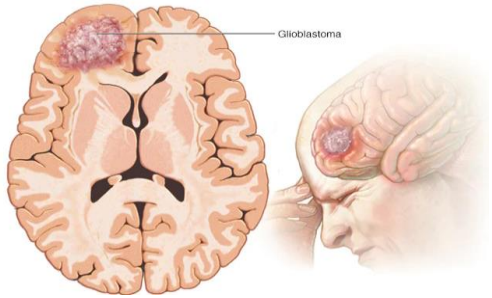
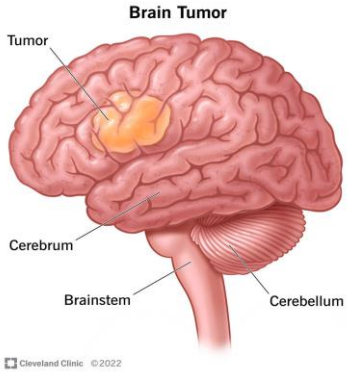


Neurosciences II Module

Central Nervous System Tumors



Dr. Ola Abu Al Karsaneh

❑ Epidemiology

-The annual incidence ranges from 10 - 17/ 100,000 for intracranial tumors and 1 - 2 /100,000 individuals for intraspinal tumors.

- 1/2 to 3/4 are primary tumors, and the rest are metastatic.

- In **children**: 20% of all pediatric tumors and are more likely to arise in the **posterior fossa**, whereas tumors in **adults** are mostly **supratentorial**.

❑ Characteristic features of the CNS tumors:

- No premalignant or in situ stages
- Even low-grade lesions may infiltrate large regions of the brain, leading to serious clinical deficits, inability to be resected, and poor prognosis.
- The anatomic site of the neoplasm can influence outcomes independent of histologic type due to local effects.
- Rarely spread outside of the CNS.

Clinical feature-Pathogenesis

•Headaches	• Increased ICP
•Papilloedema	• Increased ICP
•Nausea or vomiting	• ICP – Medulla ob.
•Bradycardia	• ICP – Parasymp.
•Seizures (convulsions).	• Irritation.
•Drowsiness, Obtundation	• Brain Stem compress
•Personality or memory	• Frontal lobe
•Changes in speech	• Temporal lobe
•Limb weakness	• Motor area
•Balance/Stumbling	• Cerebellum
•Eye movements or vision	• Optic tract, occipital

❑ Etiology

- **Environmental:**

  -Radiation: Often 5-25 years after treatment

  -Immunosuppression

  -Viral & Chemical carcinogens

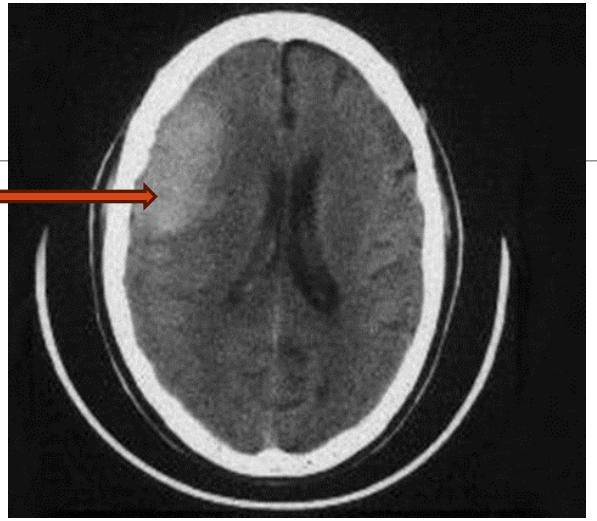
- **Genetic:**

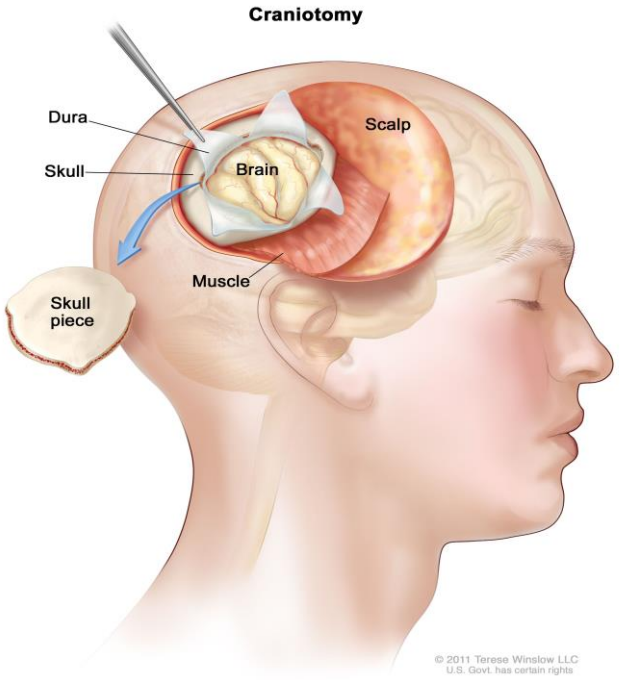
  -Sporadic (as P53, EGFR …).

  -Familial (inherited familial tumor syndromes).

❑ Approach

- History
- Physical and neurological examination
- Lumber puncture (including cytology)
- CT
- MRI
- Brain angiography
- Biopsy





❑ Classification

- Classified according to:

- *Cell of origin & degree of differentiation*.

-However, slowly growing entities may undergo **transformation** into more aggressive tumors.

- The **WHO grading system** is important for treatment and prognosis

❑ Classification

1. Gliomas:

- Astrocytoma and variants
- Oligodendroglioma
- Ependymoma

2. Neuronal Tumors

- Central neurocytoma
- Gangliogliomas
- Dysembryoplastic neuroepithelial tumor

3. Embryonal (Primitive) Neoplasms

-Medulloblastoma

4. Other Parenchymal Tumors

- Primary CNS Lymphoma
- Germ Cell Tumors

5. Meningiomas

6. Metastatic Tumors

❑ Most common intracranial tumors

Adults	Children
Metastatic	Astrocytoma
Glioblastoma multiforme (GBM)	Medulloblastoma
Anaplastic astrocytoma	Ependymoma
Meningioma	

1. Glioma

1. Astrocytoma:

- Commonest glial tumor.
- **WHO Grading depends on:**
    1. **Nuclear pleomorphism**
    2. **Mitotic activity**
    3. **Necrosis**
    4. **Vascular proliferation**

- High-grade tumors can arise from the transformation of low-grade gliomas **OR** can occur *de novo.*

A. Pilocytic astrocytoma:

- **Children and young adults**.
- Commonly **cerebellum** (sometimes 3rd ventricle, optic nerve & occasional cerebral hemisphere).
- Relatively benign

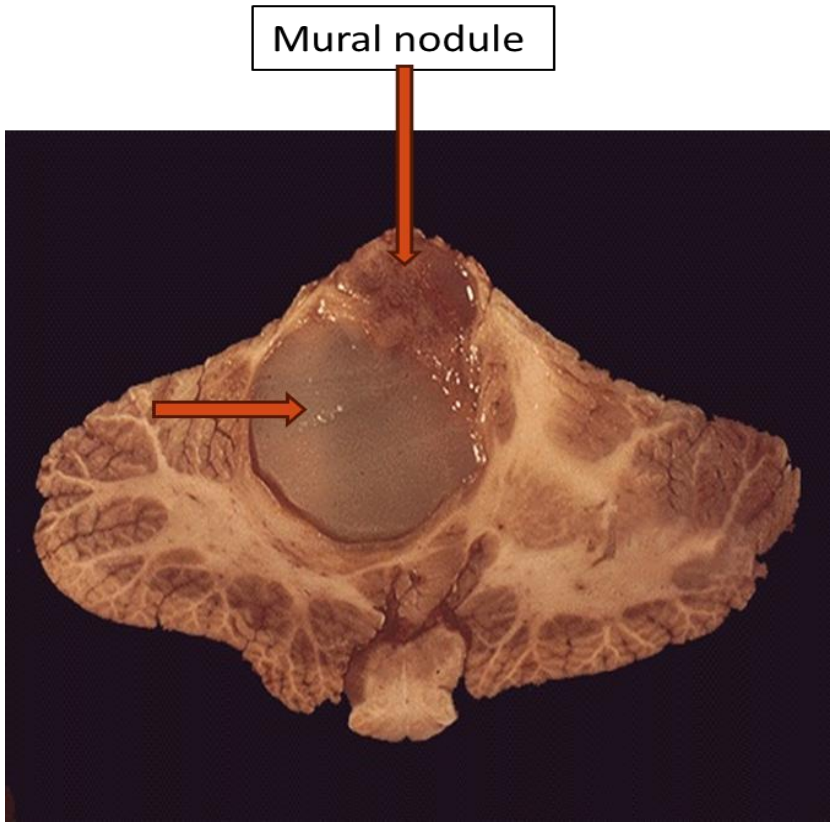
B. Diffuse (Fibrillary) astrocytoma:

- **4th to 6th decade**.
- Commonly in the **cerebral hemisphere**
- Presents with seizures, headaches, and focal neurologic deficits
- Variable grades:
  - Diffuse astrocytoma (well-differentiated), grade II
  - Anaplastic astrocytoma, grade III
  - Glioblastoma multiforme (GBM), grade IV

❖ Pilocytic Astrocytoma (**WHO grade I**)

➢ **Gross:**

-Often cystic (with mural nodule) or well-circumscribed solid mass.



