CNS PATH: Brain Tumors

NORMAL CORTEX	PRIMARY NEUROGLIAL TUMOR: Glioma	METASTATIC TUMOR
– **NEUROPIL-LIKE** background: delicate meshwork of neuronal & glial processes – **Astrocytes:** large, irregular nuclei – **Oligodendrocytes:** open chromatic pattern; uniform, round nuclei – **Pyramidal neurons:** large, open vesicular nucleus ○ **Neurofilament protein +** (intermed. filament in neurons)	– Diffuse, poorly-defined ***infiltrating*** border – **NEUROPIL-LIKE** background *resembling normal cortex* – **GFAP+** (intermediate filament in neuroglial tumors)	– **Sharp, well-demarcated border** – "Pavement-like" **EPITHELIAL** appearance – **Cytokeratin+** (epithelial) – ***Mostly from BREAST or LUNG primary***

Note: "Malignant" means *rapidly growing*. "Benign" means *slowly growing*.

BRAIN TUMORS

Tumors within the Central Nervous System can arise due to:

Sporadic/environmental causes:

Mutations due to unknown cause, or Radiation, or chemical exposure

Familial causes:

NF-1, NF-2, VHL, Li-Fraumeni syndrome, Turcot syndrome, and Gardener's syndrome

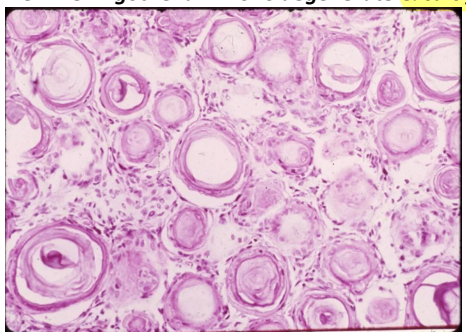
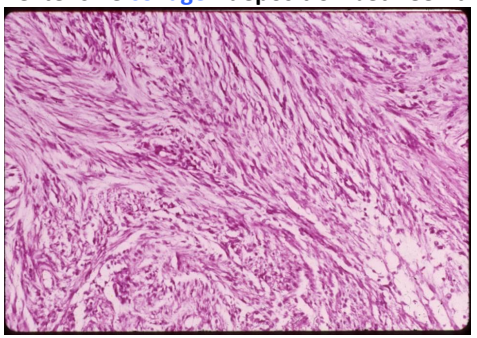
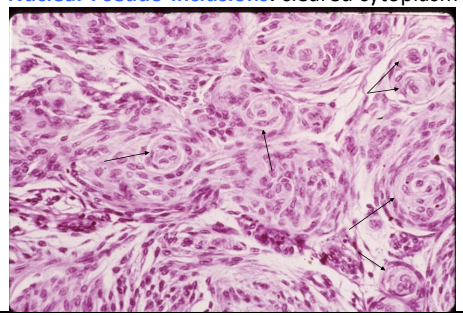
1. **Meningioma**
2. **Schwannoma**
3. **Glial Tumors** (Astrocytoma, Oligodendroglioma, Ependymoma)
4. **Neuronal Tumors**
5. **Embryonal Remnant** (Medulloblastoma; Craniopharyngioma)
6. **Retinoblastoma**
7. **Primary CNS Lymphoma**
8. **Metastatic**

- **Turcot syndrome**: Mutation in **APC, or MLH 1** gene. A rare, **inherited** disorder in which patients develop colon & rectum **polyps,** and **brain tumors.**
- **Gardner syndrome.** Mutation in **APC** gene. It is a rare, **inherited** disorder in which patients develop large and small **intestines** polyps, **and osteoma.** Patients can also develop **brain tumors**, and fibromas.

Common features: Headache, Seizures, Focal neurological deficit

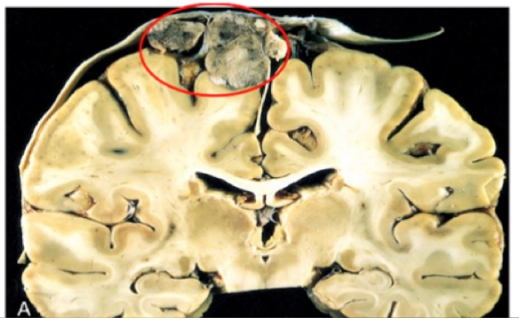
Non-Neuroglial Tumors: Meningiomas (22q11 of NF2); **Adults**

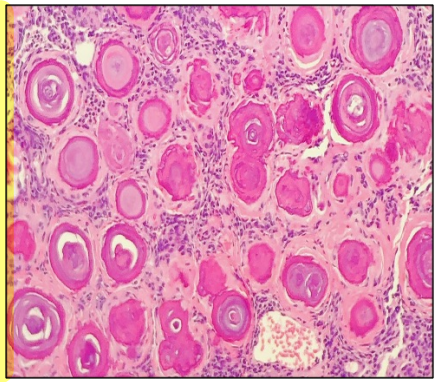
- BENIGN tumor arising from meningothelial cells of arachnoid matter, usually attached to dura

