Part 1. CNS - Glial Neoplasms

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Tumor Types (Broad Overview)

Can characterize tumors by the neuro cells which they resemble/are derived from.

- **Glial cells**
  - Astrocytomas
  - Oligodendrogliomas
  - Ependymomas
- **Neurons**
  - Medulloblastomas
  - Neurocytomas
- **Mixed Glial and Neuronal**
  - Gangliogliomas
  - Glioneurocytic
- **Coverings of the Nervous System**
  - Meningiomas
  - Schwannomas
  - Neurofibromas

Peripheral to Central (Broad Overview)

Can also organize tumors from peripheral (nervous system) to central (nervous system).

- Peripheral Nerve and Nerve Root Tumors
  - Neurofibroma, Schwannoma
- Spinal Cord
  - Extrinsic - Meningioma
  - Intrinsic - Glial
    - Astrocytoma, Ependymoma
- Brain
  - Extrinsic - Meningioma
  - Intrinsic - Glial Neuronal Tumors (see above)

WHO Grading

Based not on tumor type, but on survival.

- GRADE I - > 10 year survival if untreated
- GRADE II - 5-10 year
- GRADE III - 3-5 year
- GRADE IV - <3 year (aggressive, Glioblastoma)

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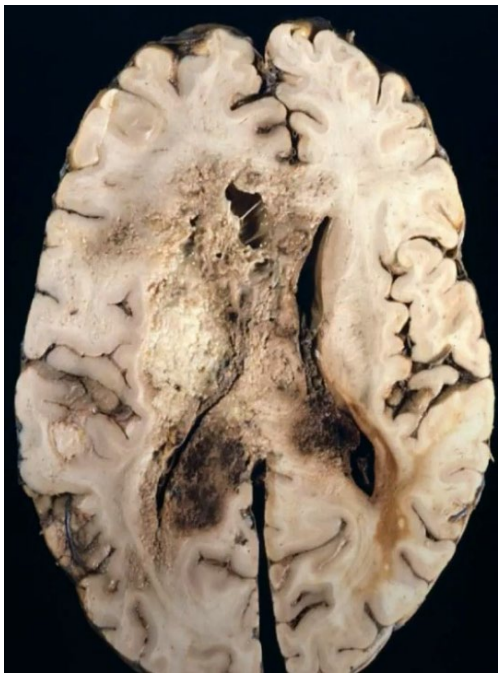
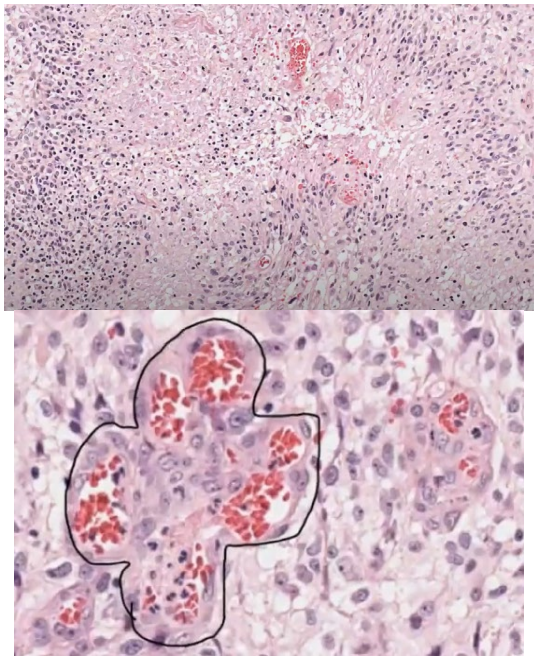
Gliomas ● Major classifications ○ Astrocytomas ○ Oligodendrogliomas ○ Ependymomas	**Most common type of primary brain tumor**
Glioblastoma, WHO Grade IV ● Epidemiology: about 18,000/year in US ○ Mostly middle-aged adults ● Most common primary brain and the most malignant ● Typically occurs in adults >45 years old ○ Also in brainstem of children, infants ● Sites: Frontal and Temporal lobes ● Cerebral hemispheres, white matter ● Imaging: large irregular, contrast-enhancing mass ○ Surrounding edema, cavitation ● Prognosis: death <1 year ● Gross findings: ○ Infiltrative, poorly circumscribed, necrotic ○ Crosses the corpus callosum ■ "Butterfly glioma"	

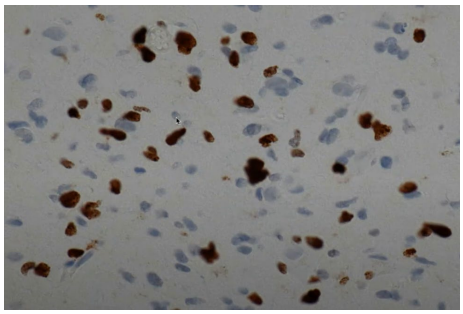
Glioblastoma, WHO Grade IV

- Histologic findings:
  - Some normal neurons
  - Hypercellularity, Cellular atypia, increased mitotic figures
  - Palisading necrosis (top)
    - Tumor cells trying to escape areas of dead tissue; walls, or “palisades”, it off
  - Microvascular proliferation (bottom)
    - Abnormal vessel growth
    - Takes on the shape of glomerulus in the kidney (“glomeruloid”)
    - Instead of thin, mononuclear blood vessels, blood vessel nuclei become more plumped, endothelial cells proliferate
      - Nuclei of multiplied endothelial cells stack on top of each other



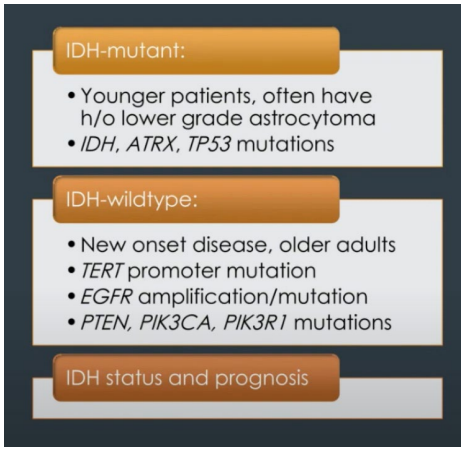
Glioblastoma, WHO Grade IV

- Ki-67 stain (positive)
  - Ki-67 is a marker of proliferation
  - Observe large amount of actively and rapidly dividing and growing cells, even in a less invasive portion of the tumor as seen to the right