➢ **Microscopic:**

-Bipolar cells with long, thin “hairlike” processes.

-Microcysts, eosinophilic granular bodies & Rosenthal fibers are commonly seen.

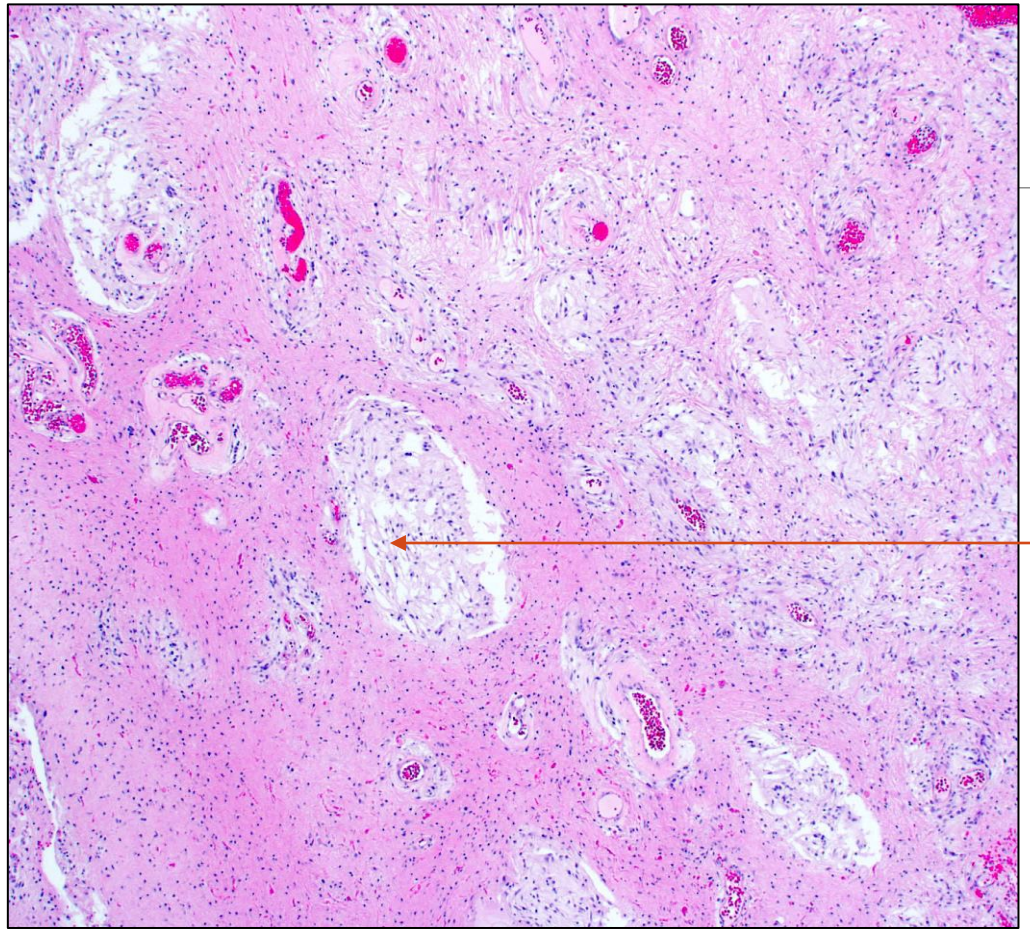
-**NO or rare** mitosis & necrosis.

- GFAP + (IHC)