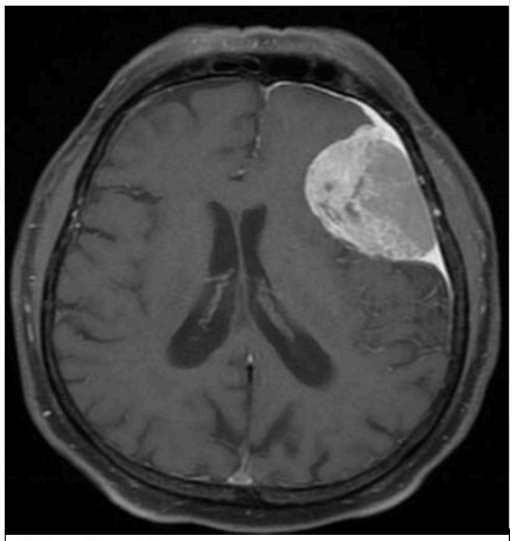
MENINGIOMAS (Grade 1): S100-, EMA+		
TRANSITIONAL MENINGIOMA	**PSAMMOMATOUS MENINGIOMA**	**FIBROUS MENINGIOMA**
Transitional btwn fibroblastic & meningothelial pattern	****PSAMOMMA BODIES****	Elongated spindle cells (FIBROBLASTS)
****MENINGOTHELIAL WHORLS**	***-When meningothelial whorls degenerate & calcify***	with extensive collagen deposition between them
Nuclear Pseudo-inclusions: cleared cytoplasm		
		

Meningioma

- Benign tumor of arachnoid cells
- MC benign CNS tumor → MC females
- Compression of cortex but no invasion
- Hearing deficit
- Encapsulated round tumor
- **Histology**: psammoma bodies
- Associated w/ NF-2 on chromosome 22q





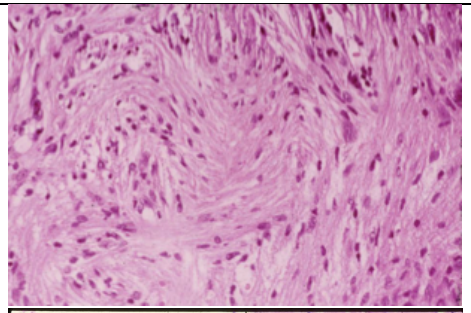
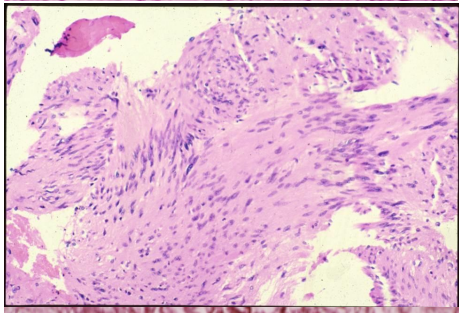
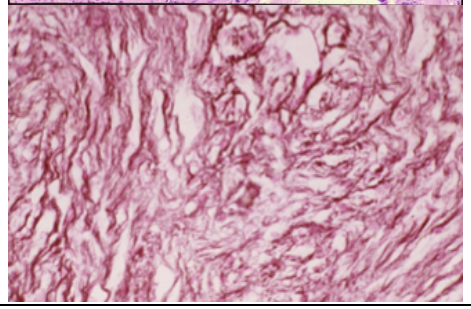


Meningioma:
- note attachment to dura

Non-Neuroglial Tumors: Schwannoma

SCHWANNOMA: S100+, EMA- *(opposite of Meningioma)***

Adults; PONTOCEREBELLAR ANGLE**

DEFINITION	Usually BENIGN tumor arising from **Schwann cells** of **CRANIAL & PERIPHERAL NERVES**
HISTOLOGY	  

Lacy reticular pattern with degenerative changes

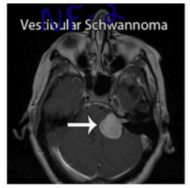
BIPHASIC:

1. Antoni A areas: more solid tumor, composed of **SPINDLE CELLS**, *resembling fibroblastic meningioma;* elongated, **CIGAR-SHAPED NUCLEI**

2. Antoni B areas: loose, vacuolated tumor

Schwannoma

- Benign tumor of schwannoma cells
- Commonly involves CN8→ loss of hearing & tinnitus
- Tumor cells = S-100+

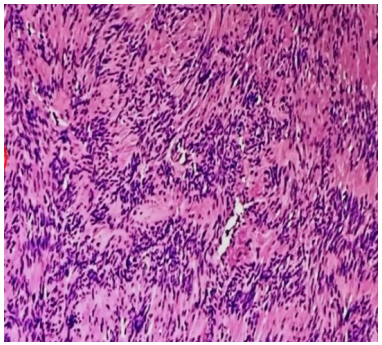


VEROCAY BODIES: *palisading* stacks of elongated CIGAR-SHAPED NUCLEI with nuclear-free (pink) areas on either side of them