Glioblastoma: IDH-Mutant vs. IDH-Wild Type

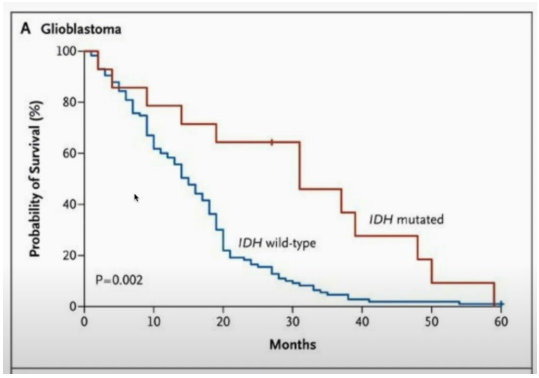
- **IDH-Mutant**
  - Younger patients
  - Often history of lower grade astrocytomas
    - Overtime becomes more aggressive
  - *IDH*, *ATRX*, *TP53* mutations
- IDH-Wild Type (prototypical)
  - New onset disease
  - Older adults
  - *TERT* promoter mutation (most common)
  - *EGFR* amplification/mutation
    - Chromosome 7 gains
  - *PTEN*, *PIK3CA*, *PIK3R1* mutations
    - Chromosome 10 loss



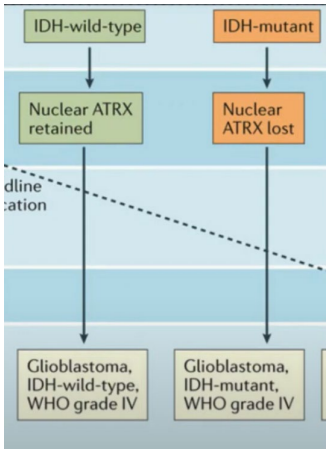
Type	Presentation	Mutations
IDH mutant	Young patients, Hx of lower grade astrocytoma	IDH (overexpression) ATRX (loss) TP53 (increased)
IDH Wild Type	Older adults, new onset	TERT promoter EGFR amplification Others: PTEN, PIK3CA, PIK3R1

Glioblastoma: IDH-Mutant vs. IDH-Wild Type

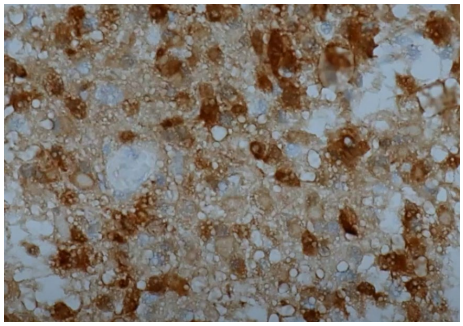
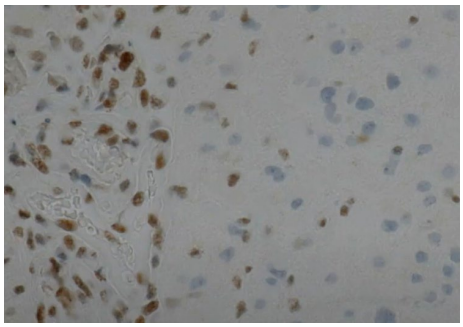
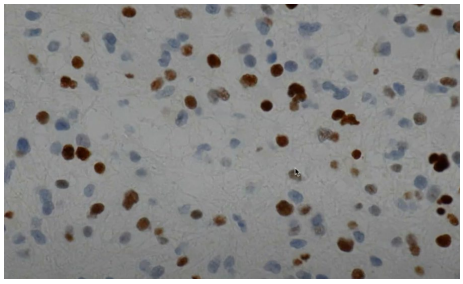
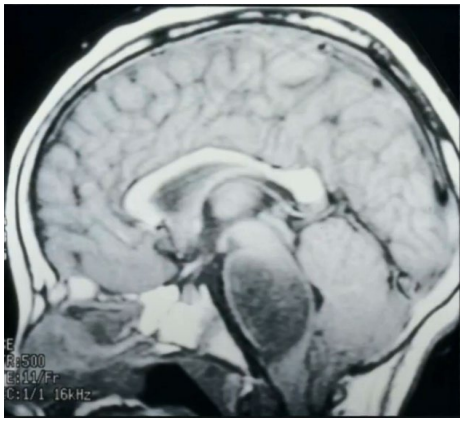
- IDH status and prognosis
  - Wild-type is aggressive < 1 year survival
  - IDH mutated >2 year survival



Yan H et. al. *N Engl J Med*. 2009;360:765-773



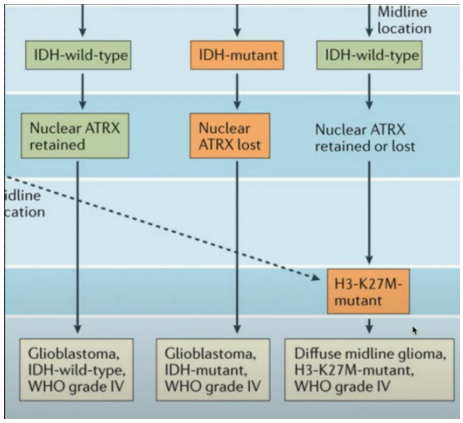
Reifenberger G., Wirsching H., Knobbe-Thomsen, C. et. al. *Nat Rev Clin Oncol*. 14, 434-452.

Glioblastoma, WHO Grade IV, IDH Staining ● IDH1 R132H (most common IDH mutation) ● IHC, positive example to the right	
Glioblastoma, WHO Grade IV, ATRX Staining ● ATRX mutation = loss of expression ● Left side of image is normal ARTX expression within endothelial cells ● Right side of image is no ATRX expression (only see nuclei with blue counterstain)	
Glioblastoma, WHO Grade IV, P53 staining ● p53 mutation leads to ↓ function, but protein accumulates ● Paradoxical ↑ in p53 expression (again, protein does not work)	
12 year old male with headaches, nausea, and vomiting ● Case study ○ Brain stem lesion (pons) ○ Hydrocephalus ○ Diffusely infiltrative ○ Looked like a glioblastoma… ○ But had an H3K27M mutation ● Dx: Diffuse midline glioma	

Diffuse midline glioma, WHO grade IV

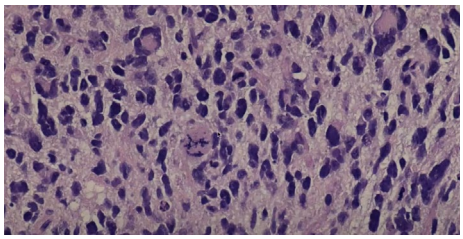
- Defined by:
  - (1) Midline location clinically
  - (2) Infiltrative growth pattern histologically
  - (3) Presence of H3K27M mutation molecularly
    - Histone 3, Lysine 27
    - Same as H3K28M (same implications for diagnosis)

Reifenberger G., Wirsching H., Knobbe-Thomsen, C. et. al. *Nat Rev Clin Oncol*. 14, 434-452.