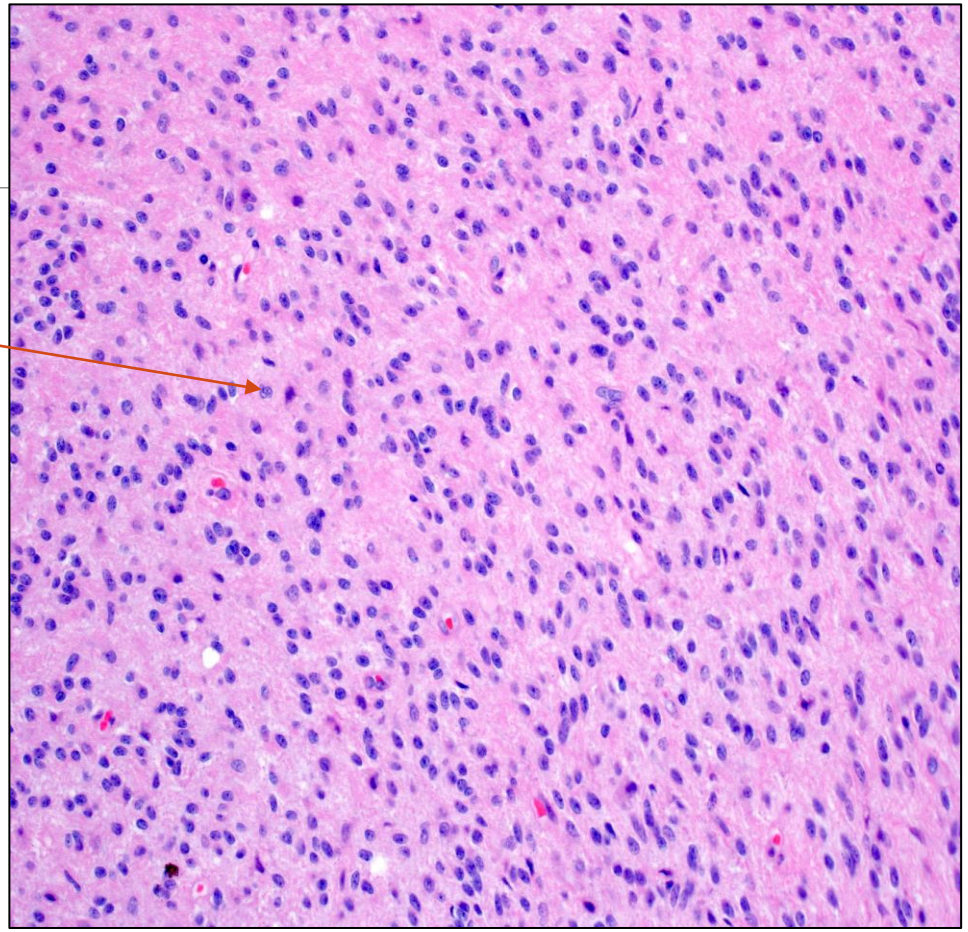
➢ **Genetics:**

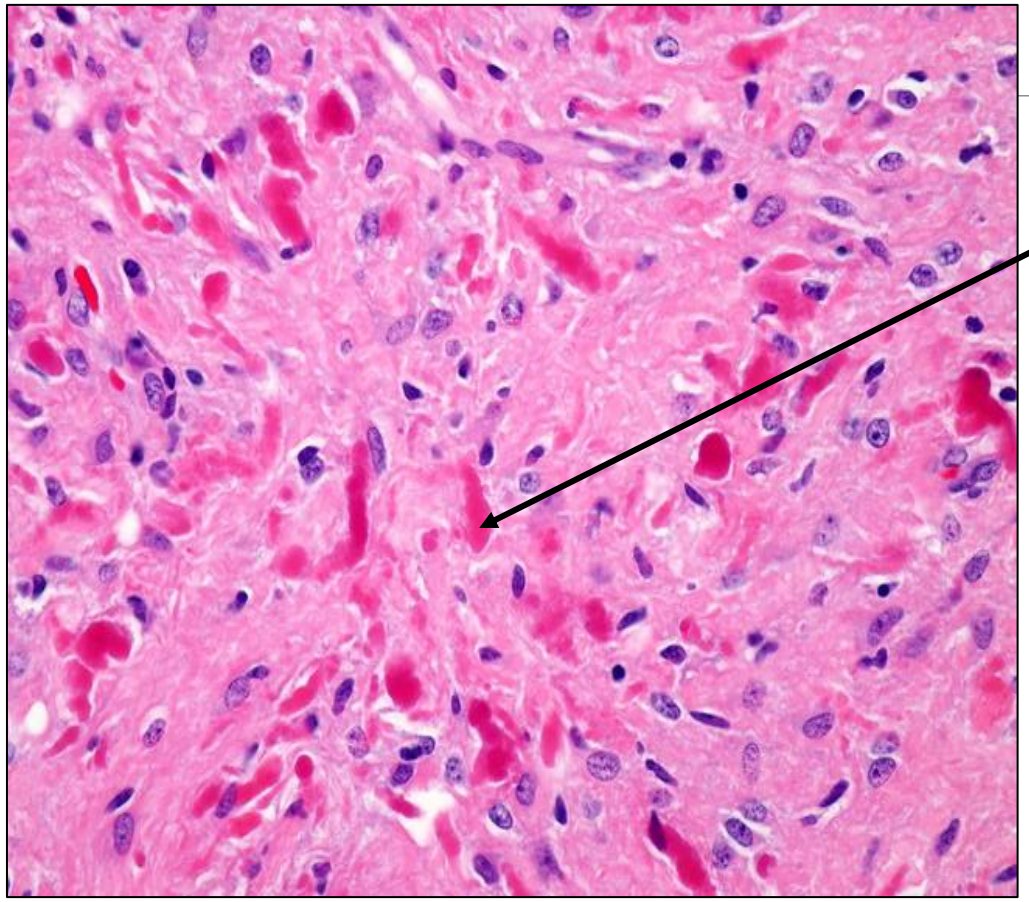
- **BRAF** mutation or translocation

- No IDH1 or IDH2 mutation



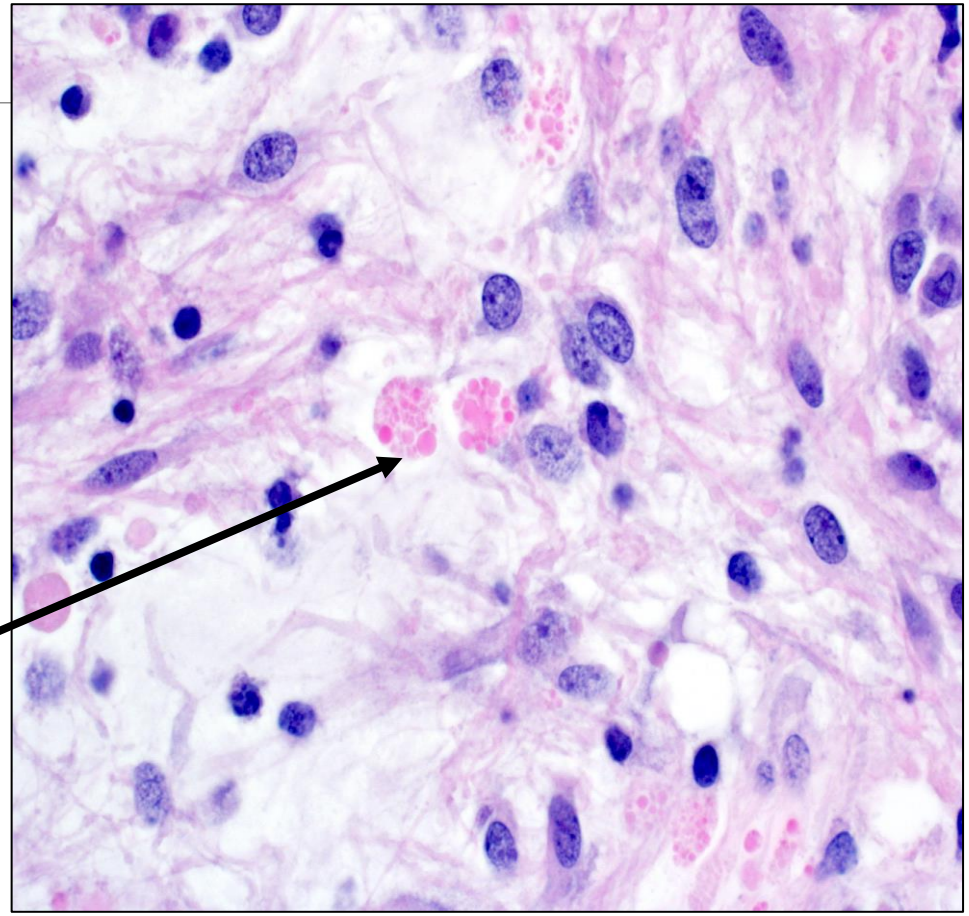
- **Biphasic appearance,** compact fibrillary, and loose microcystic





- Rosenthal fibers

- Granular eosinophilic bodies



❖ Diffuse Astrocytoma (**WHO grade II**)

- Can be static or progressive; the mean survival is > 5 years.

- Well differentiated

➢**Gross:**

- **Poorly defined infiltrative** tumors that distort the invaded brain without forming a discrete mass

- The cut surface: either firm or soft and gelatinous; +/- cystic degeneration

➢ **Microscopic:**

- Mild to moderate increase in the number of glial cell nuclei, variable pleomorphism.

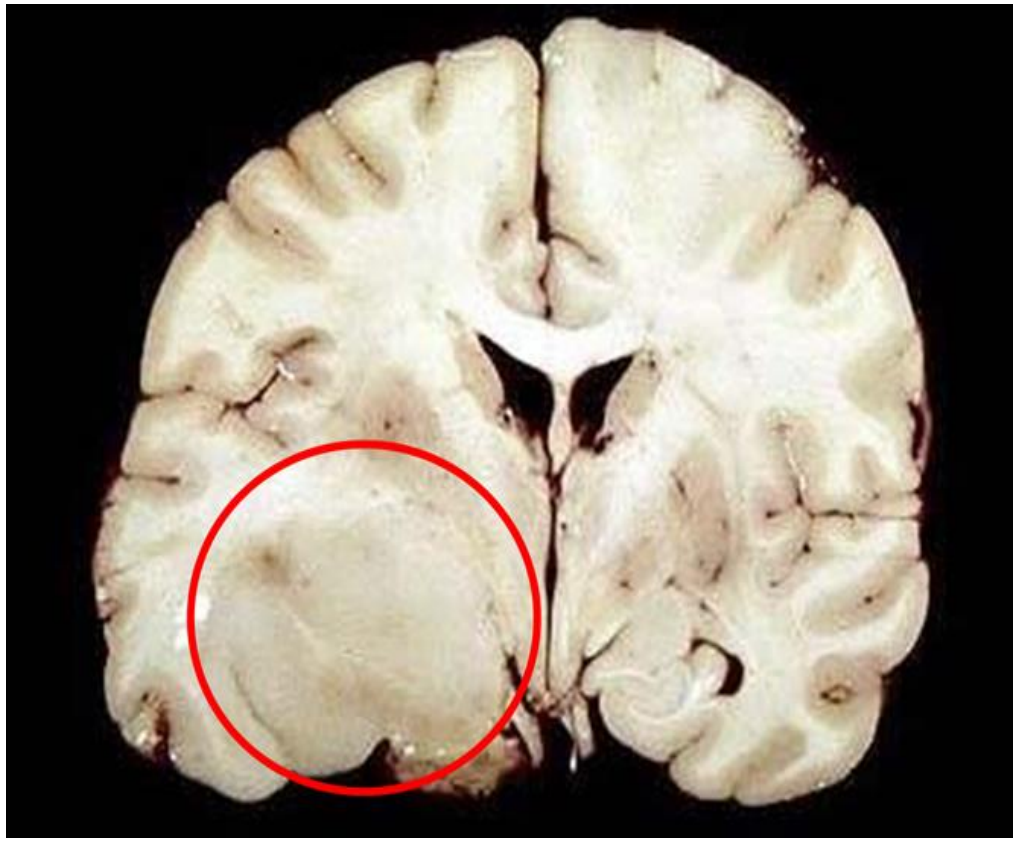
- Fibrillary background.