Use the **RETICULIN STAIN** to distinguish Schwannoma from Fibrous Meningioma

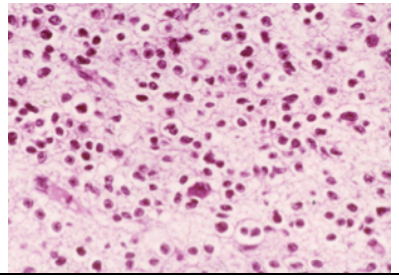
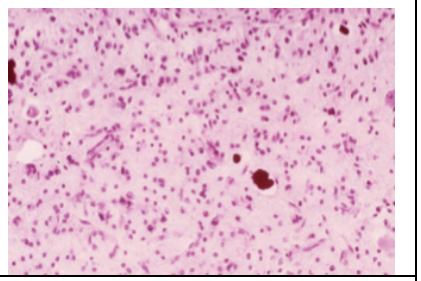
-Schwannomas have ***extensive delicate reticulin network surrounding each cell***

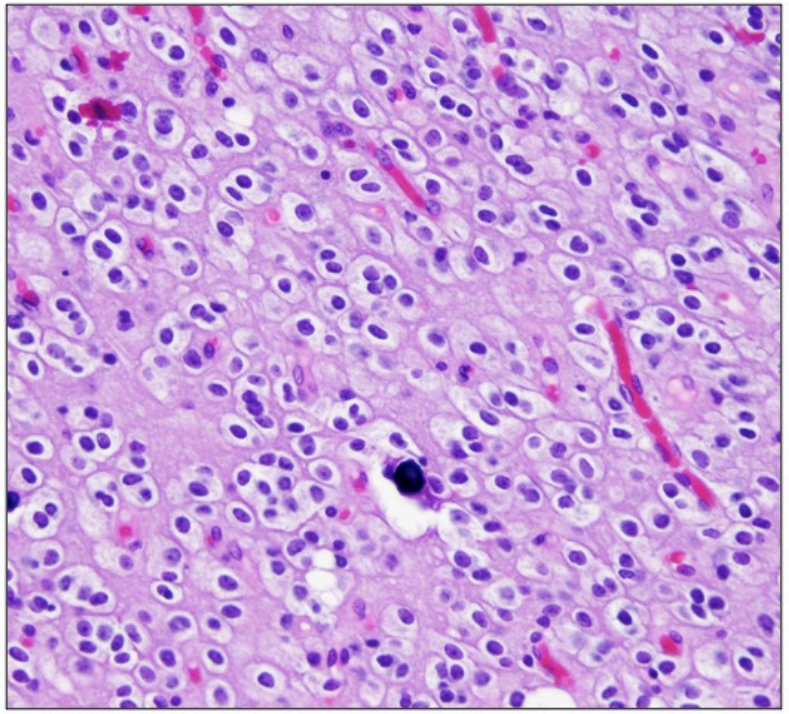
-Meningiomas has ***dense bands of reticulin surrounding groups of cells***



Primary Neuroglial Tumors: Oligodendroglial Tumors

***Loss of 1p & 19q:** Better prognosis than Astrocytic Tumors

	OLIGODENDROGLIOMA Adults
CLINICAL COURSE	Curable
RADIOLOGY	**NON-enhancing, intra-axial**
GROSS	Well-circumscribed gelatinous mass
HISTOLOGY	**FRIED-EGG appearance + CHICKEN-WIRE capillary pattern + DYSTROPHIC CALCIFICATIONS**  
TREATMENT	Same as for comparable grade astrocytic tumor



- MALIGNANT Tumor of the oligodendrocytes.

- Circumscribed
- Cystic
- Calcified

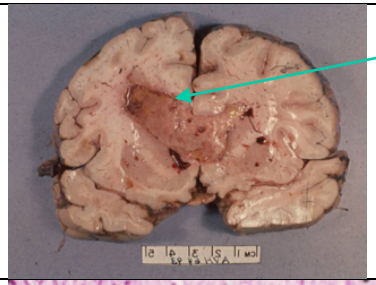
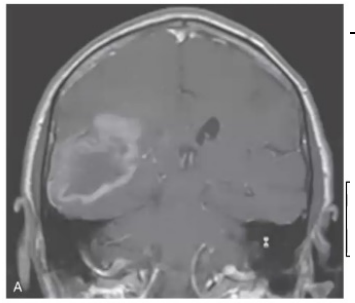
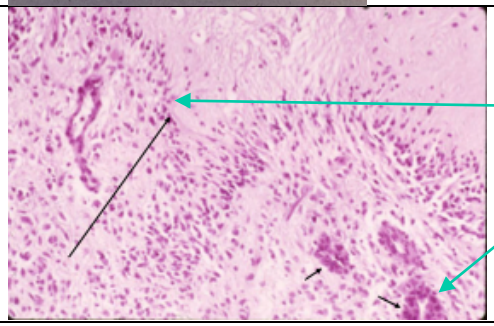
Oligodendroglioma: Circumscribed, Calcified tumor in white mater of frontal lobe, Fried Egg cells