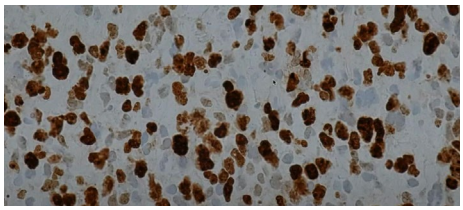
Diffuse midline glioma, WHO grade IV

- Atypical mitotic figures, hypercellularity
- Looks like any other glioblastoma histologically without any special staining, history



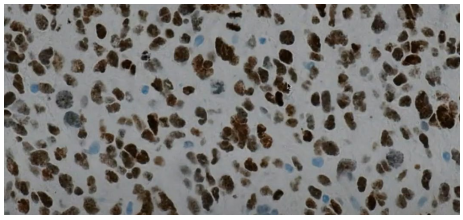
Diffuse midline glioma, WHO grade IV, Ki-67 staining

- Supports ↑ cell proliferation, aggressive growth



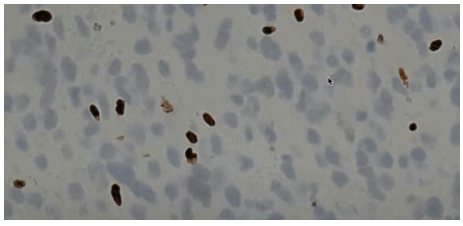
Diffuse midline glioma, WHO grade IV, H3K27M staining

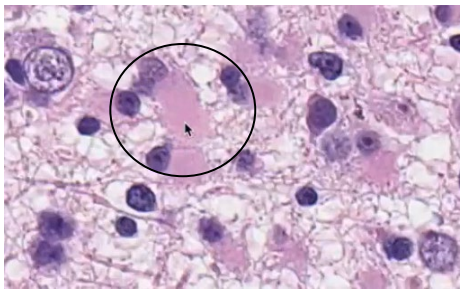
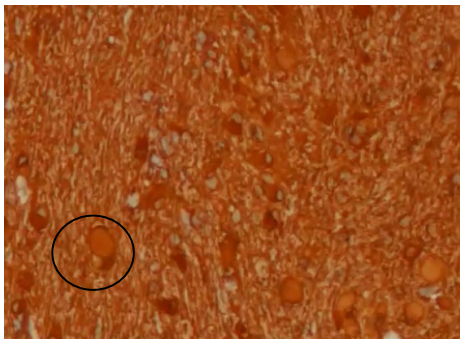
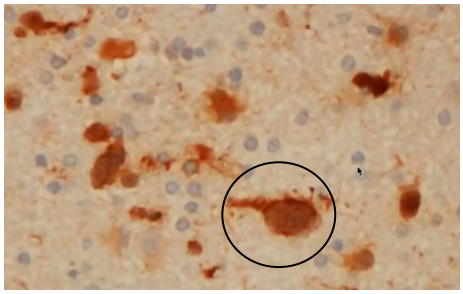
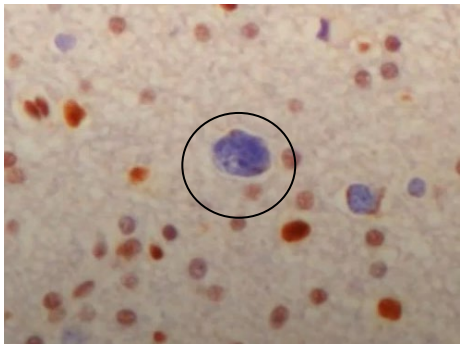
- Very positive stain, supports H3K27M mutation
- Implications of H3K27M
  - ↓ trimethylation at Lysine 27
  - This leads to ↑ Histone 3 activity and ↑ gene expression
  - Ultimately, unregulated cell growth and neoplastic changes



Diffuse midline glioma, WHO grade IV, H3K27M trimethylation staining

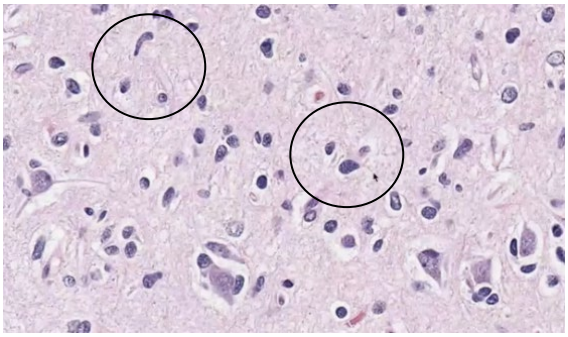
- When staining for trimethylation of H3K27M, we do not see it (suggesting appropriate cell growth/activity)



Anaplastic astrocytoma, IDH-mutant, WHO Grade III ● Molecular features; *IDH*, *ATRX*, and *TP53* mutations ● Typically presents in fifth decade of life ● ↑ nuclear atypia/cellularity, proliferation ○ Unlike glioblastomas, they do not have palisading necrosis and microvascular proliferation on histology ○ Classic feature: domesticities ■ Eccentric nuclei with abundant eosinophilic cytoplasm (circled) ● Prognosis: death 2-5 years	
Anaplastic astrocytoma, IDH-mutant, WHO Grade III ● IHC staining, Gliofibrilliary acidic protein (GFAP) + ● Positive in majority of glial neoplasms ● Highlights domesticites (example circled)	
Anaplastic astrocytoma, IDH-mutant, WHO Grade III ● IHC staining, IDH1 R132H ● Positive (example circled)	
Anaplastic astrocytoma, IDH-mutant, WHO Grade III ● IHC staining, ATRX ● Tumor cells have lost their ATRX ○ Only stain blue with counterstain (example circled)	

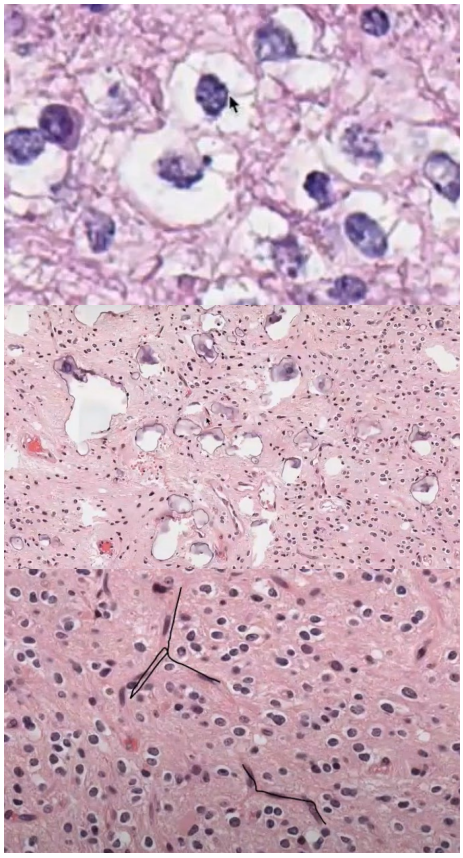
Anaplastic astrocytoma, IDH-mutant, WHO Grade II

- Epidemiology: 0.6/100,000; young adults
- Molecular features; *IDH*, *ATRX*, and *TP53* mutations
- Symptoms: seizure, headache, focal neurologic deficits (FNDs)
    - Weakness, numbness
- Imaging/Gross: Ill-defined growth pattern
- Survival 5-10 years
- Histology
    - Mild to moderate ↑ cellularity
    - Mild nuclear pleomorphism
    - Fibrillary background do to astrocyte cell processes
    - Indistinct transition from neoplastic to reactive