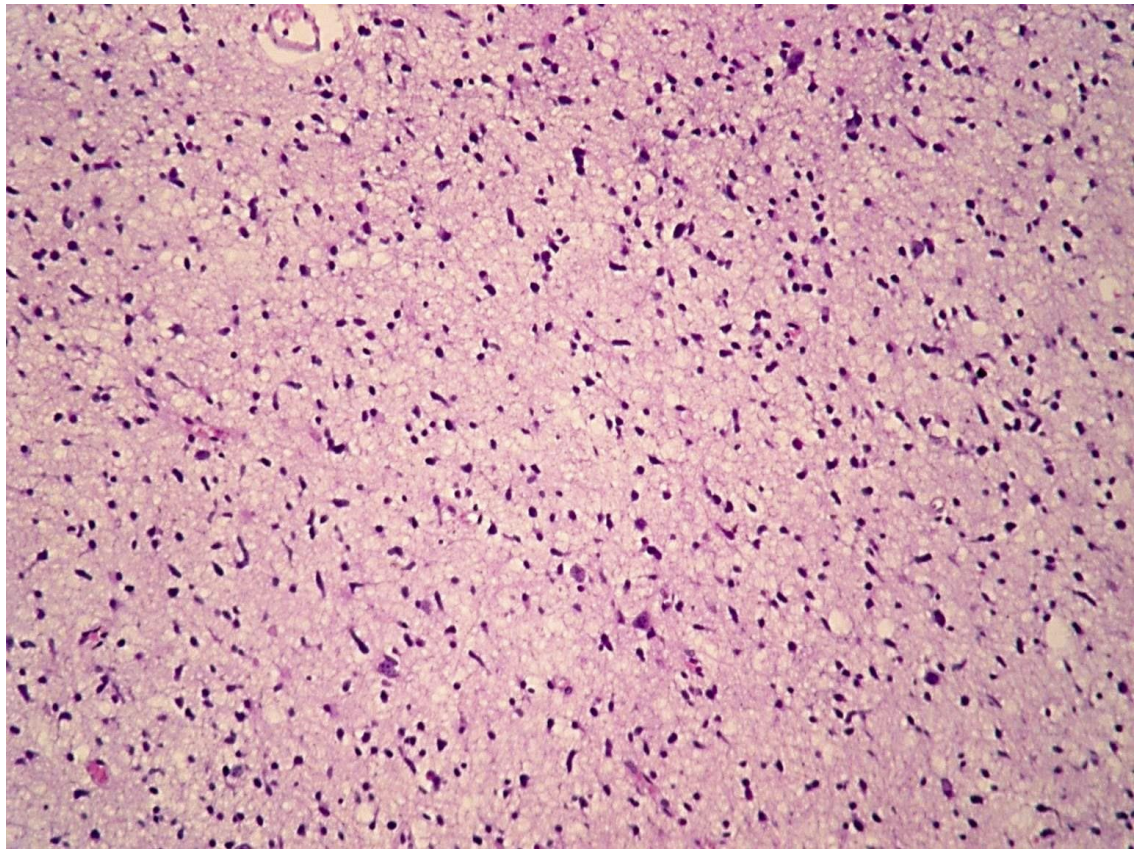
- No distinct transition between neoplastic and normal tissue.

- GFAP +

➢**Genetics:** **IDH1**, IDH2 genes mutations

Moderately hypercellular astrocytic tumor consistent with CNS WHO grade II





❖ Anaplastic Astrocytoma (**WHO grade III**)

➢ **Gross:**

- As grade II

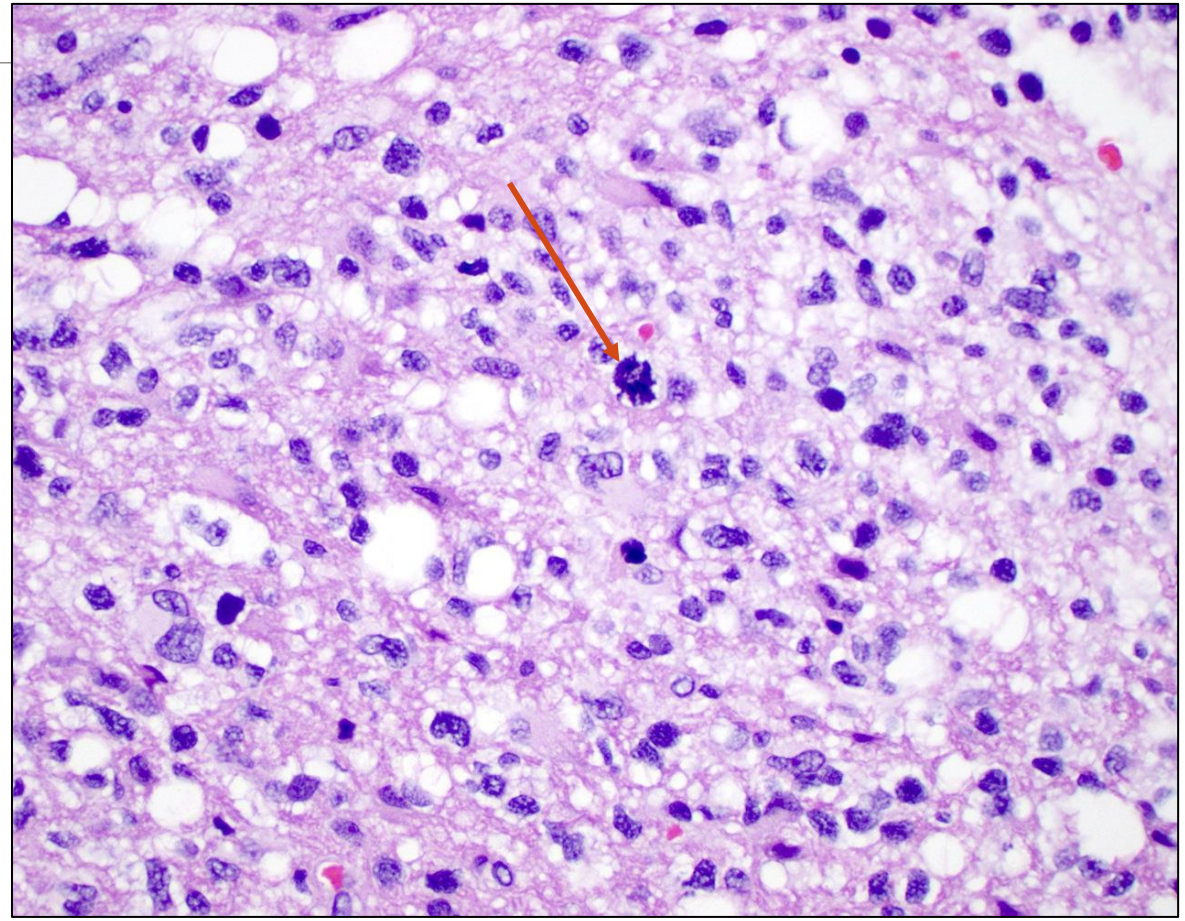
➢**Microscopic:**

- More densely cellular and have greater nuclear pleomorphism; **mitotic figures** are present

- GFAP +

➢**Genetics:**

- **IDH1,** IDH2 genes mutations



❖ Glioblastoma Multiforme (GBM), **WHO grade IV**)

- **CT/MRI:** Supratentorial **ring enhancing tumor** with surrounding edema

➢ **Gross:**

- Variation from region to region is characteristic (Some are firm and white, others are soft and yellow (tissue necrosis), and others cystic degeneration and hemorrhage

➢ **Microscopic:**

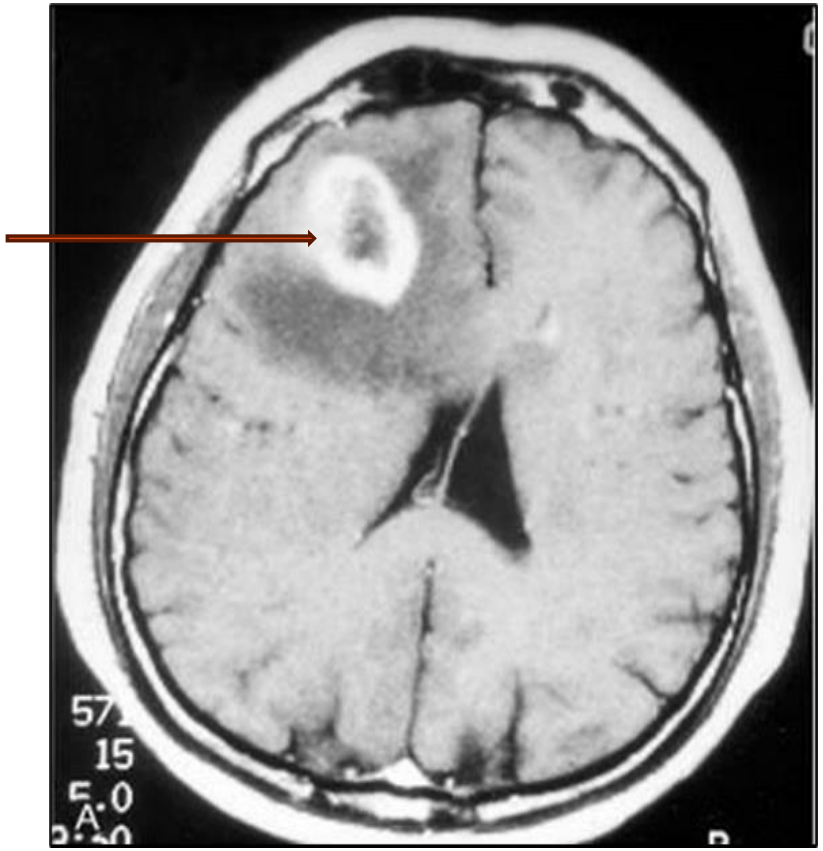
- Similar to anaplastic astrocytoma with:

