausea, ataxia.
Propensity to spread through CSF.

Embryonal neuroepithelial tumor consisting of densely packed **small round undifferentiated cells**.
High N:C ratios. Variable **rosettes** (Homer-Wright)
Usually mild to moderate pleomorphism.
High mitotic rate.

IHC: Diffuse CD56, NSE.
Frequent synaptophysin and NeuN

Classified by molecular *and* histologic findings
DNA methylation profiling is the standard method for grouping. Virtual slide 1 Smear

Commonly altered pathways:
SHH Pathway = "Sonic Hedge Hog"
WNT Pathway—often through CTNNB1 (β-catenin)

		WNT-activated	SHH-activated		Non-WNT/Non-SHH	
			TP53-Wildtype	TP53-Mutant	Group 3	Group 4
Age		Childhood	Infancy or Adult	Childhood	Infancy/ Childhood	All
Proportion		~10%	~20%	~10%	~25%	~35%
Usual Histology		**Classic**	**Desmoplastic/ Nodular**	**Large cell/ Anaplastic**	**Classic**	**Classic**
Genetic Changes		**CTNNB1 mutations** Monosomy 6	**PTCH1 mutation/loss** Among others	**TP53 mutation** Among others	**MYC amplification** Among others	**KDM6A, SNCAIP** Among others
Prognosis		**Excellent**	**Low-risk** (Standard if classic histology)	**Poor**	**High-risk** (Standard if classic histology)	**Standard**
Immunohistochemistry	**β-catenin** (WNT pathway)	**Nuclear +** Cytoplasmic	Cytoplasmic	Cytoplasmic	Cytoplasmic	Cytoplasmic
	GAB1	Negative	**Cytoplasmic**	**Cytoplasmic**	Negative	Negative
	FilaminA	Cytoplasmic	Cytoplasmic	Cytoplasmic	Negative	Negative
	YAP1	Nuclear + Cytoplasmic	Nuclear + Cytoplasmic	Nuclear + Cytoplasmic	Negative	Negative

Medulloblastoma Histologic Subtypes:

Classic—see prior page (lack features below). Most common histology.

Desmoplastic/Nodular—nodular reticulin-free zones ("pale islands") with intervening densely packed, poorly differentiated cells that produce an intercellular network of reticulin fibers.

↕ *Significant overlap. Both SHH-pathway, TP53-wt. Good prognosis. Often considered together.*

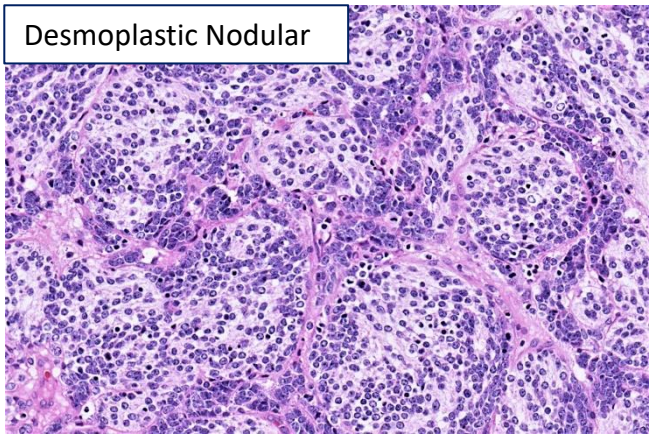
Extensive Nodularity—many, large, reticulin-free nodules of neurocytic cells against a neuropil-like matrix. Narrow internodular strands.

Anaplastic—marked nuclear pleomorphism with particularly numerous mitoses and apoptoses. Frequent nuclear molding and cell wrapping.

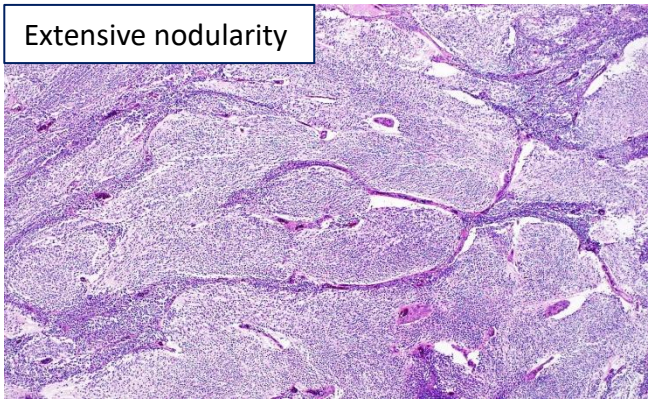
↕ *Significant overlap. Often group 3 or SHH, TP53-mutant. High risk. Often considered together.*

Large Cell—Large, monomorphic cells with prominent nucleoli.

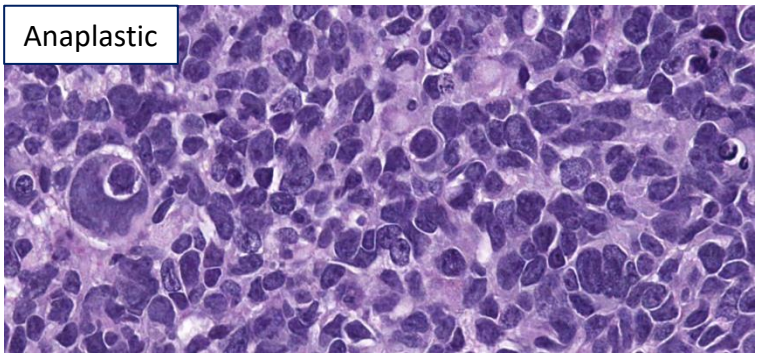
Desmoplastic Nodular



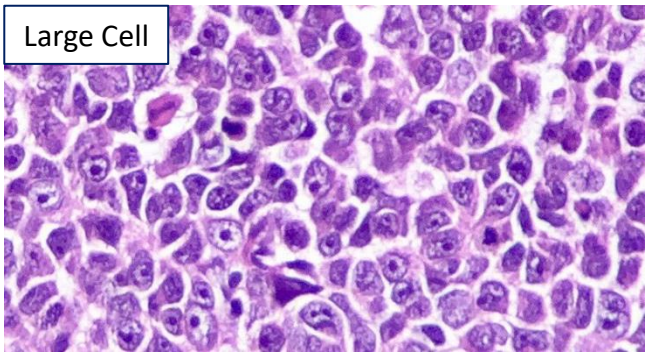
Extensive nodularity



Anaplastic



Large Cell



Medulloblastoma Diagnostic Criteria

WHO Diagnostic Criteria: Medulloblastoma, WNT-activated

Essential:
Medulloblastoma
AND
WNT pathway activation
[can demonstrate with nuclear β-catenin]
OR
Compatible DNA Methylation profile

WHO Diagnostic Criteria: Medulloblastoma, SHH-activated and TP53-wild type

Essential:
Medulloblastoma
AND
Wildtype TP53
AND
SHH pathway activation
OR
Compatible DNA Methylation profile

WHO Diagnostic Criteria: Medulloblastoma, Non-WNT/non-SHH

Essential:
Medulloblastoma
AND
No WNT or SHH pathway activation
OR
DNA Methylation profile aligned with group 3 or 4

WHO Diagnostic Criteria: Medulloblastoma, SHH-activated and TP53-mutant

Essential:
Medulloblastoma
AND
Mutant TP53
AND
SHH pathway activation
OR
Compatible DNA Methylation profile

WHO Diagnostic Criteria: Classic Medulloblastoma, Histologically defined

Essential:
Medulloblastoma
AND
Absence of histological features qualifying for the diagnosis of desmoplastic/nodular medulloblastoma or medulloblastoma with extensive nodularity
AND
Absence of predominant areas with severe cytological anaplasia and/or large cell cytology
AND
Retained expression of SMARCB1

Atypical Teratoid/Rhabdoid Tumor (“*AT/RT*”) **WHO grade 4**

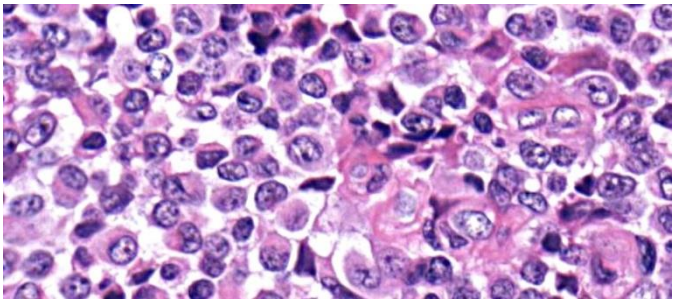
High-grade malignancy composed of poorly-differentiated cells and a variable number of rhabdoid cells, with the potential to differentiate along neuroepithelial, epithelial, and mesenchymal lines

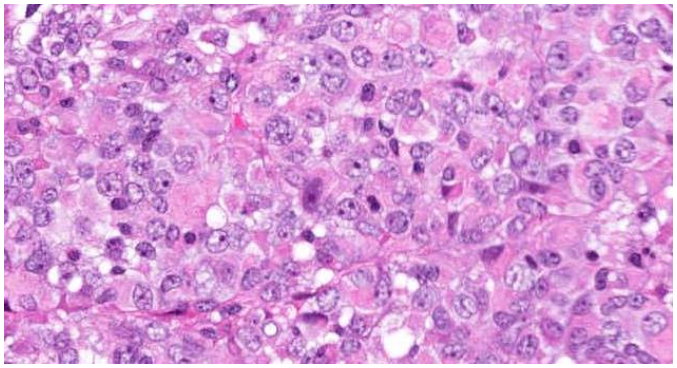
Most often in **young children**. Variable location.

Heterogeneous morphology.
Classic: **Rhabdoid cells** with eccentric nuclei with vesicular chromatin and prominent nucleoli. Abundant **mitoses**. Geographic **necrosis**.

Most tumors contain *other* poorly-differentiated elements with neuroectodermal, epithelial, and/or mesenchymal differentiation, including a small cell embryonal component, spindle cell component, or even gland-like areas.

Virtual slide





Molecular/IHC (required for Dx): **Loss of SMARCB1 (INI1)** or (rarely) SMARCA4 (BRG1)—part of SWI/SNF chromatin remodeling complex.
(+)EMA, SMA, Vimentin
(+/-)GFAP, CK, Synaptophysin, NFP
Ki67 usually >50%

Aggressive course.

If INI1 and BRG1 are intact (or you are unable to test for these)→ “*CNS embryonal tumor with rhabdoid features*”

***WHO Diagnostic Criteria*:**
Atypical teratoid/Rhabdoid tumor

Essential:
A CNS embryonal tumor with a polyimmunophenotype
AND
Loss of nuclear SMARCB1 or SMARCA4 expression
OR (for unresolved lesions)
Compatible DNA methylation profile

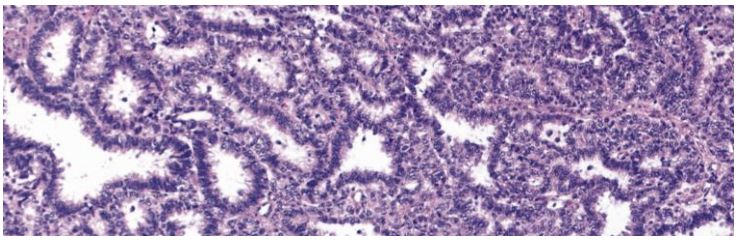
Desirable:
Rhabdoid cells
SMARCB1 or SMARCA4 alteration

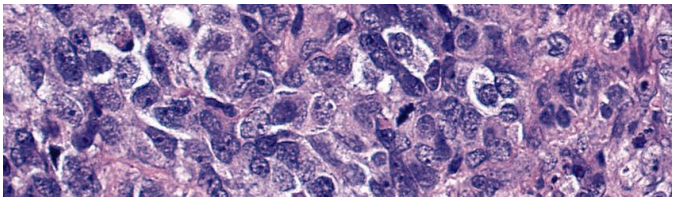
Cribriform Neuroepithelial Tumor (“*CRINET*”)

***Provisionally* defined** as:
Non-rhabdoid neuroectodermal tumor with cribriform strands and ribbons, showing loss of nuclear SMARCB1

Presents in **Childhood**. Located in **ventricles**. Previously often diagnosed as Choroid plexus carcinoma, but negative for Kir7.1.