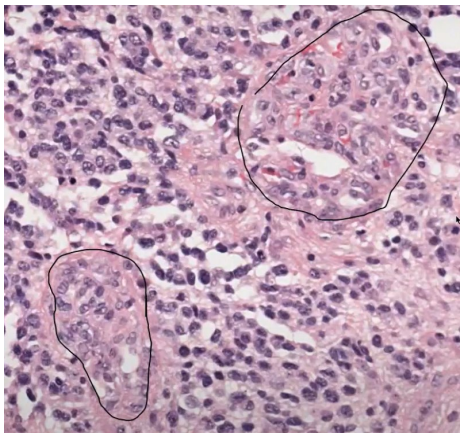
Oligodendroglioma, IDH-mutant and 1p/19q co-deletion, WHO Grade II

- Usually affect the cerebral hemispheres of adults
- Symptoms: seizures for years prior to diagnosis
- Histology:
    - Fried egg appearance (perinuclear cytoplasmic clearing with round, regular nuclei) - top image
        - May not be present in a frozen section during surgery because this is actually an artifact of processing (paraffin embedded tissues)
    - Microcalcifications, microcysts - middle image
    - Chicken-wire vessels - bottom image
        - Really fine capillaries that often branch at different angles
        - Examples highlighted
- Molecular features: *IDH* mutation, *TERT* promoter mutation, chromosome arms 1p/19q co-deletion (must be present to make diagnosis)

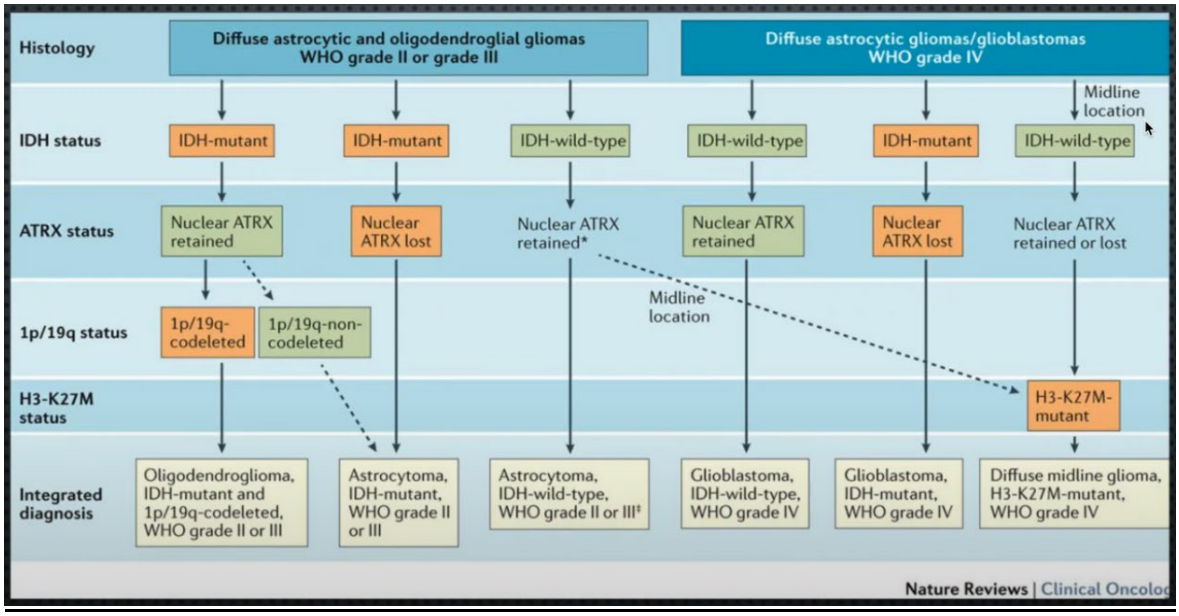


Oligodendroglioma, IDH-mutant and 1p/19q co-deletion, WHO Grade III

- Prognosis: median survival 11 years
- Histology: ↑ cellular and pleomorphism, microvascular proliferation, necrosis, or >5 mitoses/10 high power fields
    - Microvascular proliferation (circled) and necrosis are not specific for glioblastomas
    - Based on clinical and histologic context
- Molecular features: *IDH* mutation, *TERT* promoter mutation, chromosome arms 1p/19q co-deletion



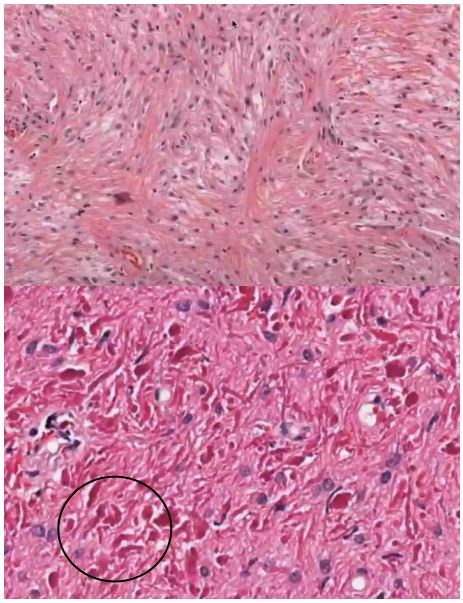
Summary of Grade II-IV Gliomas



Reifenberger G., Wirsching H., Knobbe-Thomsen, C. et. al. *Nat Rev Clin Oncol*. 14, 434-452.

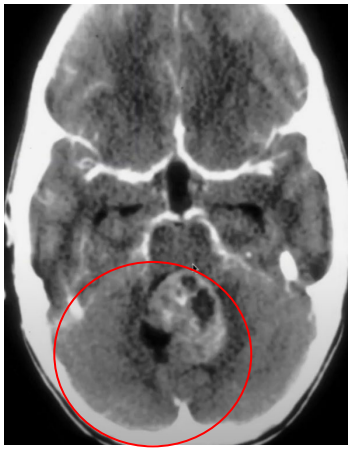
Pilocytic Astrocytoma, WHO Grade I

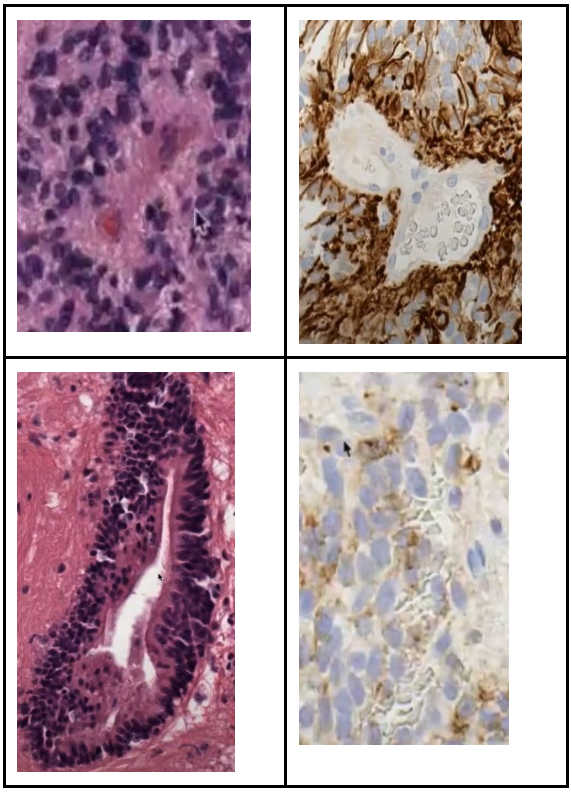
- Relatively “benign”
- Population: children and young adults
- Location: Cerebellum >> Floor/Walls of 3rd Ventricle, optic nerves, cerebral hemispheres
- Molecular; BRAF:KIAA fusions (no defining mutations however, this is the most common)
    - MAPK pathway alterations
- Histology:
    - “Hair-like” neuronal process - top image
    - Rosenthal fibers - bottom image
        - Eosinophilic globules (example circled)