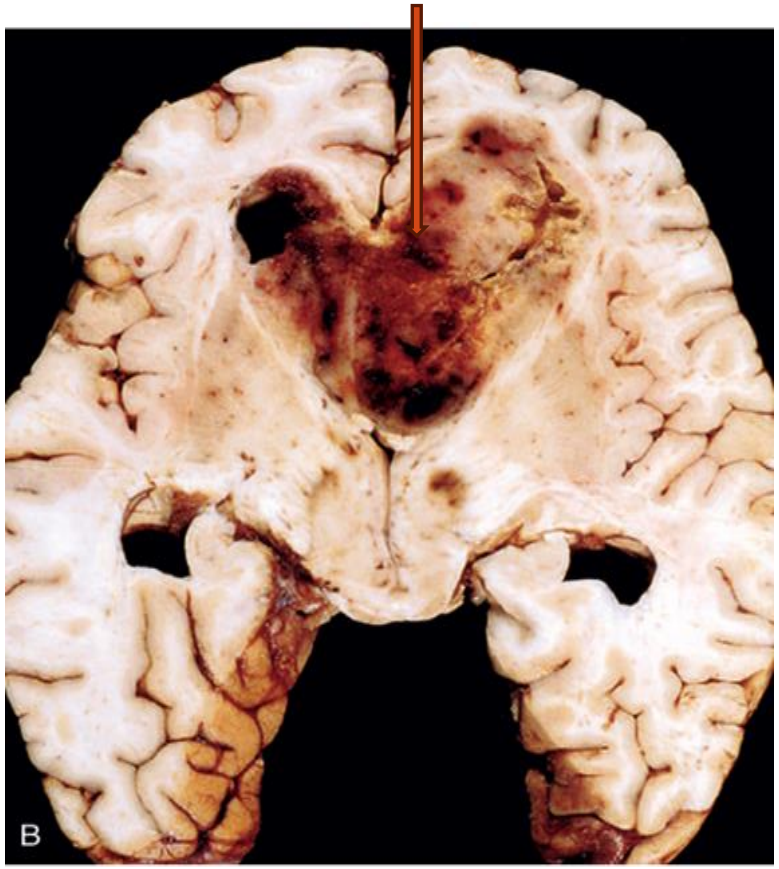
- Necrosis (bands of necrosis with palisaded tumor cells along the border) or microvascular (glumeruloid) proliferation.

- GFAP +

➢ **Genetics:**

- Inactivation of p53 & Rb
- Activation of PI3K.
- Amplification of EGFR
- **Prognosis:** Very poor; with treatment, the median survival is only *15 months*.

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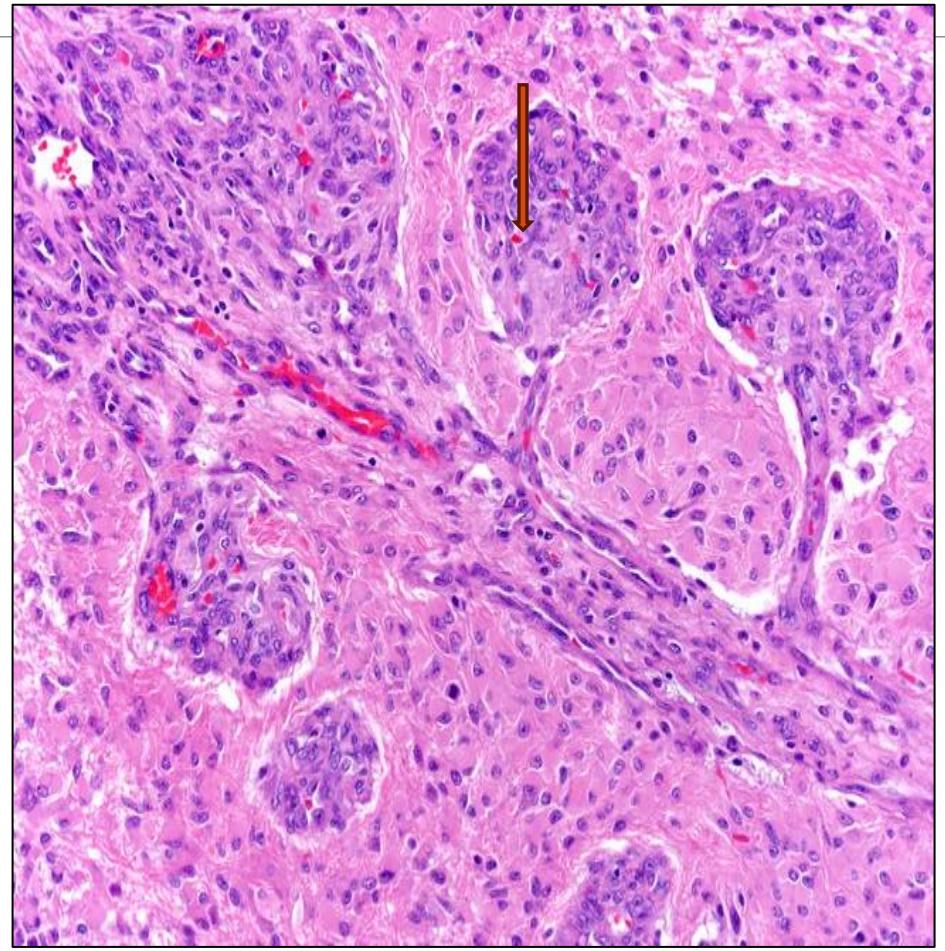
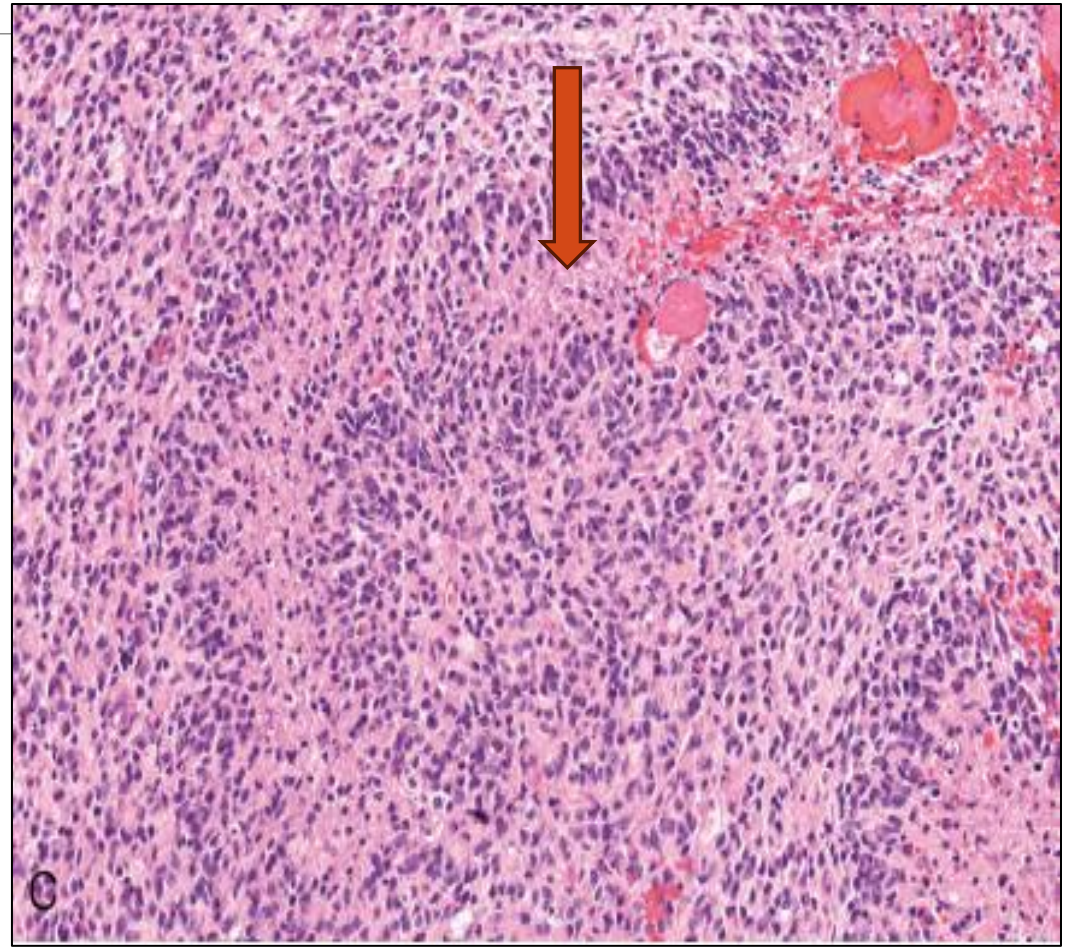
Vascular proliferation



Palisaded necrosis



2. Oligodendroglioma (WHO Grade II or III):

- More in the 4^{th} and 5^{th} decades of life.