Astrocytoma: Two types

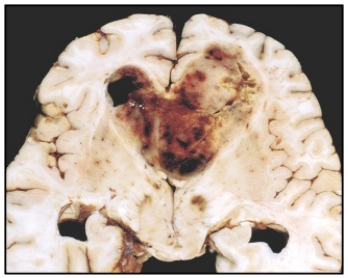
(i) **Glioblastoma:** Butterfly lesion (crossing corpus callosum) in cerebrum; GFAP +ve
Pseudopalisading cell arrangement

GLIOBLASTOMA MULTIFORME (GRADE 4): GFAP+

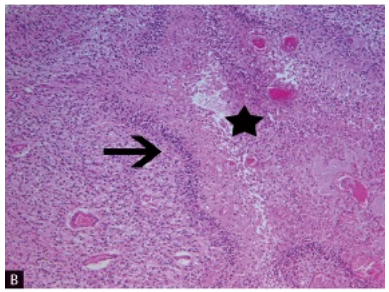
Adults; Cerebral Hemispheres

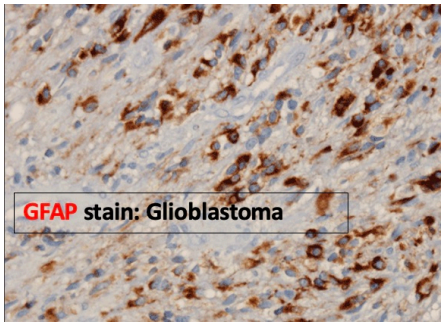
PRESENTATION	"Patient brought to ER with **new onset seizure**. She recovers from the seizure. MRI shows large, expanded mass lesion displacing the rest of the brain."	
CLINICAL COURSE	Poor prognosis; death within 5 years	
MOLECULAR BIO	**PRIMARY GLIOBLASTOMA** 1. **CLASSICAL: EGFR amplification/overexpression** **2. Mesenchymal:** NF1 mutation **3.** Neural: EGFR amplification/overexpression **4. Proneural: PDGF-A overexpression, IDH-1 activating mutation (R132H)**	**SECONDARY GLIOBLASTOMA** **P53 mutation, PDGF-A overexpression most common** Other mutations: **MGMT**, VEGF, Telomerase
RADIOLOGY	Large, expanded, ***infiltrating*** mass lesion	
GROSS	 Poorly-defined border **Diffuse INFILTRATION across the corpus collosum – "BUTTERFLY LESION"**	
HISTOLOGY	 **TUMOR NECROSIS** + surrounded **by PSEUDOPALISADING** tumor cells **ENDOTHELIAL PROLIFERATION** (in response to trophic factors secreted by the tumor)	
TREATMENT	Surgery, radiotherapy, & chemotherapy – ***NOT with intent to cure,*** *only resecting what can be removed ("gross total resection") in order to improve prognosis*	

1. **Glioblastoma multiforme:** infiltrating
   - MC malignant CNS tumor in adults
   - Tumor of astrocytes
   - Crosses corpous callosum
   - Characterized by regions of necrosis surrounded by anaplastic tumor cells w/ pseudopalisading pattern
   - GFAP +



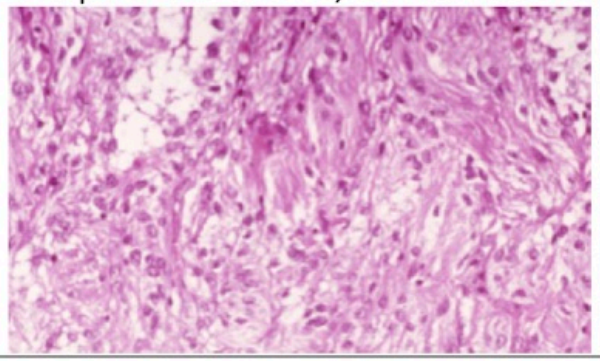
Glioblastoma: Large mass with areas of hemorrhagic necrosis. Tends to cross the midline.