Ependymoma, WHO Grade I

- Epidemiology: 5-10% of primary brain tumors in children; in adults, a/w NF2
- Sites: arise next to the ependymal ventricular system
- Sx: headaches, n/v due to CSF obstruction (hydrocephalus)
- Prognosis: dependent on location and molecular features
    - Example to the right is in 4th ventricle
- Histology (see chart)
    - Perivascular pseudorosettes - top left
        - Tumor cells collect around blood vessels and send down their processes towards the vessels, making a "pseudorosette"
    - GFAP staining - top right
    - May try to form "new ventricles" with "true lumen" - bottom left
    - Intracytoplasmic lumens filled with epithelial membrane antigen (EMA), "perinuclear dot-like positivity" - bottom right





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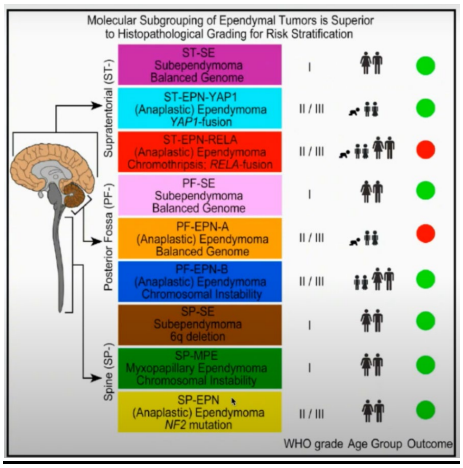
Summary of Molecular Subgrouping of Ependymal Tumors vs. Histopathological Grading for Risk Stratification

- Not high yield/need to know at this point
- Represents integrative diagnosis patterns for Ependymal tumors

Pajtler et. al., 2015, *Cancer Cell*. 27, 728-743



Part 2. Meningioma

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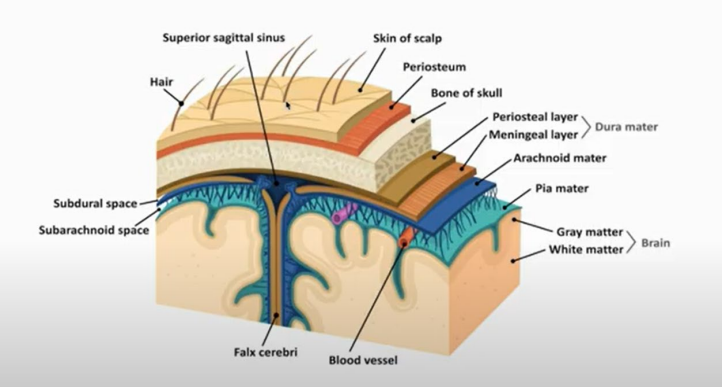
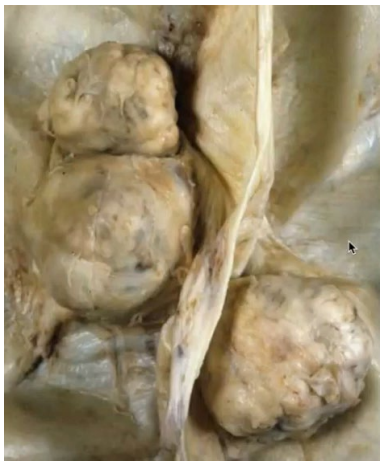
Review of Normal Brain Anatomy



*Meningiomas arise from cells of arachnoid layer and adhere to dura mater

Meningiomas

- Epidemiology: Most common primary brain tumor
- Etiology: Radiation risk
  - Express progesterone receptor (PR) and may grow rapidly during pregnancy
- Presentation: slow growing; may be asymptomatic; headache; seizures
- Site: Attached to the dura or within ventricular system
  - Meningiomas arise from cells of arachnoid mater and often grow into/attach to the dura mater ("dural tail" on imaging)
- Prognosis: most meningiomas are Grade I (low grade), but meningiomas can go bad (Grades II-III)



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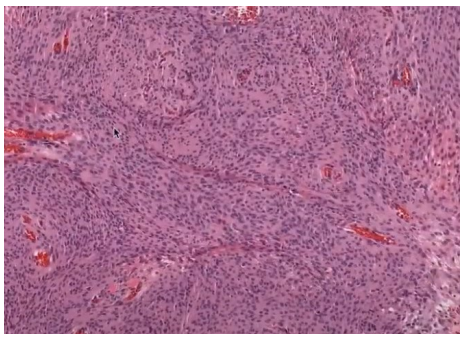
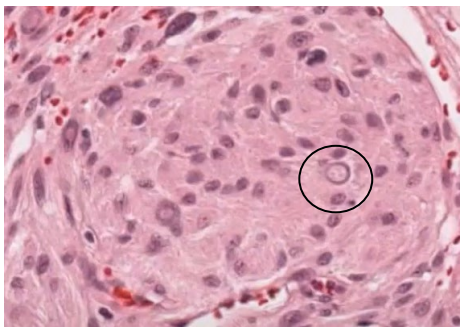
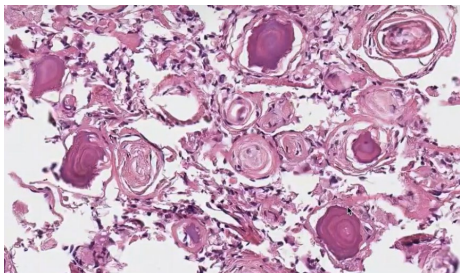
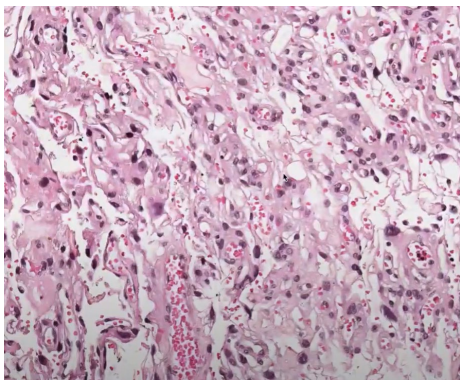
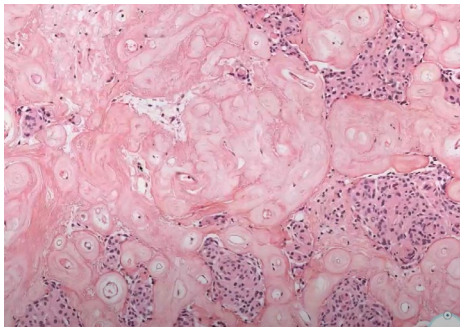
Grade I Meningiomas ● Common histologic variants: ○ **Meningothelial** ■ Whorls, fascicles ■ Ovoid nuclei with inconspicuous nucleoli and fine chromatin	
Grade I Meningiomas ● Common histologic features: ○ **Nuclear pseudoinclusions** ■ Invaginations of the nucleus that appear as similar color as to the surrounding cytoplasm ■ Example circled ○ **Inconspicuous cell borders**	
Grade I Meningiomas ● Common histologic variants: ○ **Psammomatous** ■ Psammoma bodies - cells that want to form a layer and coat the brain, instead they form concentric layers around each other ■ Middle becomes calcified ■ "Concentric layers of calcifications"	
Grade I Meningiomas ● Common histologic variants: ○ **Microcystic angiomatous** ■ Formation of multiple cysts within the meningioma ■ Corresponding prominent vascularity observed	