Seem to respond to therapy with long-term survival (limited data, not graded yet)



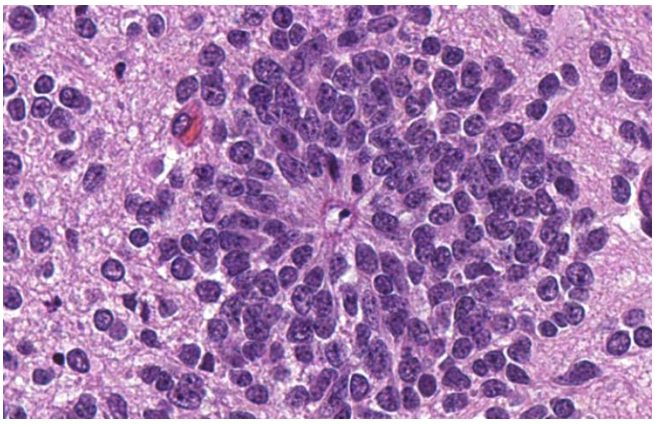


***WHO Diagnostic Criteria*:**
Cribriform Neuroepithelial Tumor

Essential:
Highly cellular tumor characterized by the presence of cribriform strands and ribbons
AND
Loss of nuclear SMARCB1 expression in tumor cells

Desirable:
Distinct expression of EMA highlighting cell surfaces

Embryonal Tumor with Multilayered Rosettes



CNS WHO grade 4

Defining molecular alteration: **C19MC** (microRNA) **upregulation** via amplifications and fusions. Rarely, DICER1 mutations (in syndrome setting).

Multilayered rosettes consisting of pseudostratified neuroepithelium with a central, round or slit-like lumen. Numerous mitotic figures. Fibrillary neuropil-like areas.

Variable morphology, in one of 3 patterns on a spectrum:
1) Embryonal tumor with abundant neuropil and true rosettes (classic, name describes morphology),
2)Ependymoblastoma (Numerous rosettes, little neuropil),
3)Meduloepithelioma (Papillary/tubular/trabecular neoplastic neuroepithelium resembling primitive neural tube)

Often **young children**. Most often cerebral.

Aggressive course.

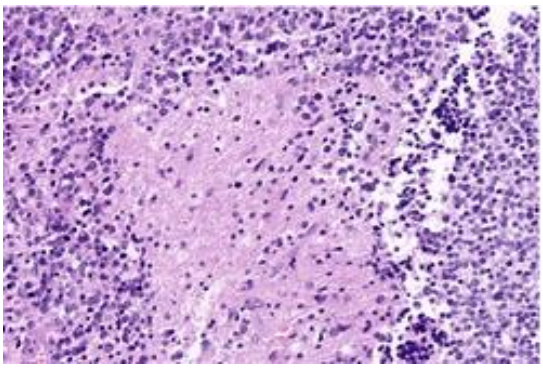
***WHO Diagnostic Criteria*:**
Embryonal tumor with Multilayered Rosettes

Essential:
A CNS embryonal tumor with the morphological and immunohistochemical features of one of the three patterns:
- Embryonal tumor with abundant neuropil and true rosettes
- Ependymoblastoma
- Meduloepithelioma

AND
Genetic alteration defining of the two molecular subtypes:
- C19MC alteration
- DICER1 mutation

AND (for unresolved cases)
Compatible DNA Methylation profile

CNS Neuroblastoma, FOXR2-activated



CNS WHO grade 4

Defining molecular alteration: **FOXR2 activation by structural rearrangements**

Embryonal neoplasm (poorly differentiated high N:C ratio cells with hyperchromatic nuclei) **with varying degrees of neuroblastic and/or neuronal differentiation, including foci of ganglion cells and neuropil-rich stroma.**

Often **young children**. Most often cerebral.

Aggressive course.

IHC: (+) OLIG2, TTF1; (-) GFAP, Vimentin

***WHO Diagnostic Criteria*:**
CNS Neuroblastoma, FOXR2-activated

Essential:
An embryonal tumor with foci of neuroblastic or neuronal differentiation
AND
Activation of FOXR2 by structural rearrangement and fusion
OR (for unresolved cases)
Compatible DNA Methylation profile

CNS Tumor with BCOR internal tandem duplication

Defining molecular alteration: **internal tandem duplication in exon 15 of BCOR**

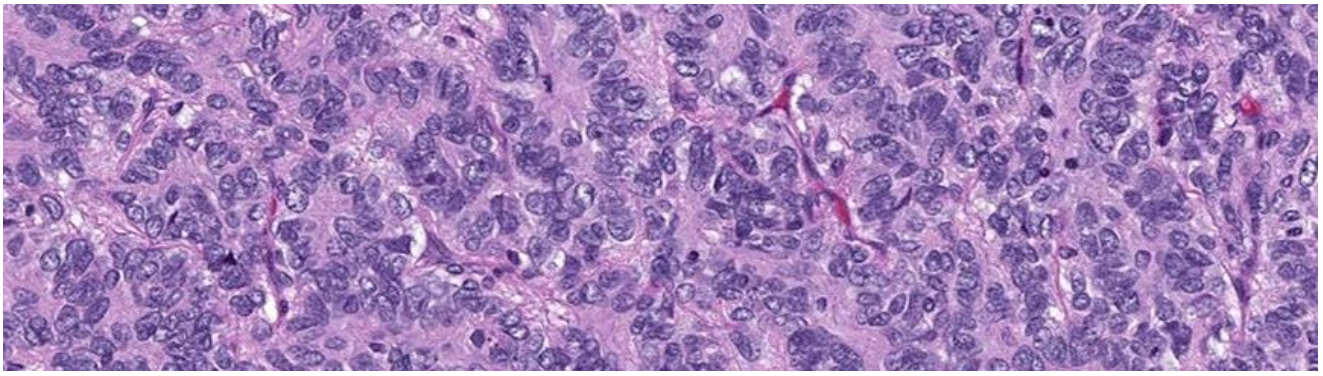
Focal pseudorosette formation.
Usually kids in cerebrum or cerebellum.

Not currently graded.

IHC: (+) BCOR, CD56, Vimentin;
(+/-) OLIG2, GFAP, S100

***WHO Diagnostic Criteria*:**
CNS Tumor with BCOR internal tandem duplication

Essential:
A malignant primary CNS tumor with a predominantly solid growth pattern, uniform oval or spindled cells with round to oval nuclei, and a dense capillary network
AND
An internal tandem duplication in exon 15 of BCOR
AND (for unresolved cases)
Compatible DNA Methylation profile



CNS Embryonal Tumor, NEC/NOS

Poorly-differentiated embryonal tumors of neuroectodermal origin that do not have the histopathologic/molecular alterations of the tumors listed above.

High-grade with aggressive clinical courses.

***WHO Diagnostic Criteria*:**
CNS Embryonal Tumor, NEC/NOS

Essential:
An Embryonal tumor originating in the CNS
AND
Absence of criteria qualifying for the diagnosis of a more specific type of embryonal CNS tumor

***Desirable*:**
Focal expression of neuronal markers and absence of glial markers

Biomarkers that might help in the classification of small cell, embryonal-appearing tumors:

Biomarker	Associated Tumor
C19MC amplification or LIN28A expression	Embryonal tumor with multilayered rosettes
SMARCB1 or SMARCA4 loss	Atypical Teratoid/Rhabdoid Tumor
H3 K27 mutations	Diffuse Midline Glioma, H3 K27M-mutant
C11orf95-RELA fusion gene or L1CAM expression	Supratentorial ependymoma
IDH1 or IDH2	Adult-type diffuse gliomas
CTNNB1 mutations (nuclear β-catenin)	Medulloblastoma, WNT-activated
GAB1 or YAP1 staining	Medulloblastoma, SHH-activated

Modified from: WHO Classification of Tumors of the Central Nervous System. 4th Edition. 2016.

Pineal Tumors

Often block aqueduct→ increased intracranial pressure→ Headache, papilledema, brainstem/cerebellar dysfunction (ataxia), nausea, etc..

Pineocytoma **CNS WHO grade 1**

Exclusive localization in **pineal region**

Two morphologic patterns:

1) **Uniform, small, mature cells** (resembling normal pineal cells) **that grow primarily in sheets and often form large pineocytomatous rosettes** (not in normal pineal gland)

2) Pleomorphic cells showing gangliocytic differentiation

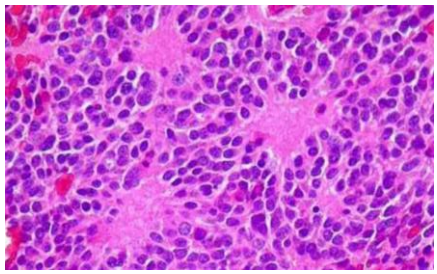
Round nuclei with fine chromatin. Lots of processes.

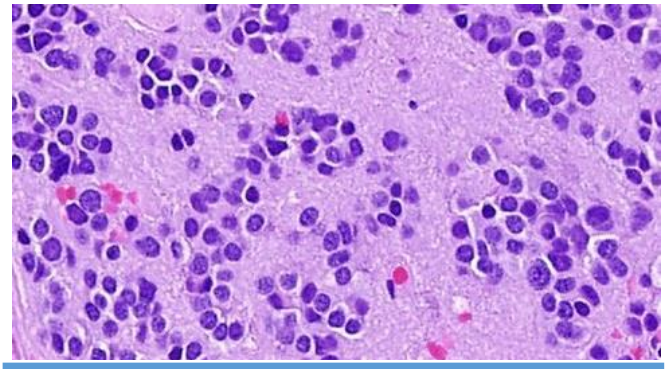
No mitotic activity (<1 per 10 HPF). Ki67 usually <1%.

Rare. Usually **adults**.

Well-demarcated, solid mass without infiltration or dissemination.

Good prognosis.





***WHO Diagnostic Criteria*: Pineocytoma**

Essential:
Demonstration of pineal parenchymal differentiation by histopathological and immunophenotypic features (e.g., positivity for synaptophysin)
AND
Absence of qualifying criteria for the diagnosis of PPTID or Pineoblastoma
AND
Low proliferative/mitotic activity
AND
Pineal region location

Pineal Parenchymal Tumor of Intermediate Differentiation ("*PPTID*")

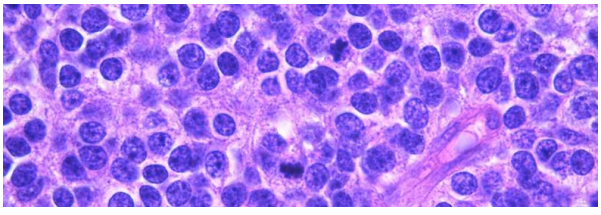
Intermediate malignancy *between* Pineoblastoma and Pineocytoma.

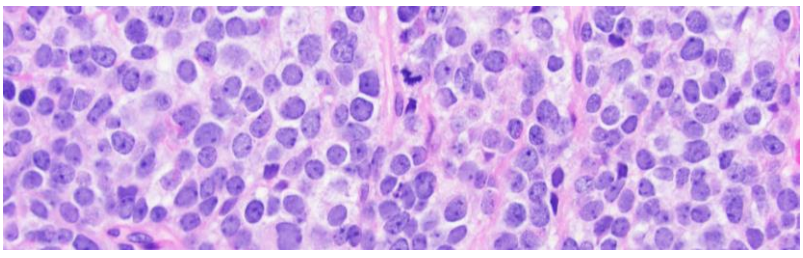
Diffuse sheets or large lobules of monomorphic round cells that appear more differentiated than in pineoblastoma.
Pleomorphic cells may be present.

Mitotic activity low to moderate.
Ki67 elevated (often >5%)

Mainly adults.
CNS WHO Grade 2-3 (Variable outcome): Majority correspond to CNS WHO grade 2, but some behave more like 3.
No current grading criteria

Molecular: Small in-frame KBTBD4 recurrent insertions.