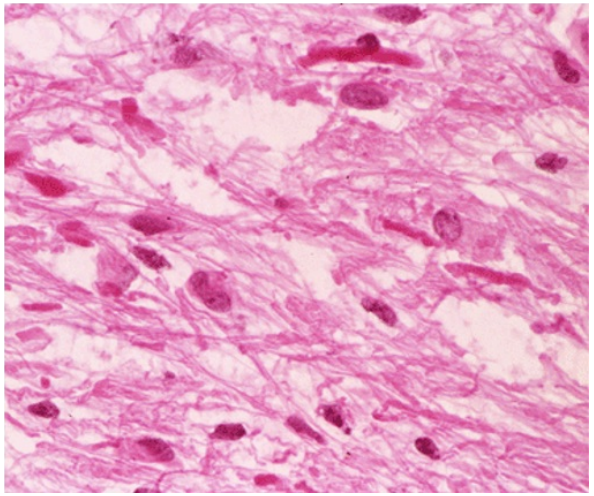


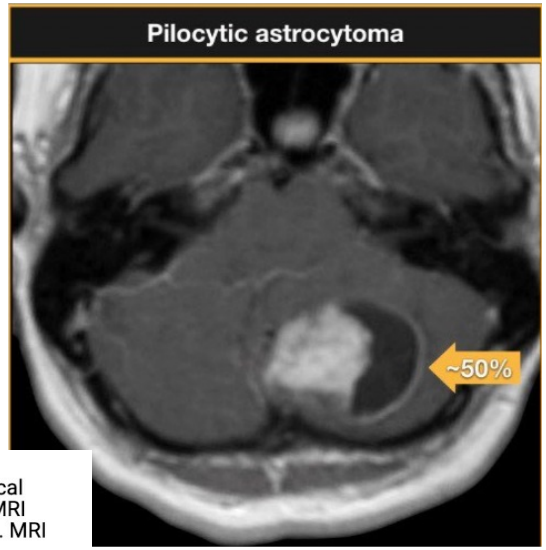


- C/F. **Headache, seizures, and focal neurologic deficit**

Primary Neuroglial Tumors: Astrocytic Tumors

	PILOCYTIC ASTROCYTOMA GFAP+ Pediatric (<20 y/o); Cerebellum, Hypothalamus, Optic Nerve
PRESENTATION	Ataxia, PROJECTILE VOMITING, vision loss
COURSE	GOOD PROGNOSIS, *especially when it occurs in the* ***Cerebellum!***
RADIOLOGY	TP53 mutation
HISTOLOGY	Thick "hair-like" processes & ROSENTHAL BODIES **Biphasic:** Dense compact areas + Looser, vacuolated areas w/ cysts 





Pediatric

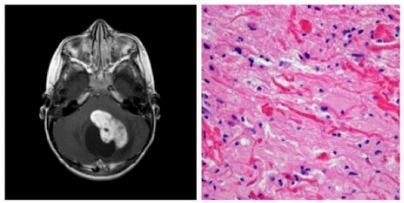
BENIGN

Non-infiltrating

- Clinical features: **Raised ICP, headache, neurologic deficit.**
- Imaging reveals a cystic lesion with a ***NODULAR*** tumor.
- Biopsy shows ***ROSENTHAL FIBERS*** (thick eosinophilic processes of astrocytes) and eosinophilic granular bodies.

A 7-year-old boy presents to the pediatric emergency department for lethargy, nausea, and vomiting. Medical history is unremarkable. Physical examination is notable for papilledema and right-sided dysmetria. An MRI brain with and without contrast demonstrates a cerebellar cystic mass. MRI and biopsy is shown in the image. What is the most likely diagnosis?

a) Craniopharyngioma
b) Meningioma
c) Pilocytic astrocytoma
d) Oligodendroglioma
e) Ependymoma
f) Glioblastoma multiforme
g) Medulloblastoma



(ii) Pilocytic Astrocytoma: Nodular cystic lesion in cerebellum; GFAP +ve, Rosenthal fibers

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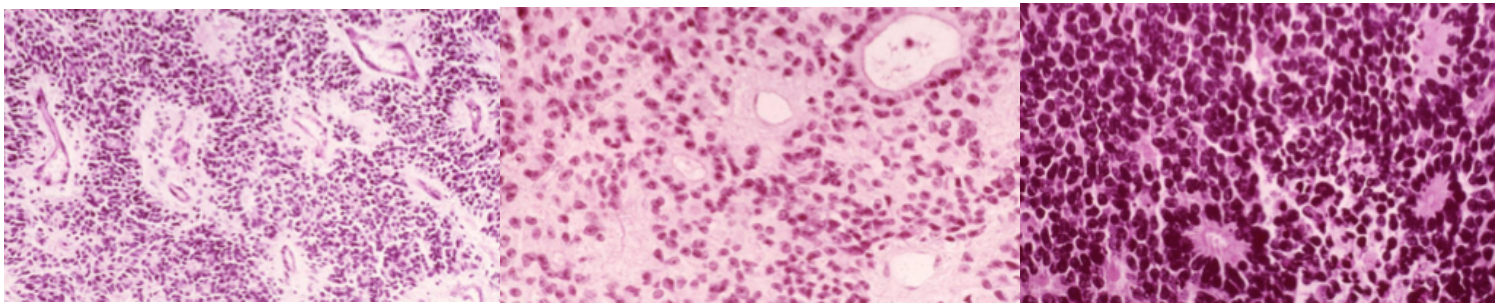
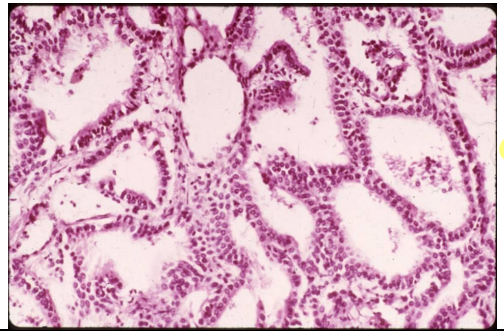
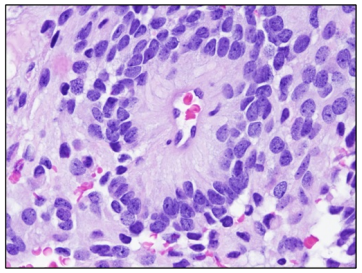
3. Ependymoma: Papillary or cauliflower like lesion in 4th ventricles, Perivascular Pseudorosettes