- Presents with neurologic complaints (seizures).

- Mostly in the cerebral hemispheres (frontal or temporal lobes).

- Survival of 10- 20 years for well-differentiated (WHO grade II) or 5-10 years for anaplastic (WHO grade III).

➢ **Gross:**

- Infiltrative form gelatinous, gray masses and may show cysts, focal hemorrhage, and calcification.

➢ Microscopic:

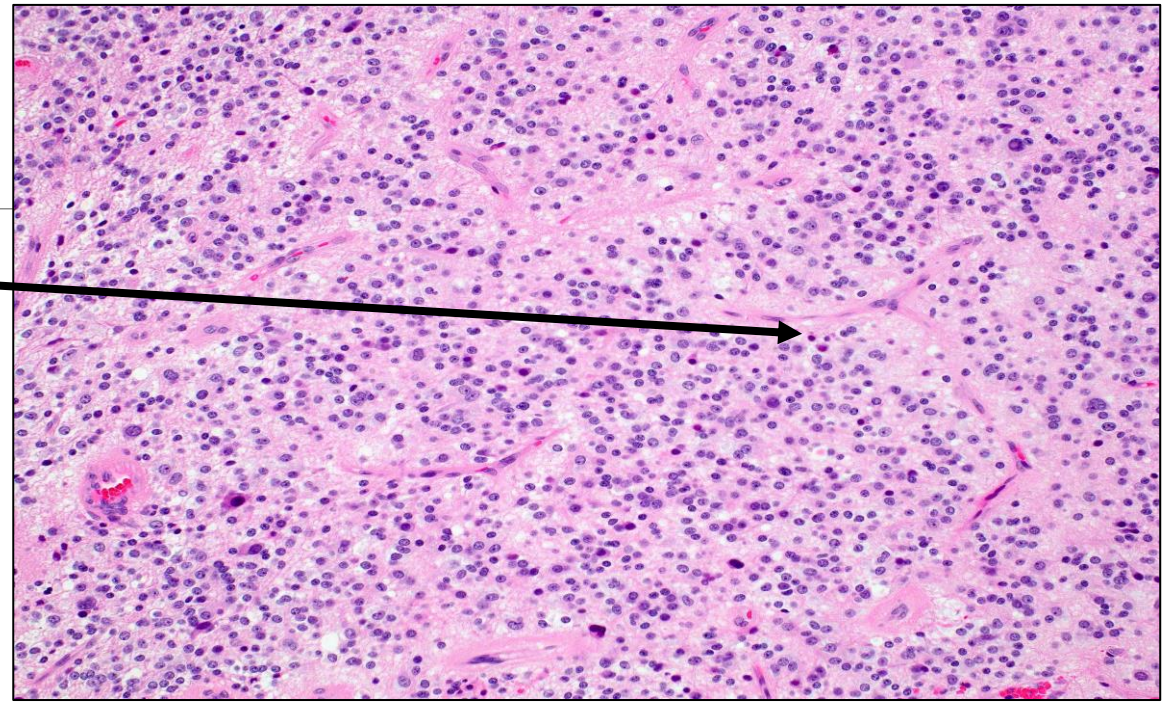
- Sheets of **regular cells** with spherical nuclei containing finely granular chromatin surrounded by a **clear halo of cytoplasm (Fried egg appearance)**

- A delicate network of anastomosing chicken wire capillaries.

- Calcification (in 90%)

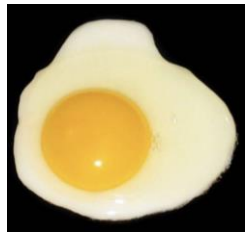
- Mitotic activity is usually low.

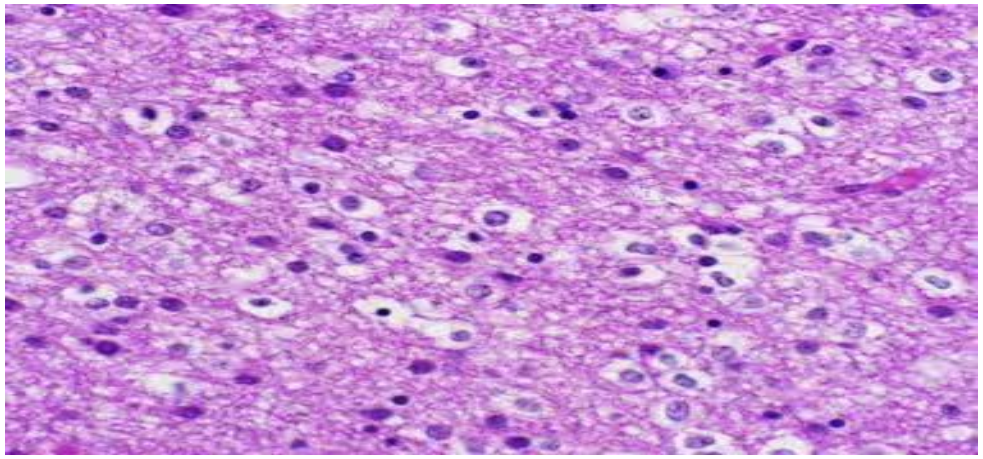
- Grade III: more aggressive with higher cell density, nuclear anaplasia, increased mitotic activity, and often microvascular proliferation & necrosis.



➢ Genetics:

- IDH mutation with Co-deletion of 1p and 19q chromosomal segments





3. Ependymoma (WHO grade II or III)

- Arise next to the ependyma-lined ventricular system.

- In the first 2 decades of life: near the fourth ventricle

- In adults: the spinal cord (most commonly).

- The clinical outcome for completely resected supratentorial and spinal ependymomas is better than for those in the posterior fossa

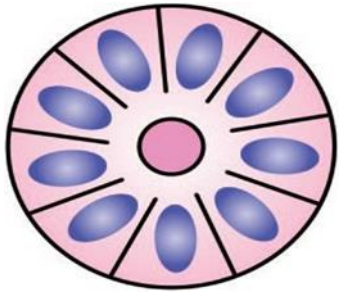
➢ **Gross**:

- Well-demarcated, solid, or papillary masses extending from the ventricular floor.

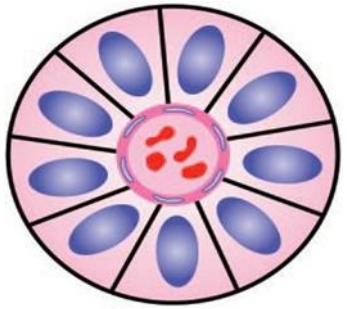
➢ Microscopically:

- Regular, round to oval nuclei and granular chromatin in a fibrillary background.