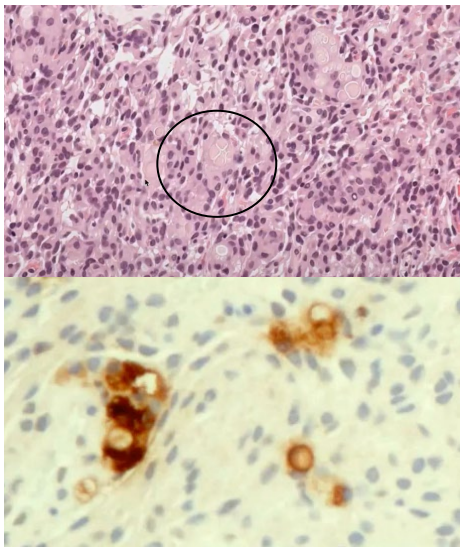
Grade I Meningiomas

- Common histologic variants:
  - **Sclerosed**
    - Often seen in older meningiomas
    - Prominent hylanation
    - Still observe classic other meningioma features in between sclerosed areas (e.g., whorls)



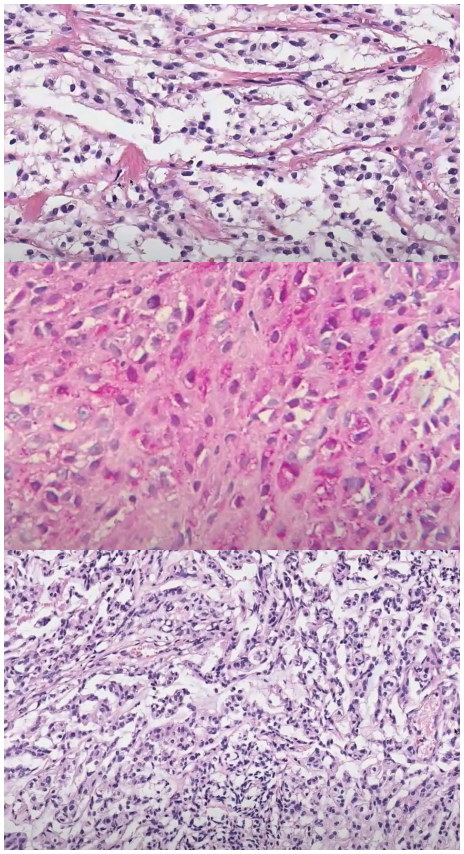
Grade I Meningiomas

- Common histologic features:
  - **Secretory**
    - Prominent secretions (example circled) - top image
    - Can mimic psammoma bodies
      - Often paler in color, not calcified
    - EMA IHC staining - bottom image
      - Observe positive EMA staining in secretions
    - Can also use CEA, or carcinoembryonic antigen, staining (not observed here)



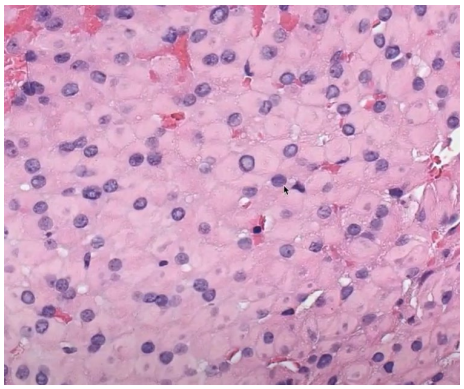
Grading

- **Atypical meningioma, WHO Grade II**
  - **Clear cell meningioma** - top image
    - Cytoplasm cleared out (not eosinophilic)
    - Thick bands of fibrous collagen in between cells
    - Clear cells highlighted on PAS stain - middle image
  - **Chordoid meningioma** - bottom image
    - Myxoid background (more blue)
    - Cells arranged in chords
    - Prominent feature of tumor
  - **Brain invasion**
  - 4 or more mitoses/10 high power fields
  - 3 of 5 criteria: hypercellularity, small cell change, prominent nucleoli, necrosis, sheeting architecture



Grading

- **Anaplastic meningioma, WHO Grade III**
  - 20 or more mitoses/10 high power fields
  - Rhabdoid features (right)
    - Eccentric nucleus
    - Abundant eosinophilic cytoplasm
    - Well-demarcated cells
    - May or may not appeared whorled
  - Papillary features
  - Overly malignant: carcinoma, melanoma, or high grade sarcoma