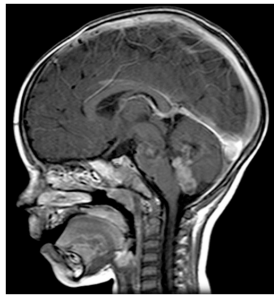
Primary Neuroglial Tumors: Ependymoma Tumors

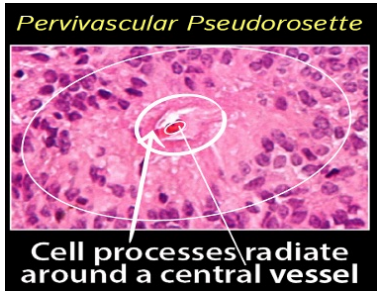
EPENDYMOMA: GFAP+ **Adults; Spinal Cord: GOOD PROGNOSIS** **Pediatrics; Intracranial (Posterior Fossa, 4th Ventricle): POOR PROGNOSIS**	
CLINICAL COURSE	*May progress to Anaplastic Ependymoma*
MOLECULAR BIO	**ADULT: SPINAL CORD EPENDYMOMA** Gain of 7, Loss of 22 NF2 mutation HOX upregulation **PEDIATRIC: INTRACRANIAL EPENDYMOMA** Gain of 1q, loss of 6q CDKN2A deletion NOTCH upregulation
HISTOLOGY	**CLASSIC FEATURE: "NUCLEAR-FREE ZONE" or GLIO-VASCULAR ROSETTES around capillaries** Tumor cells have uniform, round nuclei  **Aplastic Ependymoma**  **PAPILLARY EPENDYMOMA** When ependymomas grow into the **VENTRICLES,** they take on a **PAPILLARY PATTERN!** **Absence of mesenchymal stroma around BVs **DDx of Papillary Lesion in Ventricles:** -Ependymoma -Choroid plexus tumor (papilloma or carcinoma) -Papillary meningioma
TREATMENT	**For PEDIATRIC POSTERIOR FOSSA EPENDYMOMAS – Gross total resection is very important!**

Ependymoma

- Malignant tumor, in children → 4th ventricle → hydrocephalus
- Perivascular pseudorosettes: located around a. blood vessel
- Adults: spinal cord = main location



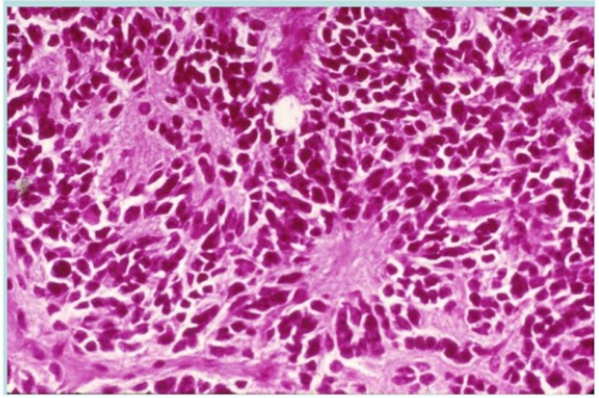




Primary Neuroglial Tumors: Medulloblastomas & Primitive Neuroectodermal Tumors (PNETs)

***Small round blue cell neoplasms**

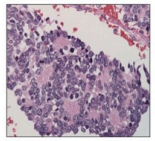
	MEDULLOBLASTOMA **Children; Cerebellum**
CLINICAL COURSE	**Poor prognosis; *highly malignant***
MOLECULAR BIO	• Malignant tumor derived from granular cells of cerebellum (neuroectoderm) • Children • Round blue cells, Homer-right rosettes [neuron origin, pinkish lumen (neutrophil)] • **Patients present with raised ICP, epilepsy, focal neurologic deficit.**
HISTOLOGY	**Small round blue cell tumor** **HOMER-WRIGHT PSEUDOROSETTES (**No central lumen!)**