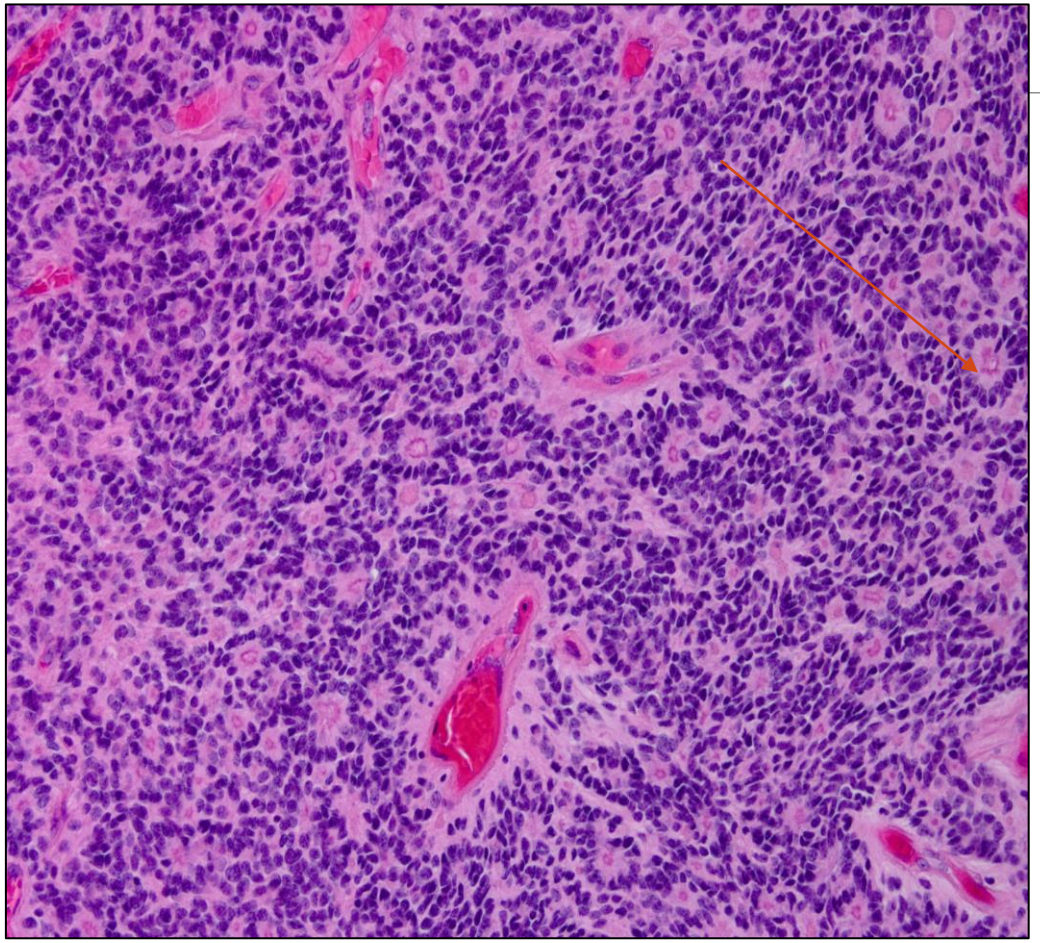
- Tumor cells may form round or elongated structures (**rosettes**, canals)

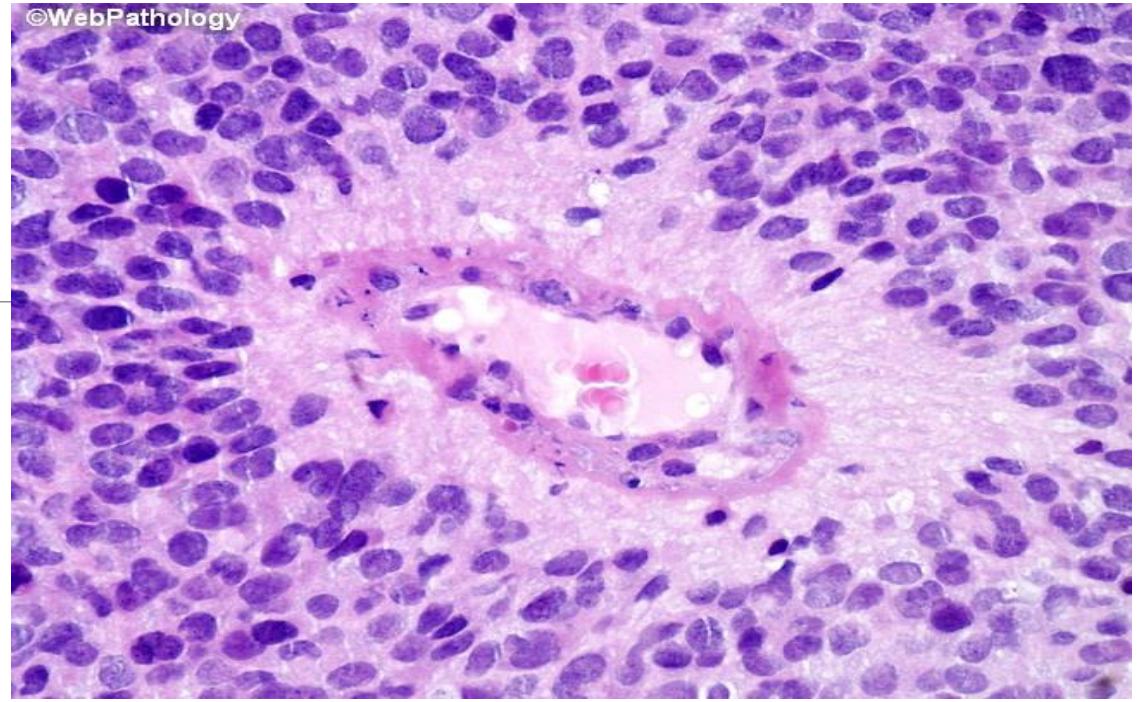


-**Perivascular pseudorosettes**: tumor cells are arranged around vessels



- **Anaplastic ependymomas** (grade III): increased cell density, high mitotic rates, necrosis, microvascular proliferation, and less ependymal differentiation.

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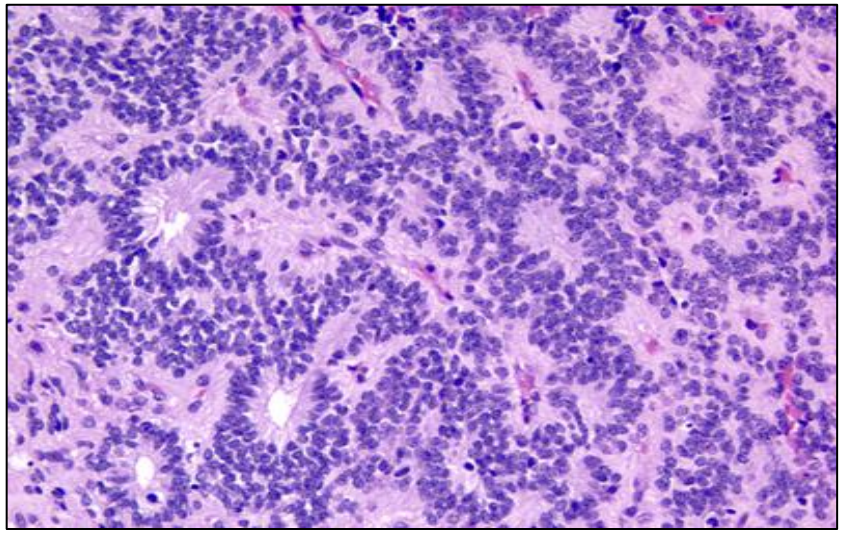
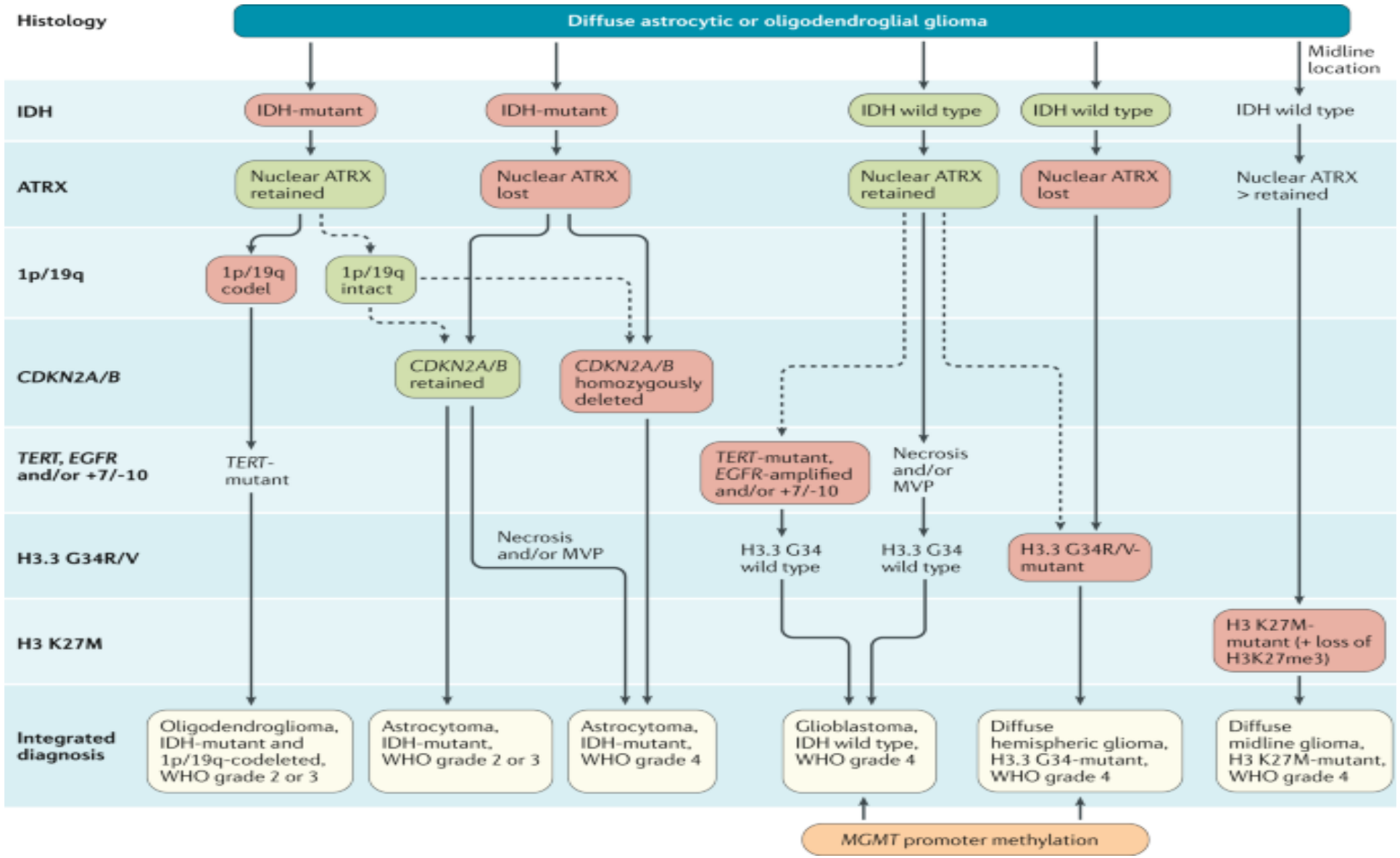