***WHO Diagnostic Criteria*: PPITD**

Essential:
Demonstration of pineal parenchymal differentiation by histopathological and immunophenotypic features (e.g., positivity for synaptophysin)
AND
Increased proliferative/mitotic activity
AND
Absence of qualifying criteria for pineoblastoma
AND
Pineal region location
AND (for unresolved cases)
Compatible DNA methylation profile

Desirable:
Molecular demonstration of KBTBD4 in-frame insertions

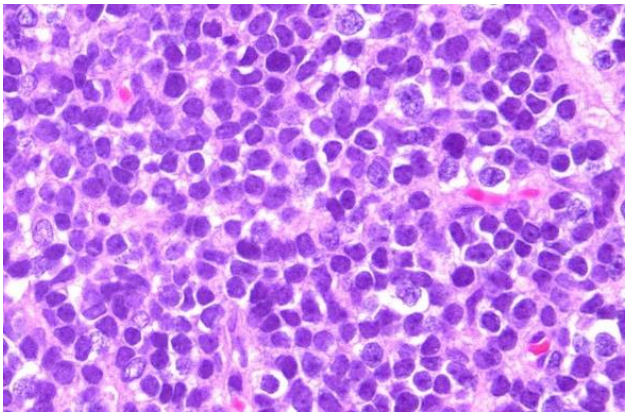
Pineoblastoma **CNS WHO grade 4**

Resembles other embryonal tumors (e.g., medulloblastoma)
Poorly-differentiated, highly cellular embryonal tumor.
Patternless sheets of small immature neuroepithelial cells.
High N:C ratio. Hyperchromatic.
Frequent mitoses. Ki67 >20%. Necrosis common.
No pineocytomatous rosettes, but may see Homer-Wright rosettes

Most often children.
Invade nearby structures and spread via CSF.

Aggressive clinical course.

DNA methylation profiling splits into 4 groups with variable survival.



***WHO Diagnostic Criteria*: Pineoblastoma**

Essential:
Histopathological features of an embryonal tumor
AND
High proliferative/mitotic activity
AND
Pineal region location

Desirable:
Retained SMARCB1 (INI1) staining
Compatible DNA methylation profile

Papillary Tumor of the Pineal Region

Neuroepithelial tumor with a combination of papillary and solid areas with epithelial-like cells and immunoreactivity for cytokeratins. Also, ependymal-like areas with pseudorosettes
Nuclei mostly round and stippled.
Moderate mitoses with moderate Ki67 (median ~7%)

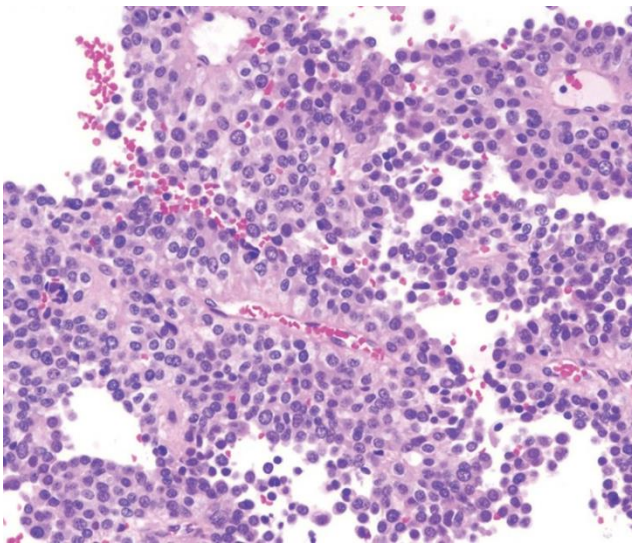
IHC: React with cytokeratins (unique), S100, NSE, (-/+)EMA. (+/-) GFAP. (-)NF

CNS WHO grade 2 or 3 (usually behave like 2; No criteria)

Frequent local recurrences.

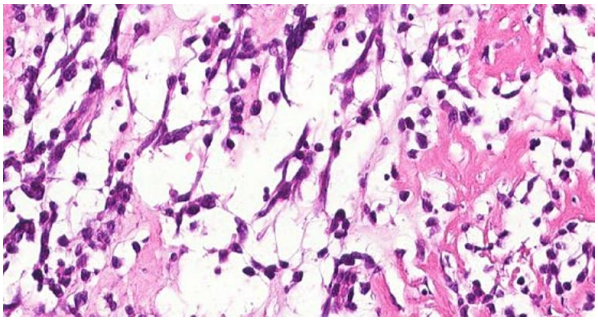
***WHO Diagnostic Criteria*: Papillary tumor of the pineal region**

Essential:
Papillary pattern with epithelial-like cells
AND
Characteristic immunohistochemical staining (e.g. + CK, CD56, SPDEF)
AND
Pineal region location
AND (for unresolved cases)
Compatible DNA Methylation profiling



Desmoplastic myxoid tumor of the pineal region, SMARCB1-mutant

Rare. Not graded.
Often younger adults.
Dense cords of small to medium-sized oval to spindled and epithelioid cells embedded in a heavily collagenized matrix.
Very low proliferation/mitotic activity. Ki67 ~3%
IHC: (+)CD34, EMA; (-) INI1 (SMARCB1)



***WHO Diagnostic Criteria*:**
DMT

Essential:
Desmoplasia and myxoid changes
AND
Lack of histopathologic changes of malignancy
AND
Pineal region Loss of tumor SMARCB1 expression
AND (for unresolved cases)
Compatible DNA methylation profile

Cranial and Paraspinal nerve tumors

See my "*Soft tissue tumor*" Notes for a complete discussion of peripheral nerve sheath tumors.

Here, I've focused on the one *unique* to the CNS.

Cauda Equina Neuroendocrine Tumor

Previously, "Paraganglioma" **CNS WHO grade 1**

Neuroendocrine neoplasm arising from specialized neural crest cells of the cauda equina/filium terminale.

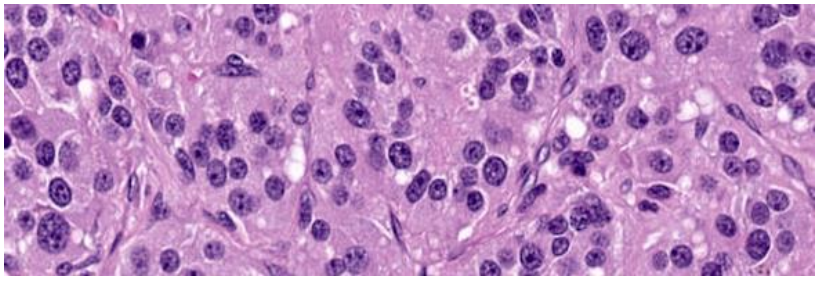
Chief cells arranged in nests or lobules ("Zellballen," cell balls), surrounded by a single layer of sustentacular cells and delicate capillaries with reticulin.

Chief cells have central round nuclei with stippled chromatin. Eosinophilic granular cytoplasm.

Can see ganglion cells and/or Schwannian stroma ("Gangliocytic neuroendocrine tumors").

IHC:
Chief cells: (+)Synaptophysin, Chromogranin, CK; (+/-) S100
Sustentacular cells: (+/-)S100, SOX10, GFAP.

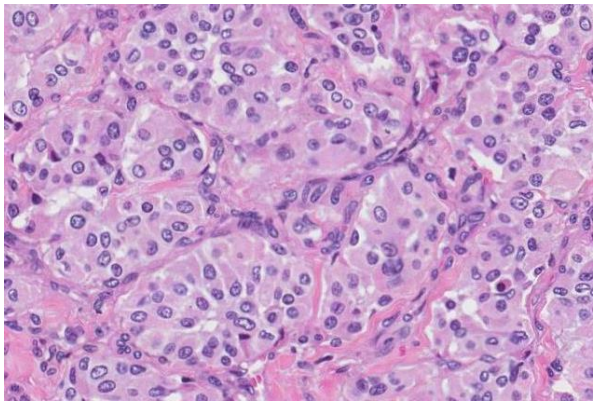
Usually adults with nonspecific symptoms like pain.
Rarely functional/secreting.



***WHO Diagnostic Criteria*:**
Cauda Equina NET

Essential:
Well-demarcated tumor with Zellballen architecture
AND
Synaptophysin or chromogranin immunoreactivity in chief cells
AND
Cauda equina location
AND (for unresolved cases)
Compatible methylation profile

Desirable:
S100-positive sustentacular cells
Cytokeratin-positive chief cells
Reticulin stain showing typical architecture



Dural Tumors

Meningioma

Dural, mostly benign, slow-growing.
Likely derived from Meningothelial cells of arachnoid layer.
Most frequent brain tumor in USA.
Often **older adults** (risk increases with age).
More common in females.

General classic findings:
Oval nuclei with delicate chromatin.
Frequent **intranuclear pseudoinclusions**.
Syncytial tumor cells with abundant eosinophilic cytoplasm.
Numerous **whorls**. Occasional **psammoma bodies**.
Virtual slide 1 2 3 4 Smear

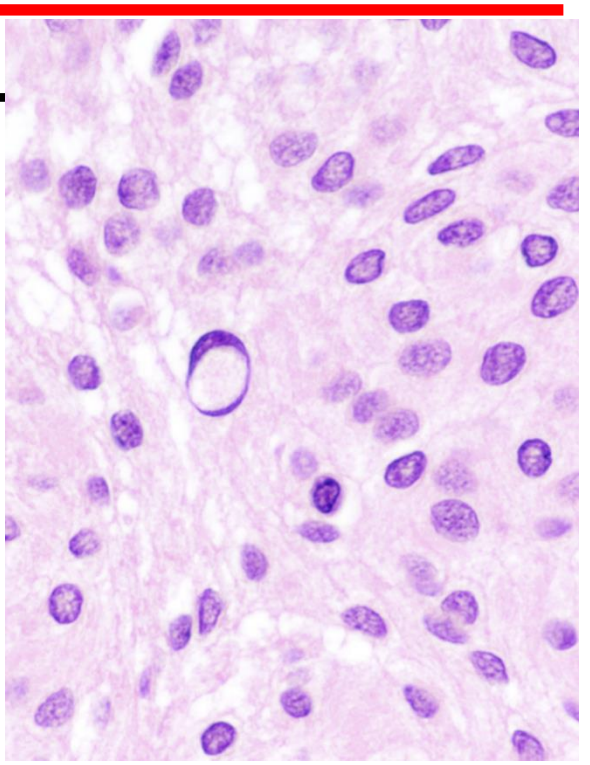
On imaging have **"dural tail"** and MRI uniform contrast-enhancement. **Grossly rubbery/firm.**

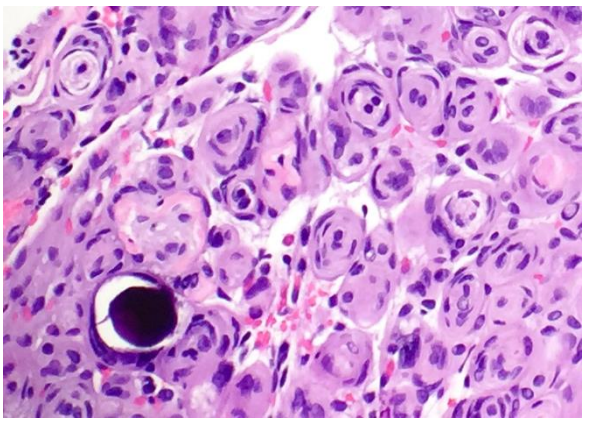
IHC: (+) Somatostatin Receptor 2A (SSTR2A) is likely the most sensitive/specific. Also, **(+) EMA, Vimentin, PR.** (+/-) S100. Ki67 varies with grade (grade 2 is often >4% and 3 is >20%).

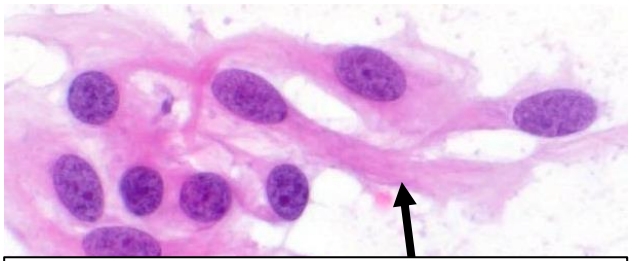
Molecular: **NF2 mutations and/or 22q deletions common.** Genetic changes are strongly associated with different subtypes but do not define them.