Part 3. Rare Glial Neoplasms

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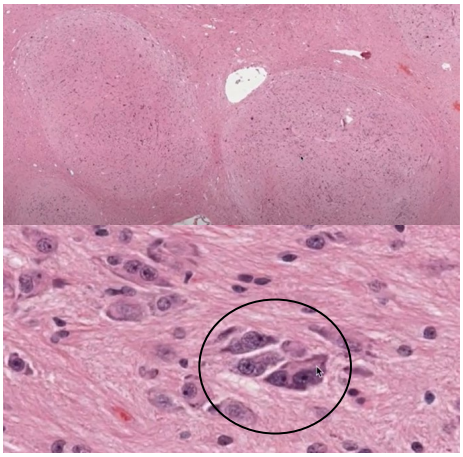
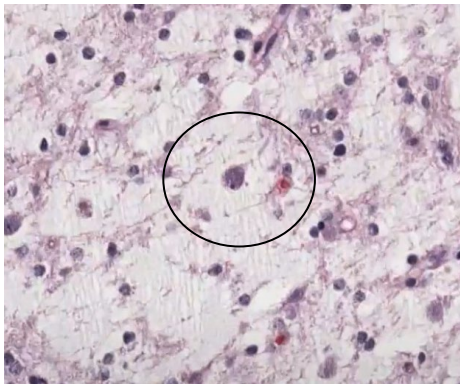
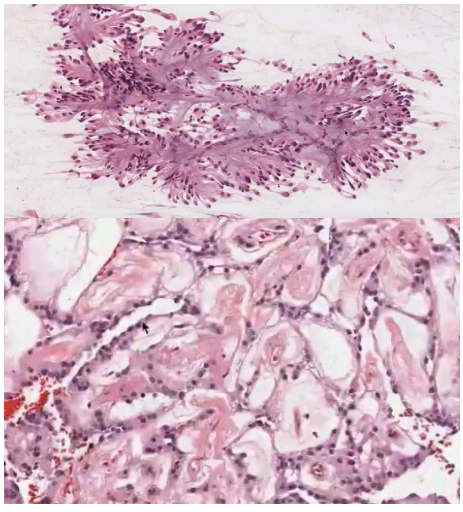
Ganglioglioma ● Epidemiology: Rare, <1% intracranial neoplasms; <30 years old ● Presentation: Seizures ● Imaging: Cystic, Temporal lobe lesion ● Micro: Mixture of mature neurons and glial tissue ○ Classically nodular - top image ○ Bi-nucleated appearing neurons, neurons crowded against each other (circled), background of additional glial tissue - bottom image ● Prognosis: Slow growing unless glial component develops anaplasia (“anaplastic glioglioma”) ● Molecular: BRAF V600E (most common)	
Dysembryoplastic neuroepithelial tumor ● Epidemiology: Rare (≈100 cases); teenagers/young adults ● Presentation: Incidental finding or epilepsy ● Imaging: Nodular cortical lesion, Temporal or Frontal cortex ● Micro: Extracellular mucin; small round cells, similar to oligodendrocytes, arranged in clusters ○ “Neurons floating in pools of mucin” (example circled) ● Prognosis: Good if surgically resected ● Molecular: BRAF V600E (most common)	
Myxopapillary ependymoma ● Site: Filum terminale of spinal cord ● Micro: Papillary and myxoid background (top image) ○ Ependymoma cells are very round and prominent ○ On H&E (bottom image), can see abundant pools of mucin surrounded by ependymoma cells ● Rx: Surgery (good prognosis if complete surgical resection achieved)	

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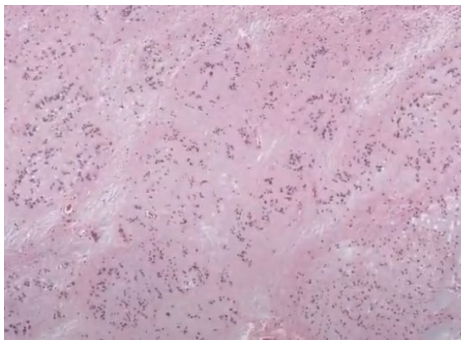
Subependymoma

- Epidemiology: Middle-aged to elderly adults
- Site: 4th ventricle (50-60%), lateral ventricle (30-40%), spinal cord
- Presentation: Hydrocephalus or asymptomatic
- May calcify
- Micro: hypocellularity, arranged in vague nodules (right)
- Rx: Resection if symptomatic



Part 4. Genetic Brain Tumors

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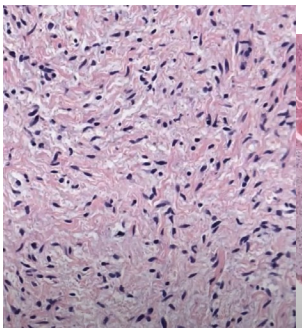
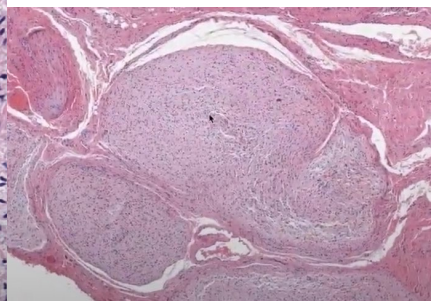
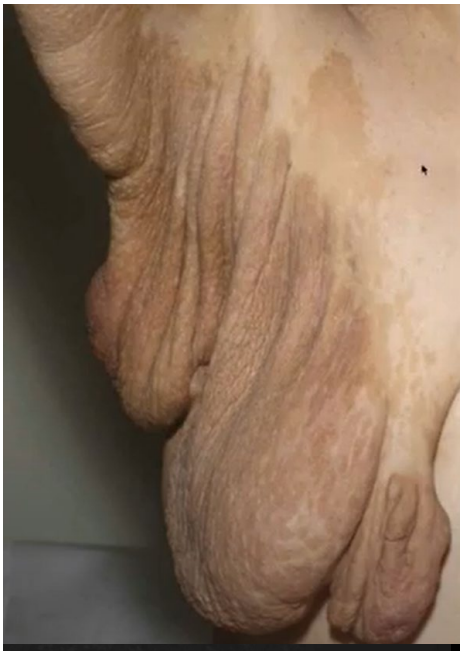
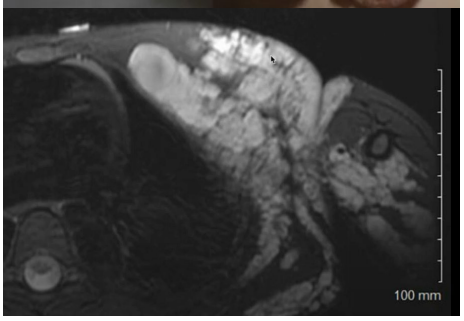
Type 1 Neurofibromatosis

- Autosomal dominant, 1 in 3000
- Presentation (variable)
  - **Neurofibromas** (plexiform - right images, solitary)
    - Micro:
      - Pointy nuclei, background of mucin, “shredded carrot” background - bottom left
      - Nodules - bottom right
  - **Optic nerve gliomas**
  - **Pigmented nodules of iris** (Lisch nodules)
  - **Pigmented skin macules** (café au lait spots - right image)
- *NF1* gene = neurofibromin tumor suppressor; GTPase that inhibits RAS
- Neurofibromas may undergo malignant transformation (malignant peripheral nerve sheath tumor)



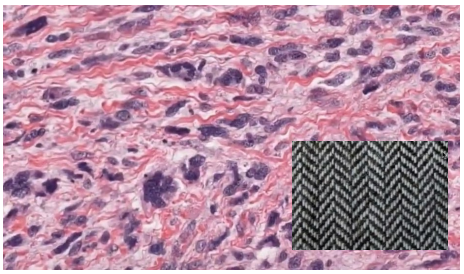






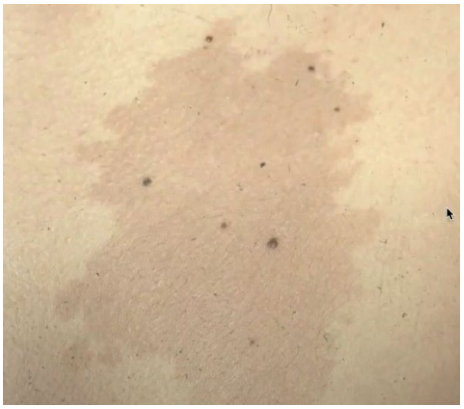
Malignant peripheral nerve sheath tumors