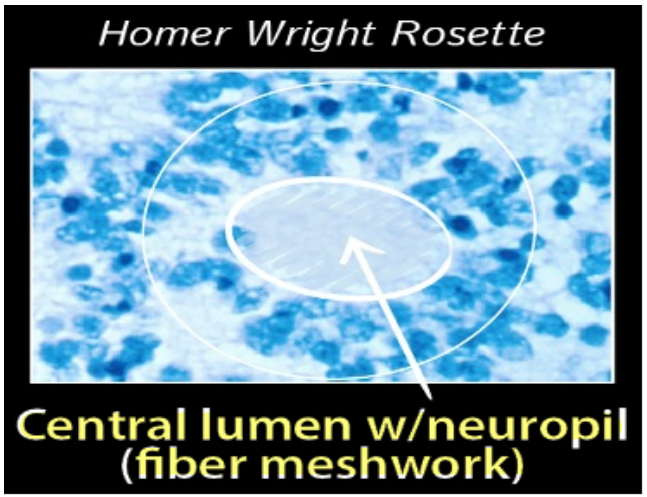
- Arise from **Neuroectodermal reminiscent.**

1. **Medulloblastoma:**

- Malignant, **granular cells of cerebellum**
- 20% of pediatric brain tumors.
- Tumors are composed of **small round cells – lymphocyte like with the pattern Homer-right rosettes (neurofibrillary material).**



- Tumor grows rapidly and spreads via CSF, poor prognosis.
- Metastasis to the **cauda equina** is termed **drop metastasis**.
- Medulloblastoma is **exquisitely radiosensitive**. With total excision, chemotherapy, and irradiation, the 5-year survival rate may be as high as 75%.



Neuronal Tumors

- Far less frequent than gliomas.
- Affect both **children and adults**.
- Tumors are lower grade, composed of cells with **neuronal** characteristics.
- Some tumors express neuronal markers, e.g. synaptophysin & neurofilaments.

1. Central neurocytoma: Arises within and adjacent to the **ventricular system**.

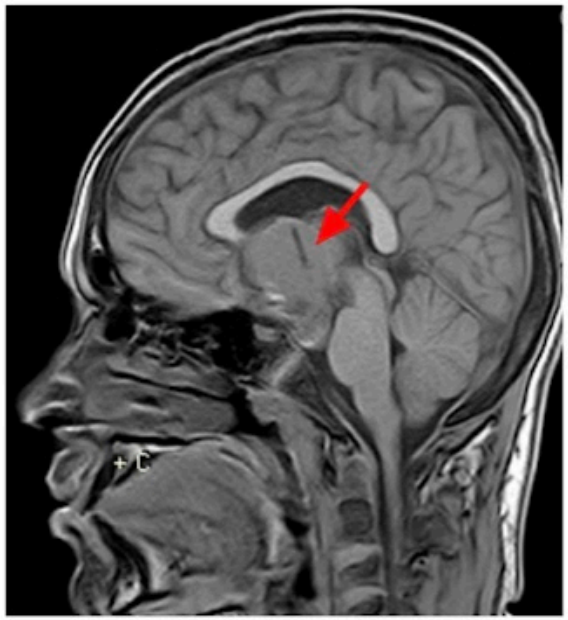
2. Dysembryoplastic neuroepithelial tumor

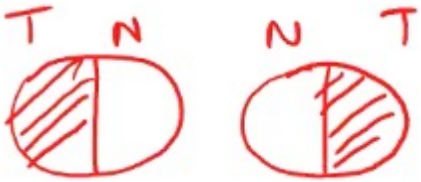
Arises in the superficial **temporal lobe**.

3. Gangliogliomas: Tumors with a mixture of glial cells and neurons. Arise in **temporal lobe**.

2. CRANIOPHARYNGIOMA

- **Benign** tumor that arises from epithelial remnants of **Rathkes pouch (ectodermal** outpouching for oral cavity).
- Presents as a **supratentorial mass** (in a child or young adult, usually in **suprasellar**, but occasionally intrasellar region).
- Symptoms result from **compression of** adjacent structures, especially: **OPTIC CHIASM: Bitemporal hemianopia**; and **Diabetes insipidus**
- Children present with growth retardation (**PITUITARY deficiency** may result, from involvement of the hypothalamus)
- **Calcifications** are commonly seen on imaging (derived from tooth-like tissue).
- Benign, but tends to recur after resection.

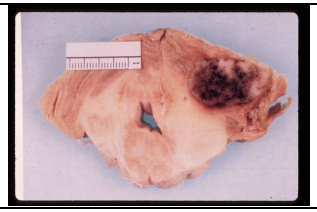
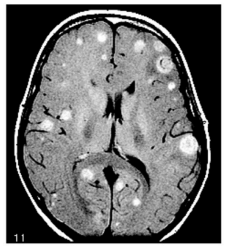
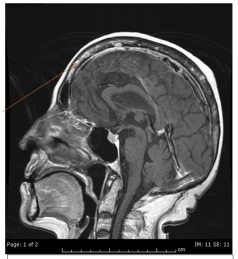




2. Craniopharyngioma:

- Benign, epithelial remnants of **Rathkes pouch** in Suprasellar region.
- Tumors are composed of large round cells - squamoid.
- Affects **OPTIC CHIASM,** and Pituitary gland (hormone deficiencies & Diabetes insipidus)