Variable histologic findings with multiple subtypes (see next page). Now, grades are assigned *regardless* of subtype.

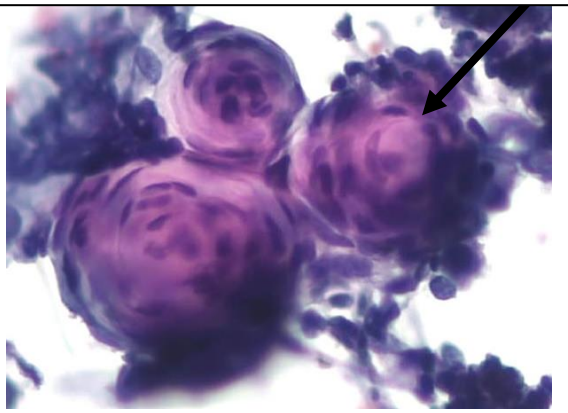
Outcome is associated with grade.
Higher grade = more likely to recur/progress







Intraoperative smears showing nuclei and whorls

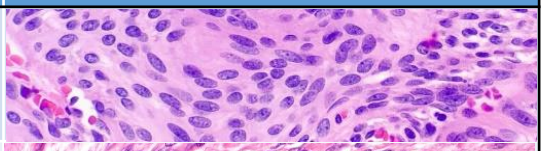
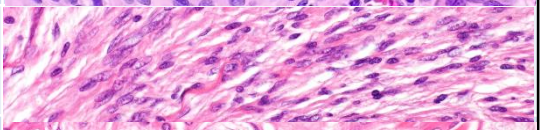
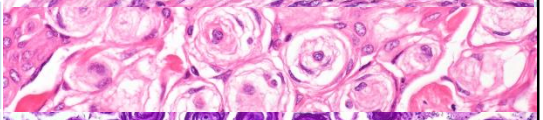
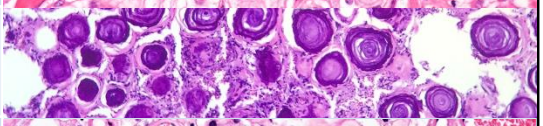
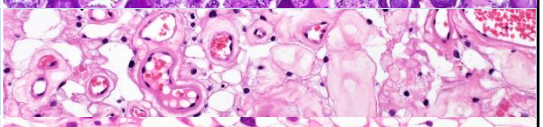
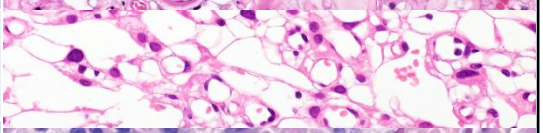
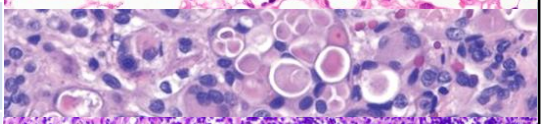
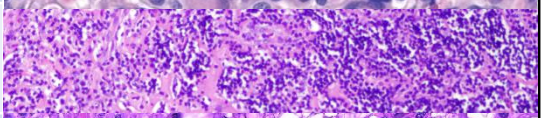
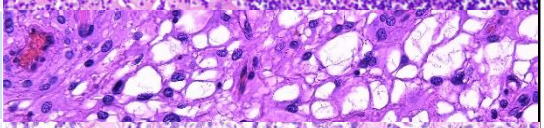
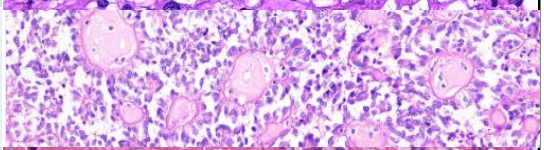
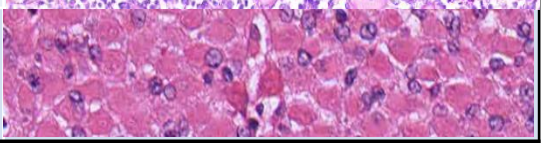
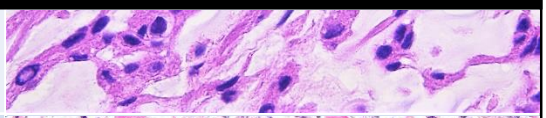
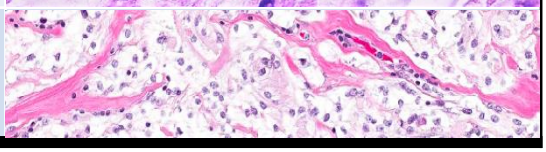


***WHO Diagnostic Criteria*: Meningioma**

Essential:
Classic histopathological features matching at least one of the meningioma subtypes
OR
Suggestive histopathological features combined with biallelic inactivation of NF2 or other classic drivers of conventional meningioma (TRAF7, ATK2, KLF, SMO, PK3CA), Clear cell meningioma (SMARCE1), or rhabdoid meningioma (BAP1)
OR
Suggestive histopathologic features combined with one of the defined DNA methylation classes of meningioma

Desirable:
Meningeal localization
EMA immunoreactivity
Strong and diffuse SSTR2A immunoreactivity
Classic copy number variations

Common Subtypes: Usually want >50% of tumor to have this morphology.
Most common subtypes are meningothelial, fibrous, and transitional.
Grading (see next page) is done regardless of type.
Chordoid and Clear cell meningiomas are automatically assigned a minimum grade of 2. Although Papillary and Rhabdoid meningiomas were previously automatically assigned a grade of 3, this is no longer the case (Nevertheless, they often do end up with a higher grade due to mitotic activity, etc…)

Type	Min. Grade	Description	
Meningothelial	**1**	Classic (typical) morphology as described on previous page. Most common. Lobulated architecture. ATKT1 mutations most common.	
Fibrous	**1**	Spindled cells forming parallel to storiform bundles with abundant collagen matrix. EMA often weak/absent.	
Transitional (mixed)	**1**	Meningothelial + Fibrous with conspicuous whorls and psammoma bodies.	
Psammomatous	**1**	Predominance of psammoma bodies over tumor cells. Often thoracic.	
Angiomatous	**1**	Numerous blood vessels (often more endothelial than meningothelial cells!)	
Microcystic	**1**	Cells with thin, elongated processes and creating a cobweb-like background.	
Secretory	**1**	Focal epithelial differentiation→ intracellular lumina with PAS-positive secretions (“pseudopsamomma bodies”).	
Lymphoplasmacyte -rich	**1**	Extensive chronic inflammatory infiltrates, often overshadowing meningothelial cells.	
Metaplastic	**1**	Has a mesenchymal component (osseous, cartilaginous, myoid, lipomatous, or xanthomatous)	
Papillary	**1** (but often higher)	Perivascular pseudopapillary pattern. Loss of cell cohesion. Resembles pseudorosettes.	
Rhabdoid	**1** (but often higher)	Rhabdoid cells (plump cells with eccentric nuclei, open chromatin, prominent nucleoli, and eosinophilic cytoplasmic inclusions). BAP1 loss by IHC.	
Chordoid	**2**	Cords or trabeculae of eosinophilic, often vacuolated cells, set in mucoid matrix (like chordoma).	
Clear cell	**2**	Polygonal cells with clear, glycogen-rich cytoplasm and prominent perivascular and interstitial collagen. Sheet-like & patternless. Loss of SMACE1.	

CNS WHO Grade 2 *("Atypical meningioma")*

4 to 19 mitotic figures in 10 consecutive HPF of each 16 mm^2 (at least 2.5/mm^2)
OR
Unequivocal brain invasion (not perivascular spread or indentation of brain without pial breach)
OR
At least 3 of the following:
- Increased cellularity
- Small cells with high N:C ratio
- Prominent nucleoli
- Sheeting (uninterrupted patternless or sheet-like growth)
- Foci of spontaneous (non-iatrogenic) necrosis

Virtual slide 2

CNS WHO Grade 3 *("Anaplastic (malignant) meningioma")*

20 or more mitotic figures in 10 consecutive HPF of each 16 mm^2 (at least 12.5/mm^2)
OR
Frank anaplasia (sarcoma-, carcinoma-, or melanoma-like appearance)
OR
TERT promoter mutation
OR
Homozygous deletion of CDKN2A and/or CDKN2B

Solitary Fibrous Tumor ("SFT")

Fibroblastic tumor with a histologic spectrum (previously considered 2 entities, SFT and "Hemangiopericytoma," but united by genetics into just SFT).

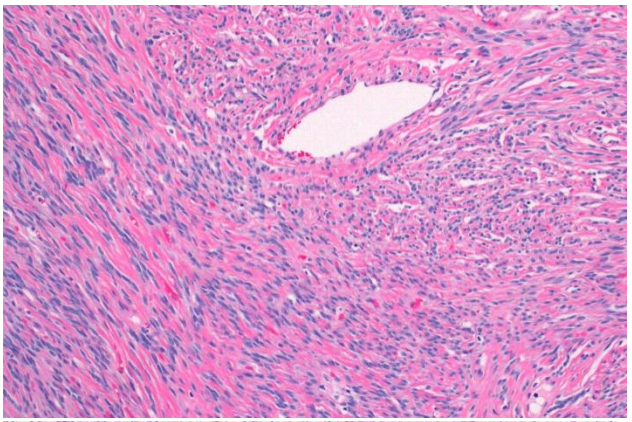
Usually **Dural** and **supratentorial**.

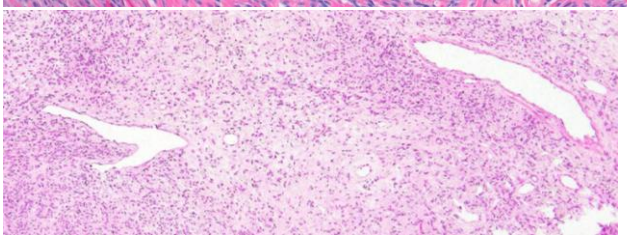
Spindled to ovoid monomorphic cells
"Patternless pattern" of short fascicles with alternating hyper and hypocellular areas with thick collagen bands.

Large, open, branching, thin-walled "**Staghorn**" hyalinized vessels.

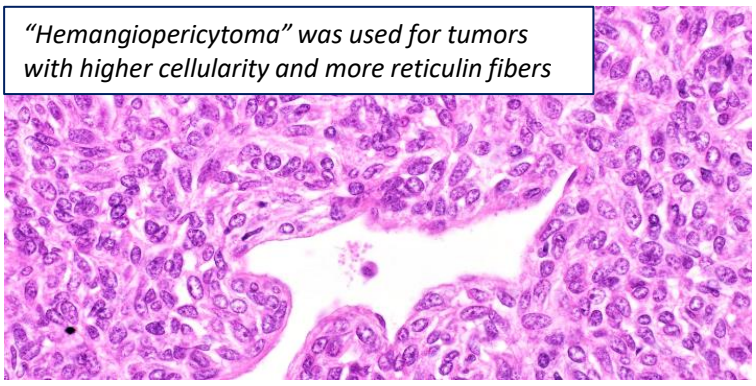
Molecular/IHC: NAB2-STAT6 fusion, best identified with **STAT6 IHC**. Also, (+) CD34, CD99

CNS WHO Grading:
Grade 1: <2.5 mitoses/mm^2 (<5 mitoses/10 HPF)
Grade 2: ≥2.5 mitoses/mm^2 (≥5 mitoses/10 HPF)
Grade 3: Above plus necrosis





"Hemangiopericytoma" was used for tumors with higher cellularity and more reticulin fibers



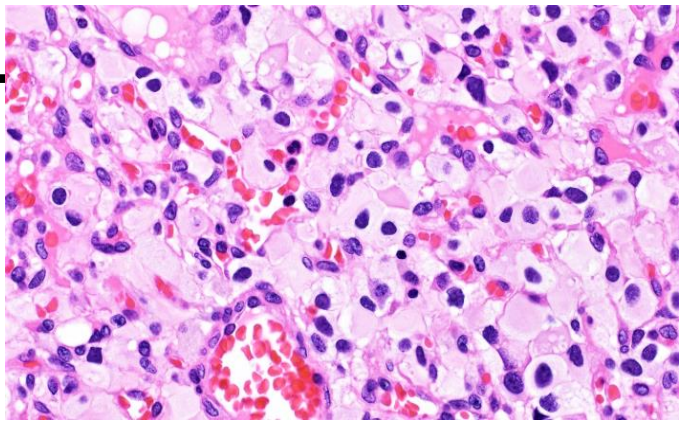
WHO Diagnostic Criteria: Solitary Fibrous Tumor