- Epidemiology: 50% arise in setting of NF1
- Pathophysiology: additional loss of p53- and RB-dependent pathways
- Highly aggressive, poor prognosis
- Micro: atypical spindled cells in "herringbone" pattern (right)



Type 2 Neurofibromatosis

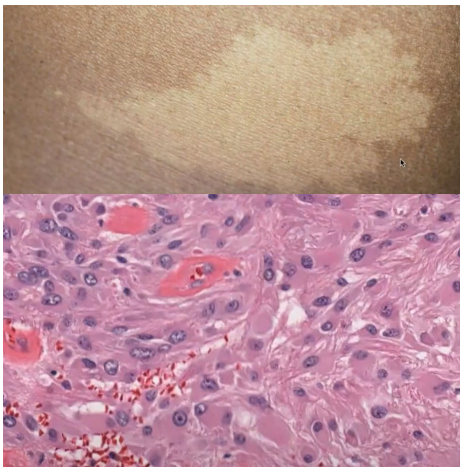
- Autosomal dominant, 1 in 40-50,000
- Characterized by:
  - **Bilateral vestibular (acoustic) schwannomas**
    - CN VIII affected
  - **Multiple meningiomas**
  - **Gliomas** (esp. Ependymomas)
  - **Pigmented skin macules** (café au lait spots) - right
- *NF2* gene (merlin) also mutated in sporadic meningiomas and schwannomas



Tuberous sclerosis

- Incidence: 1/10,000-50,000
- Autosomal dominant, variable penetrance
- Mental retardation, seizures
- **Hamartomas*** and benign neoplasms of the brain and other tissues
  - Renal angiomyolipomas, retinal glial hamartomas, cardiac rhabdomyomas, shagreen patches, subungual fibromas
  - (Subependymal) giant cell astrocytomas (SEGA)
    - Very responsive to mTOR inhibitor therapy (rapamycin), may not need surgical resection
    - Micro: large glial cells (almost "domesticitic") occurring adjacent to the ventricle, abundant eosinophilic cytoplasm - bottom image
  - Other cortical tissues involvement, subependymal nodules
  - Hypopigmented skin macules (ash leaf spots) - top image
- *TSC1* (hamartin) and *TSC2* (tuberin)
- Liver, pancreas, kidney cysts

*benign, non-neoplastic malformations

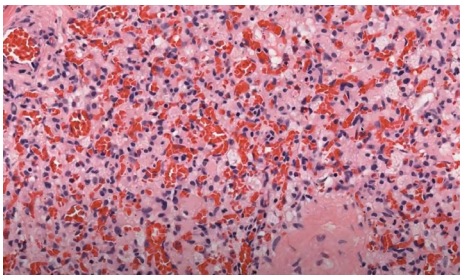


Von Hippel-Lindau disease

- Autosomal dominant, 1 in 30-40,000
- Characterized by:
  - Hemangioblastoma of cerebellum, brain stem/spinal cord
  - Cysts of liver, pancreas, kidney
  - Renal cell carcinoma
- Pathophysiology: pVHL downregulates HIF-1a wich regulates VEGF, erythropoietin (EPO)

Hemangioblastoma

- Epidemiology: M>F, 20-40 years
- 25% in VHL patients/75% sporadic
- Sites: Cerebellum, retina, spinal cord
- Micro: vascular. ↑ blood vessel/capillary formation, vacuolated-appearing stromal cells (right)
- Symptoms: due to increased ICP, due to erythrocytosis 2/2 ↑ EPO
- MRI: Cystic lesion with enhancement



Other Tumor syndromes

- Li Fraumeni, *TP53*/17p, astrocytomas, bone and soft tissue sarcoma
- Turcot, *FAP*/5q, medulloblastoma and GBM, GI polyps, colorectal cancer
- Gorlin, *PTCH*/9q, desmoplastic medulloblastoma, nevoid basal cell carcinoma, odontogenic keratocysts

Part 5. Nerve Sheath Tumors

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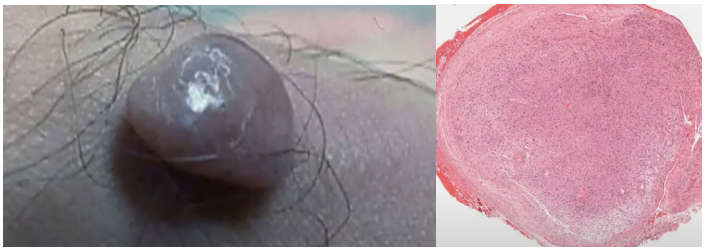
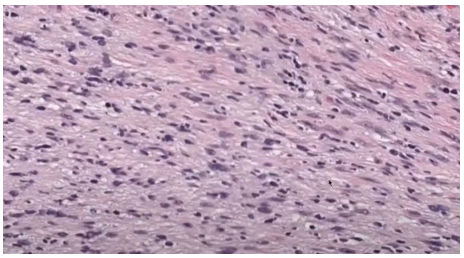
Schwannoma

- Extrinsic to nerve (grow adjacent to nerves, push them off to side/compress them) - bottom left
- Well-circumscribed - bottom right
- Any of the cranial nerves (with the obvious exceptions of Cn I and II) are potential sites
- Histologic appearance (two characteristic patterns):
    - **Antoni A** - dense, hypercellularity, elongated/pointy nuclei arranged in fascicles (A)
        - Verocay bodies - elongated nuclei arranged in waves next to each other with relative adjacent acellular areas (B)
    - **Antoni B** - looser, more white space, less dense (C)



A.



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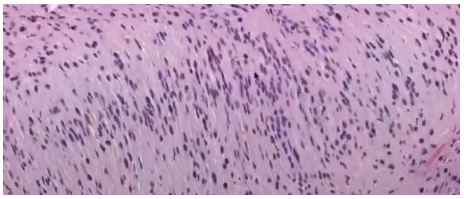

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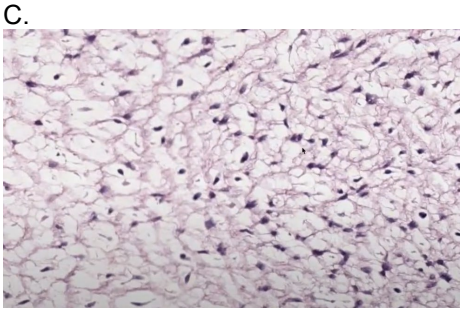
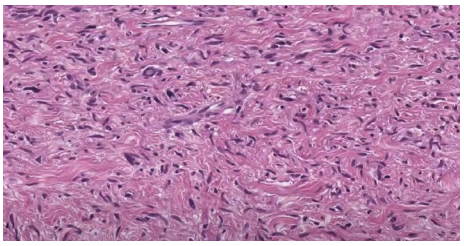


Neurofibroma

- Intrinsic nerve (grow in between nerve fibers)
- Axons intertwined
- "Shaved carrot" appearance on micro due to wavy collagen formation and elongated nuclei (D)
- Intracellular mucin commonly seen

D



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