Metastatic Tumors

METASTATIC CARCINOMA: GFAP+, Cytokeratin+	
DEFINITION	Most often from a **BREAST** or **LUNG** primary carcinoma
GROSS	 **Sharp, well-demarcated border** Common tumors giving rise to metastasis: 1. **Lung** 2. **Breast** 3. **Skin (melanomas)** 4. **Kidney** 5. **Gastrointestinal tract**
MORPHOLOGY	 Multiple mass lesions in brain parenchyma  Meningeal carcinomatosis: note opacities in meninges. - sharply demarcated **multiple masses** at the junction of gray & white matter - meningeal carcinomatosis: seen with carcinoma of lung & breast
TREATMENT	Treatment **with intent to cure:** resection, chemotherapy, radiation

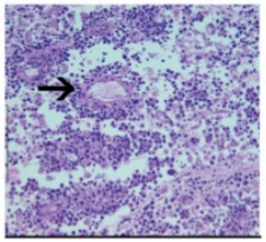
Primary CNS Lymphoma **AIDS & Transplant Patients**	
CLINICAL COURSE	***Diffusely infiltrating*** like a Glioma
TREATMENT	Radiotherapy & chemotherapy

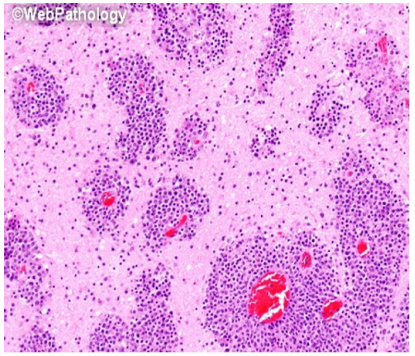
Primary CNS Lymphoma

- Multiple tumor nodules within brain parenchyma
- Mostly diffuse large B-cell lymphoma w/ EBV
- MC CNS neoplasm in immunocompromised pts
- B cell marker = CD20→ target for therapy

Clinical

- Fever, weight loss, raised ICP, seizures, focal neuro deficits





PCNSL: Perivascular Monotonous blue cells

RETINOBLASTOMA

Most common intraocular tumor in Children

Presents with *leukocoria*

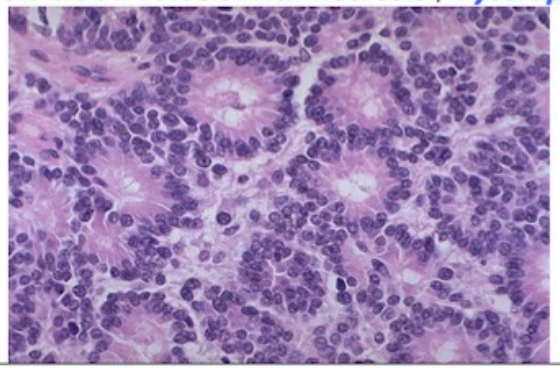
RB1 mutation

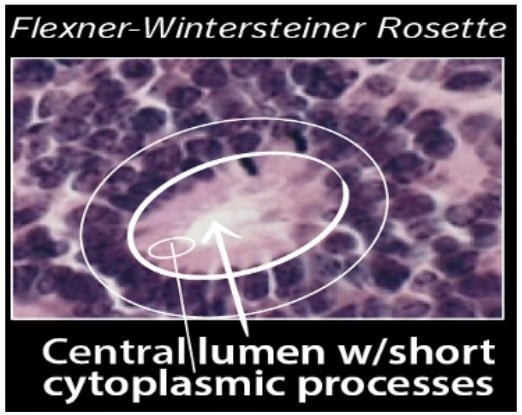
2 hit model: familial→ 1 mut needed, sporadic→ 2 mut needed

Small round blue cell tumor

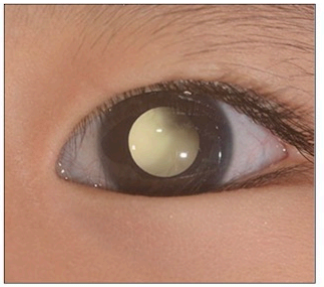
FLEXNER-WINTERSTEINER ROSETTES (Has central lumen!)**

*Tumor cells encircle blood vessels with **necrosis** + Dystrophic Calcification*



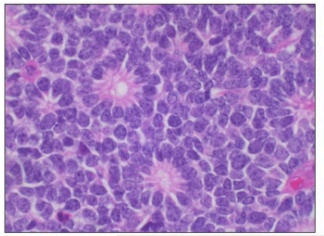


- A **malignant** tumor of the retina.
- 90% of cases are **below 5 years** of age
- association with **RB** gene **mutation**
- **Familial** in 40%
- **Sporadic** in 60%



Morphology:

- Tumor shows **small round blue cells, and Flexner-Wintersteiner rosettes**



Clinical:

- leukocoria (**white pupillary reflex – cat's eye reflex**)
- strabismus, **ocular pain**

Flexner-Wintersteiner rosette
- characteristic of retinoblastomas,
- it consists of tumor cells surrounding a central lumen
- that contains cytoplasmic extensions from the tumor cells

Treatment

- Local **chemotherapy** (intravenous, or intra-arterial)
- Cryotherapy