Essential:
Variably cellular tumor composed of spindled to ovoid cells arranged around a branching and hyalinized vasculature
AND
Variable stromal collagen deposition
AND
STAT6 nuclear expression

Desirable (in select cases):
Demonstration of NAB2::STAT6 gene fusion

Unique Mesenchymal Tumors

Hemangioblastoma **WHO grade 1**



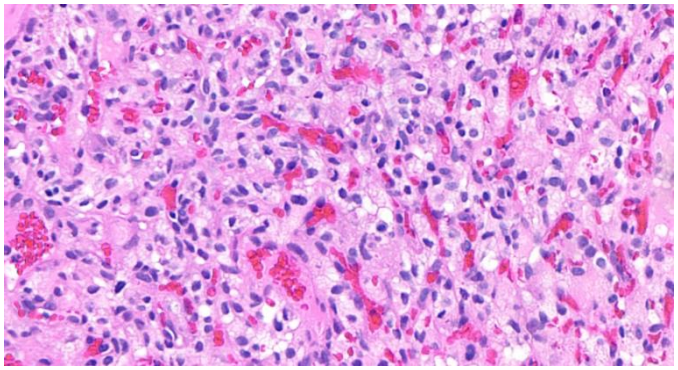
Two characteristic components:
1)Large stromal cells that are vacuolated with often clear cytoplasm.
2) Abundant vascularity

Most common in **Adults**.
Most common in **cerebellum**. Can get anywhere.
Associated with **Von Hippel-Lindau disease**.

Molecular: VHL tumor suppressor inactivated in both sporadic and VHL-associated cases

IHC: **Stromal cells (+) Inhibin**, **D2-40, Brachyury** (cytoplasmic); Endothelial cells express vascular markers (+ CD31, CD34, ERG…)

Important to differentiate from metastatic clear cell RCC, especially if in setting of VHL disease! In contrast, RCC stains with: PAX8, AE1/AE3, EMA



***WHO Diagnostic Criteria*: Hemangioblastoma**

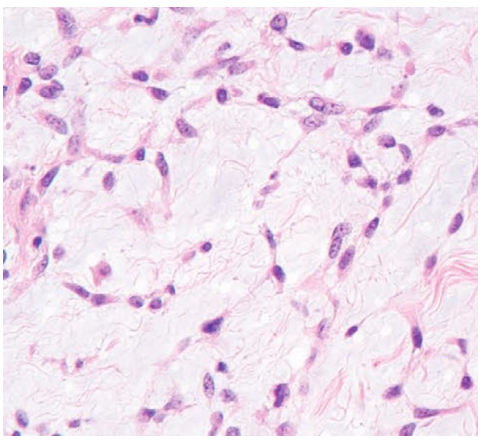
Essential:
A tumor composed of large, multivacuolated, and lipidized stromal cells with occasional hyperchromatic nuclei, as well as a rich capillary network.
AND
Stromal cells with immunohistochemistry positivity for markers such as inhibin (at least focally)
OR
Loss or inactivation of VHL gene
OR
In a patient with von Hippel-Lindau syndrome

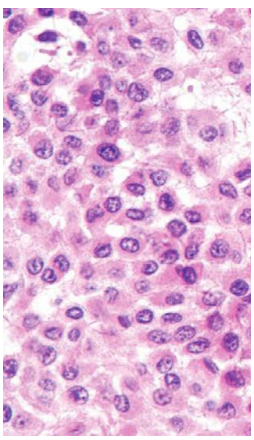
Desirable:
In patients with VHL syndrome, absence of immunohistochemical staining for markers of RCC.

Virtual slide 1 2 3

Intracranial mesenchymal tumor, FET::CREB fusion-positive

Provisional entity. Variable morphology. Defined by fusion of FET RNA-binding protein family gene (usually EWSR1, rarely FUS) with a member of the CREB family of transcription factors (CREB, ATF1, or CREM). Usually children or young adults.



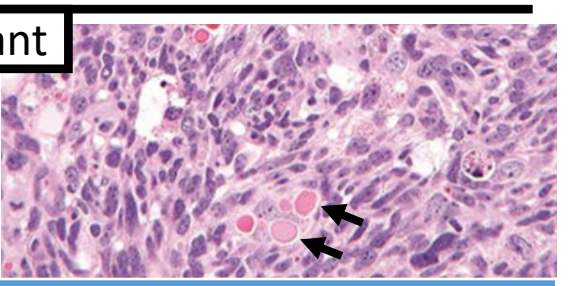


***WHO Diagnostic Criteria*:**

Essential:
Primary intracranial neoplasm
AND
Variable morphological features including spindle cells, mucin-rich stroma, hemangioma-like vasculature, or epithelioid cells in a mucin-poor collagenous stroma
AND
Demonstration of a FET::CREB family fusion

Desirable:
CD99, EMA, and desmin immunoreactivity

Primary intracranial sarcoma, DICER1-mutant



Very rare. Usually younger **kids.**

Primary intracranial sarcoma composed of spindled or pleomorphic cells, often with eosinophilic cytoplasmic globules.

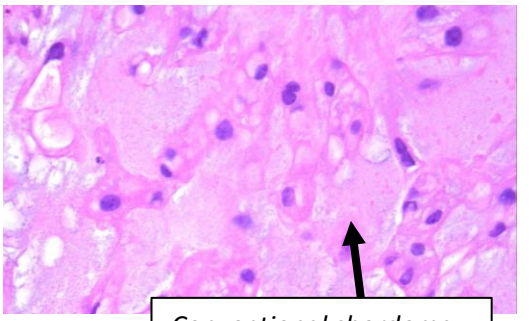
Defined by DICER1 mutation (germline or somatic)

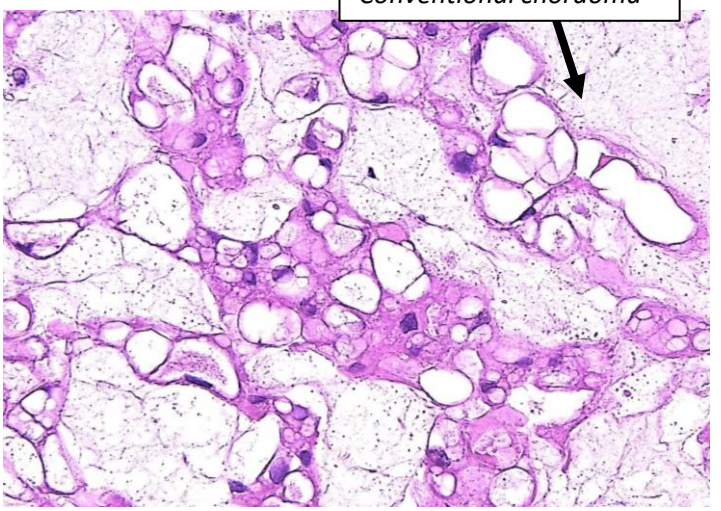
IHC: Often muscle differentiation (+ SMA, desmin; +/- Myogenin).
Also, sometimes cartilaginous differentiation.

***WHO Diagnostic Criteria*:**

Essential:
Primary intracranial sarcoma
AND
Pathogenic DICER1 mutation (germline or somatic)
AND (for unresolved cases)
Compatible DNA methylation profile

Chordoma





Family of bone tumors demonstrating **notochordal differentiation**. Almost always arise from **axial skeleton**, particularly in the skull base (**clivus**) and **sacrococcygeal region**.

Lobules separated by fibrous stroma.
Cells arranged in cords or ribbons separated by myxoid matrix.
Large cells with **clear to eosinophilic cytoplasm** that vacuolated or **bubbly** ("***physaliphorous***," Greek for having bubbles)

IHC: **(+) Brachyury**, S100, CK, EMA
Virtual slide 2

***WHO Diagnostic Criteria*:**

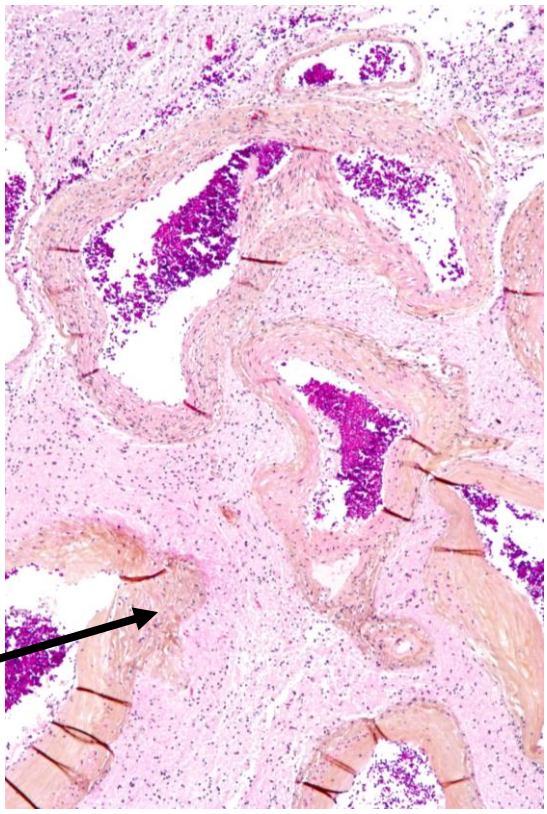
Essential:
Midline axial bone tumor
AND
Lobules of cohesive and physaliphorous cells in myxoid or chondroid matrix
AND
Brachyury immunopositivity
AND (in the case of epithelioid/solid forms)
Loss of SMARCB1 (INI1) expression

	Conventional chordoma	Chondroid chordoma	Dedifferentiated chordoma	Poorly-differentiated chordoma, SMARCB1-deficient
Clinical	Adult	Adult	Adult, sometimes after radiation	Kids
Histology	Classic	Chondroid matrix	High-grade Sarcomatous areas	Epithelioid (no physaliphorous) and solid growth
IHC	(+) CK, EMA, S100, Brachyury Intact INI1		(+/-)Brachyury, S100 (-) CK, EMA, Intact INI1	Loss of INI1 (+) Brachyury, CK, S100, EMA
Outcome	Frequent local progression (~50%). Rare metastases (<10%)		Frequent metastases (~30%). Frequent local progression (~50%)	

Modified from: WHO Classification of Tumors of the Central Nervous System. 5th Edition. 2021.

Other Mesenchymal tumors

Pretty much any mesenchymal tumor can involve the CNS!
For more details, refer to separate Soft Tissue/Bone Guides.



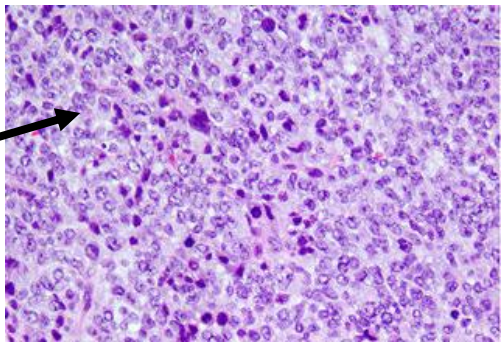
Hemangiomas and Vascular malformations:
Benign vascular lesions. Often typical neuroimaging findings.

Hemangiomas are usually in the spine and consist of tightly packed capillary-sized and cavernous vessels.

Cavernous malformations are most common supratentorially and consist of multiple tightly packed sinusoidal vessels with fibrotic walls lacking arterial or venous features, with little or non interposed CNS tissue.

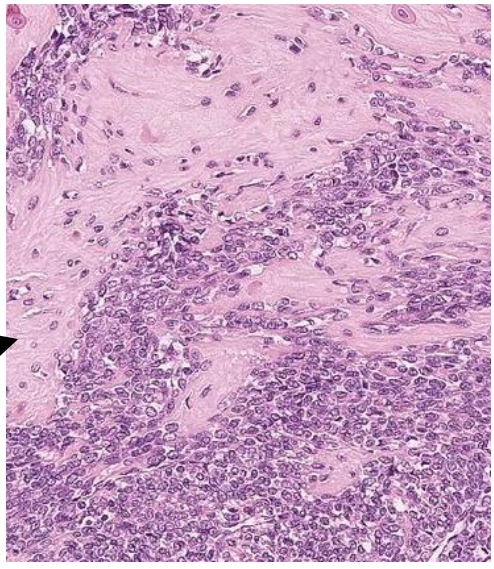
Cerebral arteriovenous malformations (AVM) are fast-flow vascular anomalies of arteriovenous connections through a nidus or fistula of malformed arteries and veins with intervening brain tissue and gliosis. Virtual slide 2

Ewing Sarcoma: Small round blue cell tumor, similar to what is seen in bone (and elsewhere). Diffuse CD99 membranous expression. FET::ETS fusions (usually involving EWSR1). Frequent NKX2.2 and/or PAX7 expression.



CIC-rearranged Sarcomas: High-grade, poorly-differentiated sarcoma defined by the presence of CIC fusion with different gene partners. Undifferentiated small round blue cells. Frequent necrosis. WT-1 often positive. CD99 usually patchy/weak (vs diffuse in Ewing).

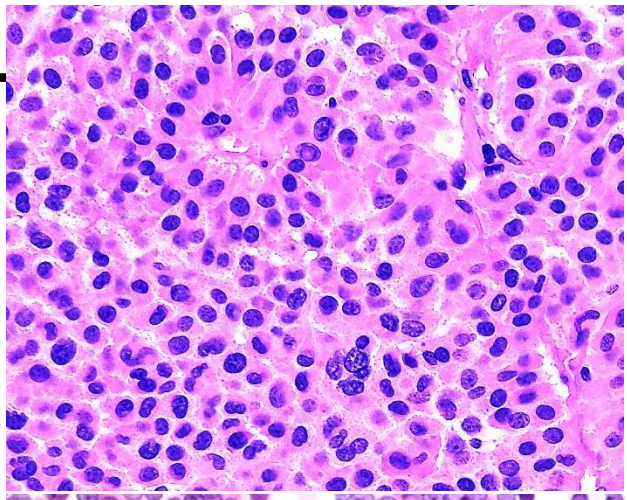
Rhabdomyosarcoma: Family of malignant primitive tumor with at least focal immunohistochemical demonstration of skeletal muscle lineage (by staining with MyoD1 and/or Myogenin) and an absence of a non-rhabdomyosarcomatous component. More common in kids. Like elsewhere, most common subtypes are embryonal and alveolar (see soft tissue notes)

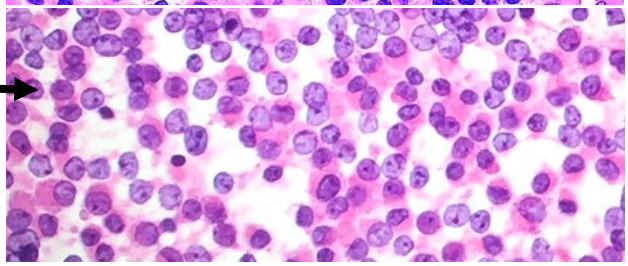


Mesenchymal chondrosarcoma: Poorly-differentiated tumor composed of small round blue cells with high N:C ratios and variable amounts of hyaline cartilage. Characteristic HEY1::NCOA2 fusions. Variable IHC with frequent expression of CD99, S100, EMA, Myogenin.

Sellar Tumors

Pituitary Adenoma





aka Pituitary Neuroendocrine Tumor (PitNET)
Most common tumor of sella turcica. Usually **Adults**.
Neoplasm of **anterior pituitary hormone-producing cells**.
Benign, but can invade adjacent structures.

Monomorphic Neuroendocrine cells. Round nuclei.
Variety of histologic growth patterns, including diffuse, papillary, and trabecular (like other NE tumors)
May have eosinophilic or basophilic cytoplasm
May have perivascular orientation.
On touch prep see cellular, discohesive, homogeneous neuroendocrine proliferation

Stains: (+) Synaptophysin, chromogranin; (-)S100
Reticulin shows dissolution of normal network.
(disruption of small normal micro-acini→ larger nests)

Subclassify by hormone secretion, use IHC panel: Growth Hormone (GH), prolactin, TSH-β, ACTH, FSH- β, LH-β, Alpha subunit (α-SU), and pituitary transcription factors: SF-1, TPIT, and PIT1

"Functioning" adenomas→ secrete hormone→ often present early with symptoms/tumor syndrome.
"Silent" adenomas do not secrete hormone, but still stain with hormone IHC.

Non-functional ones often present with mass effect. **Press on optic chiasm→ bitemporal hemianopsia**, diplopia, headache. Usually sporadic, but can occur in MEN1, DICER1 syndrome, etc…
Virtual slide 1 2 Virtual Smear

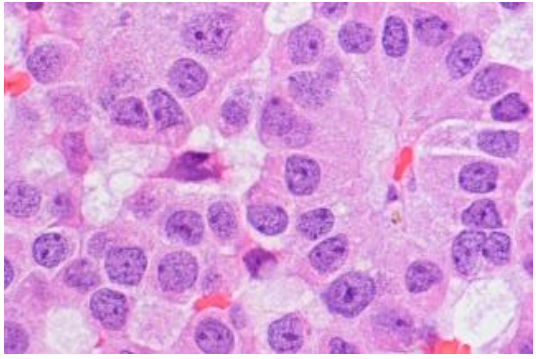
Treatment: Usually Transsphenoidal resection is #1; may also consider pharmacotherapy or radiation

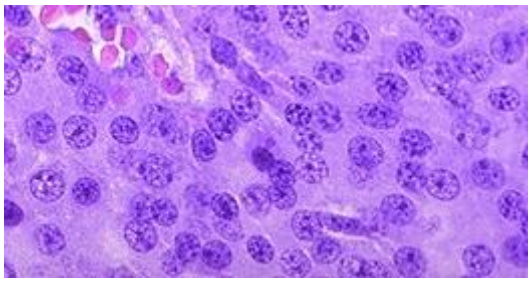
Type	Hormone Secreted	IHC	
Lactotroph	Prolactin	Prolactin, PIT1,	**Most common** (up to ½ of all adenomas). Presentation depends on sex: females present with **galactorrhea** & **amenorrhea**, men present with sexual dysfunction and mass effect.
Corticotroph	ACTH	ACTH, TPIT	Excess glucocorticoid→ **Cushing's Disease**.
Gonadotroph	FSH-β, LH-β, and/or α-SU,	FSH-β, LH-β, α-SU, SF1	Most are non-functioning and present with mass effect. Can result in hypogonadism: menstrual disturbances in women and sexual dysfunction in men.
Somatotroph	Growth Hormone	GH, PIT1,	Present with **gigantism** and/or **acromegaly**. Eosinophilic.
Thyrotroph	TSH	TSH-β, α-SU, PIT1,	Rare. Present with **hyperthyroidism**.
Null Cell	None	None	Present due to mass effect
Plurihormonal	Multiple	Multiple, PIT1	Some established adenoma subtypes excrete 2 hormones, like mammosomatotrophs (GH and prolactin) and are not considered in this group. Presentation depends on hormones.

***WHO Diagnostic Criteria*:**
Pituitary adenoma/Pituitary neuroendocrine tumor (PitNET)

Essential:
Sellar/suprasellar location
AND
Histological features of a low-grade neuroendocrine tumor that display destruction of the normal anterior gland acinar structure
AND
Subclassification based on immunoreactivity for pituitary hormone and/or lineage-specific transcription factors

Desirable:
Reticulin fiber disruption
Low-molecular-weight cytokeratins, in particular for somatotroph and corticotroph tumors.
Tumor proliferation as indicated by either mitotic count or Ki67 expression

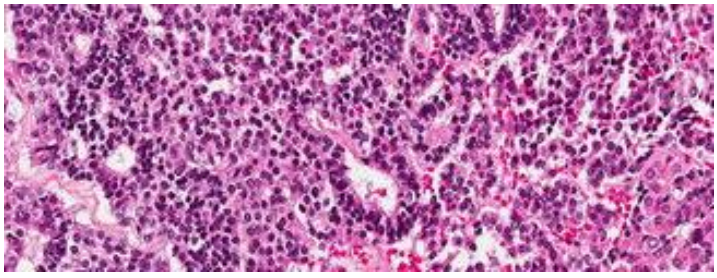




Pituitary Blastoma

Rare developmental tumor seen in <u>young children.</u>

Three components:
1) Primitive blastema-like cells,
2) Neuroendocrine cells,
3) Rathke pouch glands.
IHC: (+) ACTH (-)Prolactin, TSH, FSH, LH
Associated with Cushing disease.
Molecular: **<u>DICER1 mutations</u>**



***WHO Diagnostic Criteria*:**
Pituitary blastoma

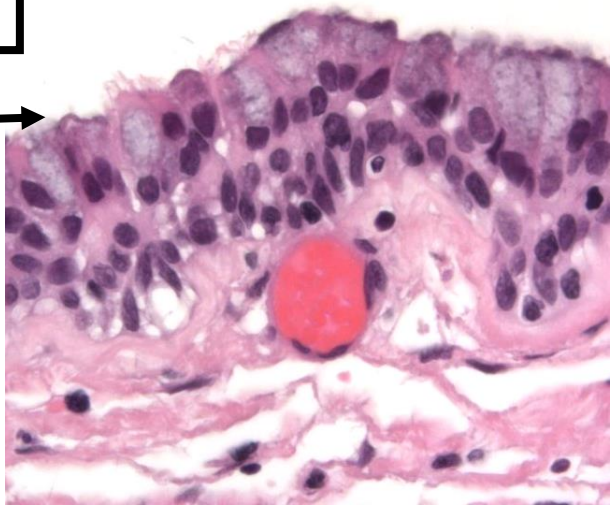
Essential:
Rathke pouch epithelial glands, primitive blastomatous cells, and secretory and folliculostellate anterior pituitary
AND
DICER1 mutation

Desirable:
Diagnosed in children < 2 yrs
Cushing syndrome
Personal or family history of DICER1 syndrome

Non-neoplastic lesions of Rathke's Cleft

<u>No</u> nuclear β-catenin or BRAF V600E staining.

<u>Rathke's Cleft Cyst:</u> Cyst wall lined by columnar or cuboidal epithelium, which is often ciliated with mucinous and goblet cells. May rupture inducing a xanthogranulomatous reaction.



<u>Xanthogranuloma</u>: Cholesterol clefts, foamy macrophages, multinucleated giant cells, chronic inflammation, necrotic debris, and hemosiderin. May see scant epithelium from Rathke's cleft cyst remnants.

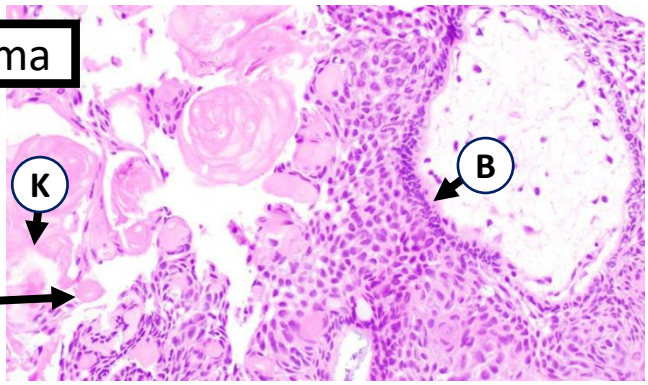
<u>Epidermoid cyst</u>: Unilocular cavity lined by squamous epithelium and filled with dry, flaky keratin (like elsewhere)

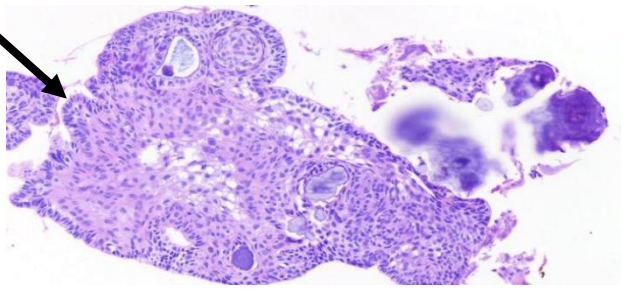
Craniopharyngioma **CNS WHO grade 1**

Benign, epithelial tumors derived from embryonic remnants of Rathke's pouch.
Usually present with mass effect (visual disturbance, headache, or endocrine changes).
Nearby gliosis, Rosenthal fibers and other reactive changes→ can form large part of "mass lesion" and mimic a pilocytic astrocytoma.
Generally favorable prognosis. Treated with surgery. Nevertheless, can recur and rarely transform.
IHC: (+) p63, HMWCK

Adamantinomatous Craniopharyngioma

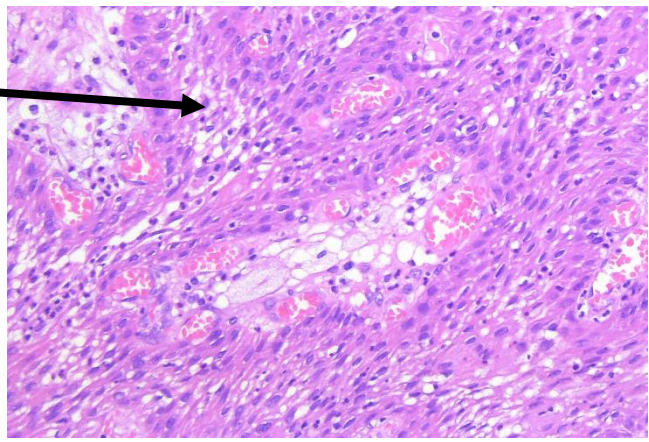
More common.
Bimodal age distribution (1st and 5th decades)
Basal layer with basal palisading (B)
Stellate reticulum (loose background), whorls, "Wet keratin"(K), Calcifications, Cholesterol clefts.
Mixed solid and cystic. Whorls.
Finger-like projections into brain tissue.
IHC/Molecular: **Nuclear expression of β-catenin**
Activating CTNNB1 mutations Virtual slide
Rarely, can undergo malignant transformation.

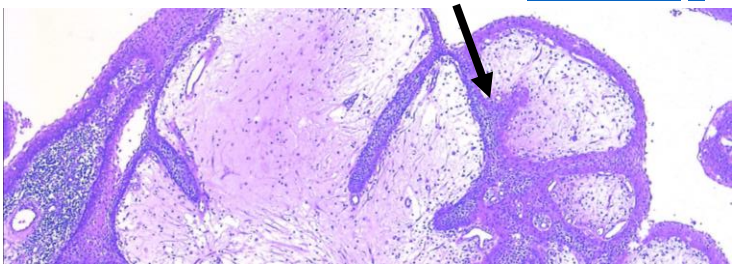




Papillary Craniopharyngioma

Almost exclusively in adults
Resembles a squamous papilloma: Non-keratinizing epithelium covering fibrovascular cores or cyst wall.
Predominantly **Solid**. Well-circumscribed.
Frequent acute inflammation.
NO stellate reticulum or wet keratin. Rare calcifications.
IHC/Molecular: **BRAF V600E mutations**. Virtual slide 2





WHO Diagnostic Criteria: Adamantinomatous craniopharyngioma

Essential:
Tumor in sellar region
AND
Squamous non-keratinizing epithelium, benign
AND
Stellate reticulum and/or wet keratin

Desirable:
Nuclear immunoreactivity for β-catenin
Mutation in CTNNB1
Absence of BRAF V600E mutation

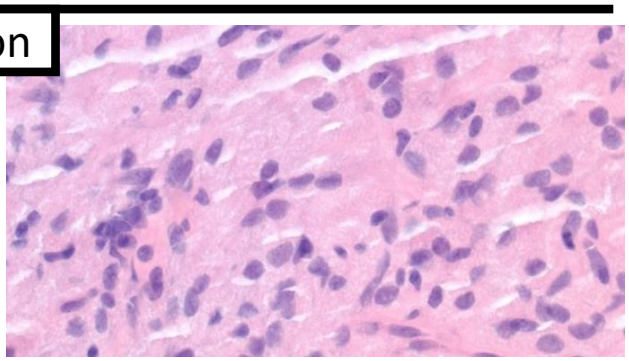
WHO Diagnostic Criteria: Papillary craniopharyngioma

Essential:
Tumor in sellar region
AND
Non-keratinizing mature squamous epithelium covering fibrovascular cores or a cyst wall

Desirable:
Immunoreactivity for BRAF V600E
Presence of a BRAF V600E mutation
Absence of nuclear β-catenin immunoreactivity
Absence of CTNNB1 mutation

These diagnoses form a *family* of low-grade neoplasms that arise from pituitcytes of the posterior pituitary or infundibulum, most likely representing a *spectrum* of a single nosological entity, all showing expression of TTF1.

Granular Cell Tumor of the Sellar Region

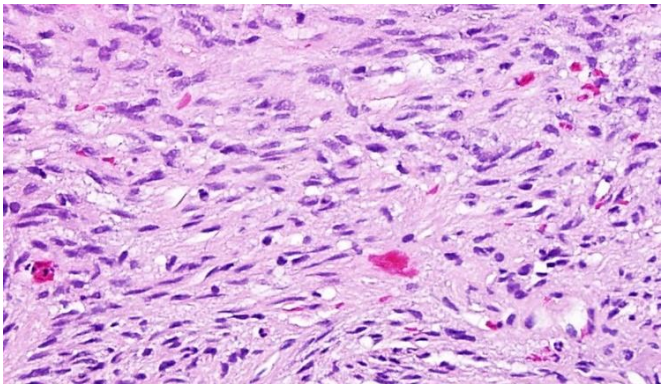


Epithelioid to spindled cells with abundant granular eosinophilic cytoplasm (full of lysosomes).

IHC: **(+) Diffuse TTF1**; (+/-) CD68, S100

Virtual slide

Pituicytoma

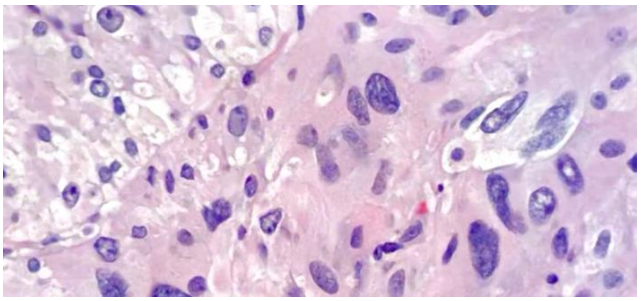


Bipolar, elongate spindled cells arranged in a fascicular or storiform pattern.

IHC: **(+) TTF1**, **S100**; (+/-) GFAP; (-) Synapto

Circumscribed, Solid. Rare.

Spindle Cell Oncocytoma



Spindled to epithelioid oncocytic cells in fascicles and poorly defined lobules.

IHC: **(+) TTF1**, **S100, EMA**; (-) Synapto

Pituicytoma	*Granular cell tumor*	*Spindle cell oncocytoma*
Essential: Bipolar spindle cell neoplasm in sheets and short fascicles	***Essential***: Neoplasm composed of polygonal cells with granular cytoplasm	***Essential***: Spindled or epithelioid tumor with eosinophilic, granular cytoplasm
AND Sellar or suprasellar location **AND** Nuclear TTF1 **AND** Absence of pituitary hormone and transcription factor expression **AND** Absence of neuronal or neuroendocrine marker expression		
Desirable: Absence of interspaced reticulin fibers	***Desirable***: Absence of interspaced reticulin fibers. PASd-positive. CD68 or a1-antitrypsin immunoreactivity	***Desirable***: Absence of interspaced reticulin fibers Antimicrobial antigen immunoreactivity

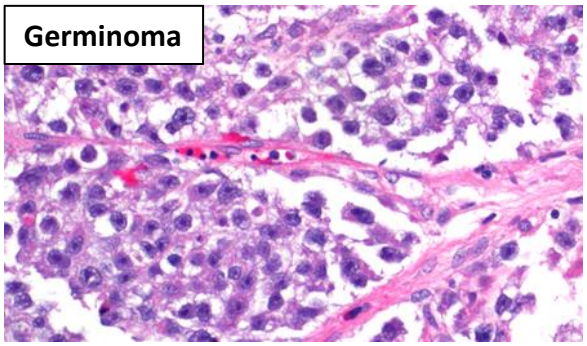
Germ Cell Tumors

Note: For more info, refer to the Testicle and Ovary guides

Morphologically identical to gonadal counterparts!
Usually **children/adolescents.**
Usually in the **midline,** most commonly **pineal gland.**
Symptoms depend on location. Can be "Mixed" GCT.

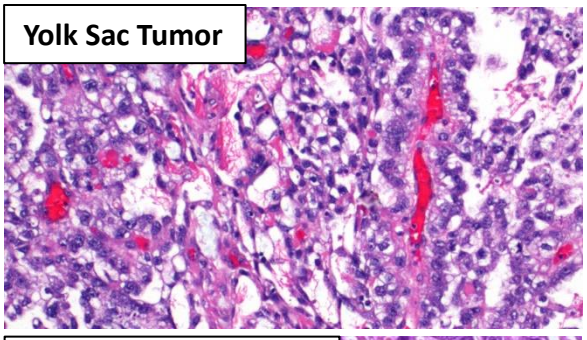
Germinoma

Large polygonal cells with clear to eosinophilic cytoplasm, distinct cell membranes, vesicular chromatin, and prominent nucleoli. Fibrous septae and **nested architecture**
Lymphocytic infiltrate; Sometimes granulomas



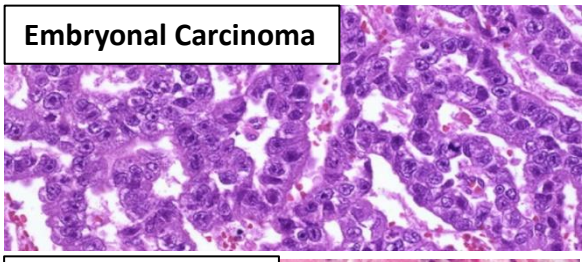
Yolk Sac Tumor

Many patterns/architecture. Often hypocellular myxoid areas
Most common = reticular/microcystic. Hyaline globules.
Classic: Schiller-Duval Bodies; Variable architecture.
Hyaline globules. **Elevated Serum AFP**



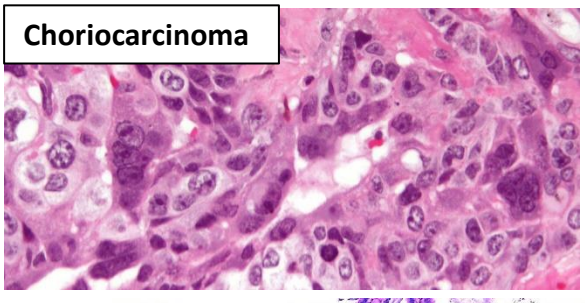
Embryonal Carcinoma

Large "Primitive" cells
Vesicular nuclei with prominent nucleoli
Coarse, basophilic chromatin. Amphophilic cytoplasm
Variable architecture (nests, sheets, glands). Aggressive.



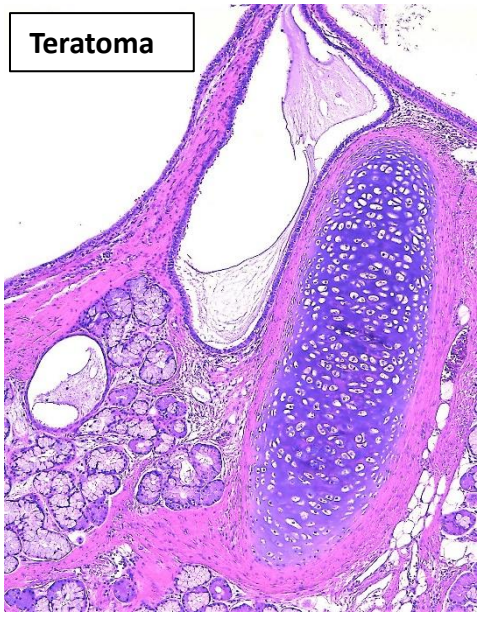
Choriocarcinoma

Malignant cytotrophoblasts (mononuclear) *and* syncytiotrophoblasts (multinucleated)
Abundant **Hemorrhage**. Elevated serum or CSF hCG.



Teratoma

Composed of tissues from 2-3 germ layers.
Common elements: Skin (with adnexal structures), Cartilage, GI, Brain, etc…
Mature→ exclusively mature (adult-type) tissues
Immature→ has immature fetal/embryonic tissue
…with somatic-type malignancy→ somatic malignancy developing in a teratoma (e.g., sarcoma or carcinoma)

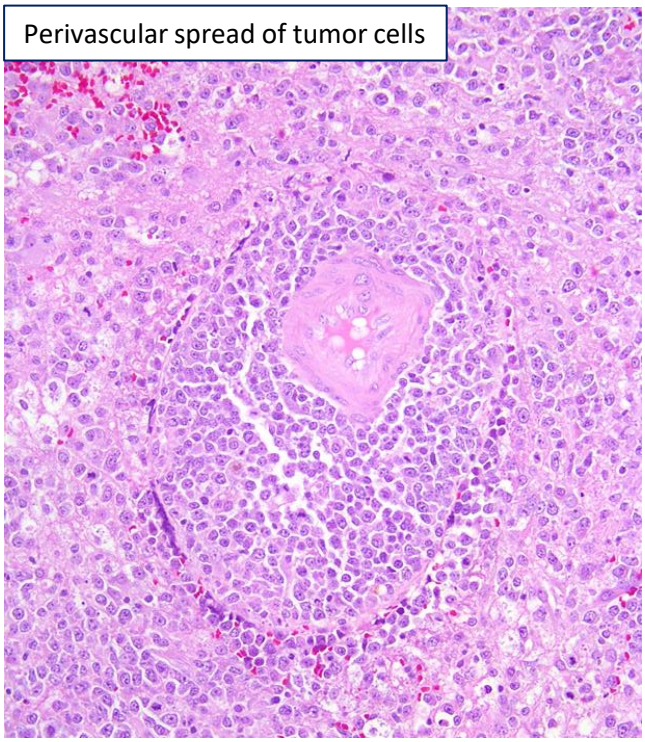


Germ Cell Tumor Immunohistochemistry:

IHC Stain	Seminoma	Embryonal Carcinoma	Yolk Sac Tumor	ChorioCA
SALL4	+	+	+	+
OCT 3/4	+	+	-	-
D2-40	+	+/-	-	-
CD117	+	-	-	-
CD30	-	+	-/+	-
Glypican 3	-	-	+	+/-

Lymphomas

Discohesive cells with scant cytoplasm.
Frequent perivascular infiltration



Diffuse Large B-cell Lymphoma of the CNS: DLBCL confined to the CNS at presentation. Often older patients with cognitive dysfunction and a single supratentorial mass. Need tissue to Dx→ important to not give steroids before surgery as may cause tumor waning making it harder to Dx.
Highly cellular, diffuse, patternless growth. Often necrosis with viable perivascular islands. Perivascular infiltration of nearby brain. IHC: (+) PAX5, CD20, CD19. NOT virus related. Virtual slide

Immunodeficiency-associated CNS lymphomas: Most common in AIDS. EBV-associated. Often multifocal.

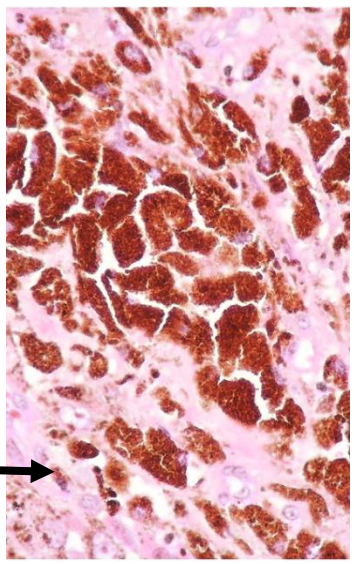
Other Lymphomas: Lymphomatoid granulomatosis, Intravascular Large B cell lymphoma, Extranodal marginal lymphoma of mucosa-associated lymphoid tissue (MALT) lymphoma of the dura.

Miscellaneous Other Tumors

Melanocytic tumors:

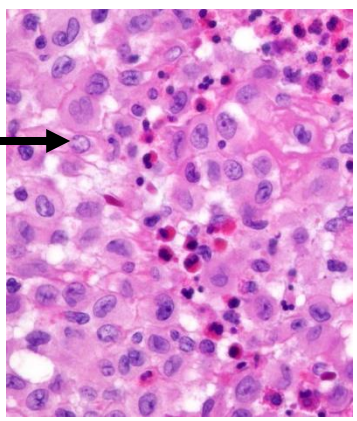
Presumably arise from leptomeningeal melanocytes. Often contain melanin.
Must consider/exclude metastatic melanoma!
IHC: (+)S100, MelanA, HMB45, MITF; Ki67 usually <2% in melanocytomas

Meningeal Melanocytosis—Diffuse/multifocal benign proliferation of cytologically bland melanocytes in subarachnoid space. Don't frankly invade brain.
Meningeal Melanomatosis—Primary CNS melanoma with diffuse spread throughout subarachnoid space. Often CNS invasion.
Meningeal Melanocytoma—Well-differentiated, solid, non-infiltrative melanocytic neoplasm
Meningeal Melanoma—Primary CNS melanoma. Solitary mass with aggressive growth.



Histiocytic tumors:

Langerhans's Cell Histiocytosis—Clonal proliferation of Langerhans cells.
IHC: (+)S100, CD1a, Langerin. May involve CNS secondarily via extension from bone or primarily. Usually children. Cells have pale cytoplasm with reniform nuclei. Classically associated eosinophils. Frequent BRAF V600E mutations.



Erdheim-Chester disease, Rosai-Dorfman disease, Juvenile Xanthogranuloma, Histiocytic sarcoma

Metastatic Tumors

Metastases are the most common CNS tumors in Adults!

Usually **multiple** lesions. Usually **well-circumscribed** (as opposed to an infiltrative diffuse glioma) 80% of metastases are to **cerebral hemispheres**, particularly in arterial border zones and at the grey-white junction. Often present with signs of increased intracranial pressure (headache, altered mental status, ataxia, etc..) Virtual slide 1

Most common sites of origin:
Men→ 1) Lung, 2)GI, 3)Melanoma, 4)Kidney
Women→ 1) Lung, 2)Breast, 3)GI, 4)Melanoma

Tumor Syndromes

AD= Autosomal Dominant

Syndrome	Gene	Nervous System Tumor(s)	Other manifestations
Neurofibromatosis Type 1 (NF1)	NF1 (AD)	Optic tract pilocytic astrocytomas, Astrocytomas, Neurofibromas, MPNST's	Café-au-lait spots, axillary freckles, osseous lesions, Lisch nodules, GIST etc..
Neurofibromatosis Type 2 (NF2)	NF2 (AD)	Bilateral vestibular schwannomas (and elsewhere), Meningiomas, Gliomas, and developmental lesions	Ocular abnormalities.
Schwannomatosis	SMARCB1 or LZTR1 (Sporadic)	Multiple Schwannomas and Meningiomas	Rare.
Von Hippel—Lindau Disease (VHL)	VHL (AD)	Hemangioblastoma	Clear cell renal cell carcinoma, Pheochromocytoma, Pancreas NET, Ear and epididymis tumors.
Tuberous sclerosis	TSC1 or TSC2 (AD)	SEGAs, Cortical hamartomas, Subependymal glial nodules	Cutaneous angiofibroma, Cardiac rhabdomyomas, Renal angiomyolipoma, Lung LAM
Li-Fraumeni Syndrome	TP53 (AD)	Astrocytoma, Glioblastoma, Medulloblastoma, Choroid plexus tumors	Multiple primary tumors in children and young adults including: Breast cancer, Soft tissue sarcomas, Adrenal cortical carcinoma, and Osteosarcoma.
Cowden Syndrome	PTEN (AD)	Dysplastic cerebellar gangliocytoma (Lhermitee-Duclos disease),	Breast, Endometrium, and Thyroid cancer. Multiple hamartomas including skin and GI
Turcot Syndrome	APC (AD)	Medulloblastoma	Colon Cancer, Osteomas, Fibromatosis,
	Mismatch repair enzymes (AD)	Gliomas	Café-au-lait macules, Lymphoma
Nevoid Basal Cell Carcinoma (Gorlin) Syndrome	PTCH1 or PTCH2 (AD)	Medulloblastoma (desmoplastic/nodular)	Skin basal cell carcinoma, Odontogenic keratocytes
Rhabdoid Tumor Predisposition Syndrome	SMARCB1 or SMARCA4	AT/RT	Kidney malignant rhabdoid tumor

Pattern-Based Approach

Modified from: "Practical Surgical Neuropathology" by Arie Perry and Daniel Brat

General Comments: Although a pattern-based approach is very useful, in many cases you might have a good idea of the Dx via "instant pattern recognition." Nevertheless, it can be helpful to judiciously consider mimickers and other diagnoses based on a pattern-based approach.

Parenchymal Infiltrate with Hypercellularity

Intact architecture, but with a hypercellular infiltrate

Diffuse gliomas
Diffuse large B cell lymphoma of the CNS
Angiocentric glioma
Encephalitis (inflammatory/infectious processes)
Active demyelinating diseases
Histiocytic disorders (e.g., Erdheim-Chester disease)
Infarcts
Metabolic/toxic diseases
Reactive gliosis

Solid Mass

A sharply demarcated lesion

Metastases
Ependymoma
Subependymoma
SEGA
Neurocytomas
Pineal parenchymal tumors
Embryonal neoplasms
Choroid plexus tumors
Hemangioblastoma
Paraganglioma
Pituitary adenomas
Astroblastoma
Chordoid glioma of the 3rd ventricle

Solid *and* Infiltrative Process

A lesion that is mostly solid, but with an ill-defined (infiltrative) margin with the adjacent brain tissue.

Pilocytic astrocytoma
Pilocytic xanthoastrocytoma
Glioblastoma/gliosarcoma
Ganglioglioma
Disembryoplastic neuroepithelial tumor
Embryonal neoplasms (e.g., Medulloblastoma)
Choroid plexus carcinoma
Germ cell tumors
Craniopharyngioma
Diffuse large B-cell Lymphoma
Sarcomas
Histiocytic tumors
Abscesses/infection

Destructive/Necrotic Process

Extensive necrosis and destruction of normal tissue

Infarcts
Glioblastoma
Radiation necrosis/treatment effect
Infection
Vasculitis
Lymphoma
Severe demyelinating disease
Metabolic/toxic disease

Vasculocentric

A disease process <u>centered around blood vessels</u>

Diffuse large B-cell lymphoma
Intravascular lymphoma
Angiocentric glioma
Ependymoma
Vasculitis
Demyelinating diseases
Amyloid angiopathy
Arteriosclerosis
Vascular malformations
Infections
Sarcoidosis
Thromboembolic disease

Extra-Axial Mass

<u>External</u> to the brain

Meningioma
SFT/Hemangiopericytoma
Hemangioblastoma
Peripheral nerve sheath tumors
Metastasis
Melanocytoma/melanoma
Paraganglioma/NET
Pituitary adenoma
Sarcoidosis
Infection
Bone tumors
Histiocytic tumors
Leukemia/lymphoma

Almost Normal Tissue

Very subtle changes

Nonrepresentative biopsy (“they missed”)
Subtle diffuse glioma
Cortical dysplasia and other malformations
Mesial temporal sclerosis
Intravascular lymphoma
Encephalitis
Cerebral malaria
Microembolic disease
Neurodegenerative diseases
Metabolic/toxic disorders
Reactive gliosis
Cerebral edema
Spongiotic/vacuolar changes
Ischemic changes

Meningeal/CSF Infiltrate

An expanded subarachnoid space filled with a cellular infiltrate

Meningeal carcinomatosis
Meningeal gliomatosis
Meningeal melanocytis/melanomatosis
Diffuse leptomeningeal glioneuronal tumor
Metastatic medulloblastoma
Leukemia/lymphoma
Histiocytic disorders
Meningitis
Sarcoidosis
Infection
Collagen vascular disease