Histology
Diffuse astrocytic or oligodendroglial glioma
Midline location
IDH
IDH-mutant
IDH-mutant
IDH wild type
IDH wild type
IDH wild type
ATRX
Nuclear ATRX retained
Nuclear ATRX lost
Nuclear ATRX retained
Nuclear ATRX lost
Nuclear ATRX > retained
1p/19q
1p/19q codel
1p/19q intact
CDKN2A/B
CDKN2A/B retained
CDKN2A/B homozygously deleted
TERT, EGFR and/or +7/-10
TERT-mutant
TERT-mutant, EGFR-amplified and/or +7/-10
Necrosis and/or MVP
H3.3 G34R/V
Necrosis and/or MVP
H3.3 G34 wild type
H3.3 G34 wild type
H3.3 G34R/V-mutant
H3 K27M
H3 K27M-mutant (+ loss of H3K27me3)
Integrated diagnosis
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted, WHO grade 2 or 3
Astrocytoma, IDH-mutant, WHO grade 2 or 3
Astrocytoma, IDH-mutant, WHO grade 4
Glioblastoma, IDH wild type, WHO grade 4
Diffuse hemispheric glioma, H3.3 G34-mutant, WHO grade 4
Diffuse midline glioma, H3 K27M-mutant, WHO grade 4
MGMT promoter methylation

2. Neuronal Tumors

- Less frequent than gliomas.

-Composed of cells with neuronal characteristics.

- Present with seizures.

1. Central neurocytoma:

-Low-grade.

-Within and adjacent to the ventricular system (lateral or third ventricle).

-Composed of evenly spaced, round, uniform nuclei and often islands of neuropil

2. Gangliogliomas

- Mixture of glial elements, usually a low-grade astrocytoma and mature appearing neurons.

- Most are slow-growing and present with seizures.

3. Dysembryoplastic neuroepithelial tumor:

- A low-grade tumor of children and young adults that grows slowly

- In the temporal lobe

- Manifests as a seizure

- **Floating neurons in a myxoid background**

3. Embryonal (Primitive) Neoplasms

1. Medulloblastoma (WHO grade IV)

-Primitive Neuroectodermal Tumor: **PNET**

- Primitive **small cell (blue cell) tumor**

- Occurs in more **children** and in the **cerebellum**.

  - Children: Midline of the cerebellum

  - Adults: Lateral of the cerebellum

- Presents with Sx &Sx of ICP(headache, nausea, vomiting)

-**Highly malignant**, and the prognosis for untreated patients is dismal; however, it is radiosensitive.

- With treatment, the 5-year survival rate may be as high as 75%.

❑ Pathogenesis

-Oncogenic pathways in these tumors are the following:

- **Wnt pathway activation**: have the most **favorable** prognosis
- **Hedgehog pathway activation**: have an **intermediate** prognosis, but the concomitant presence of TP53 mutation confers a very poor prognosis.
- **MYC overexpression** due to MYC amplification: have the **poorest prognosis**

➢ **Gross:**

- Well circumscribed, friable and extend to involve the leptomeninges

---

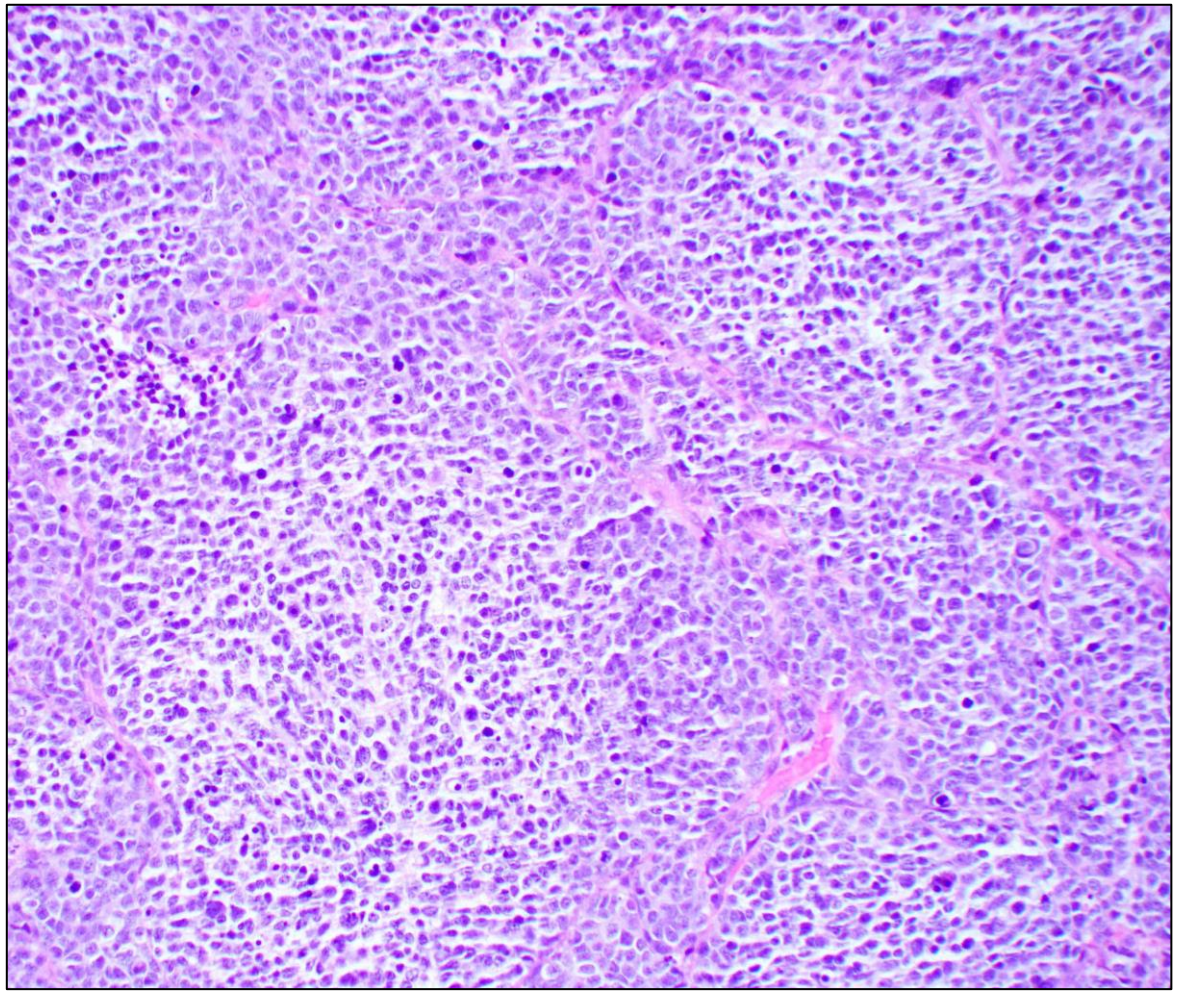
➢ **Microscopic:**

- Densely cellular, with sheets of anaplastic ("**small blue**") cells.

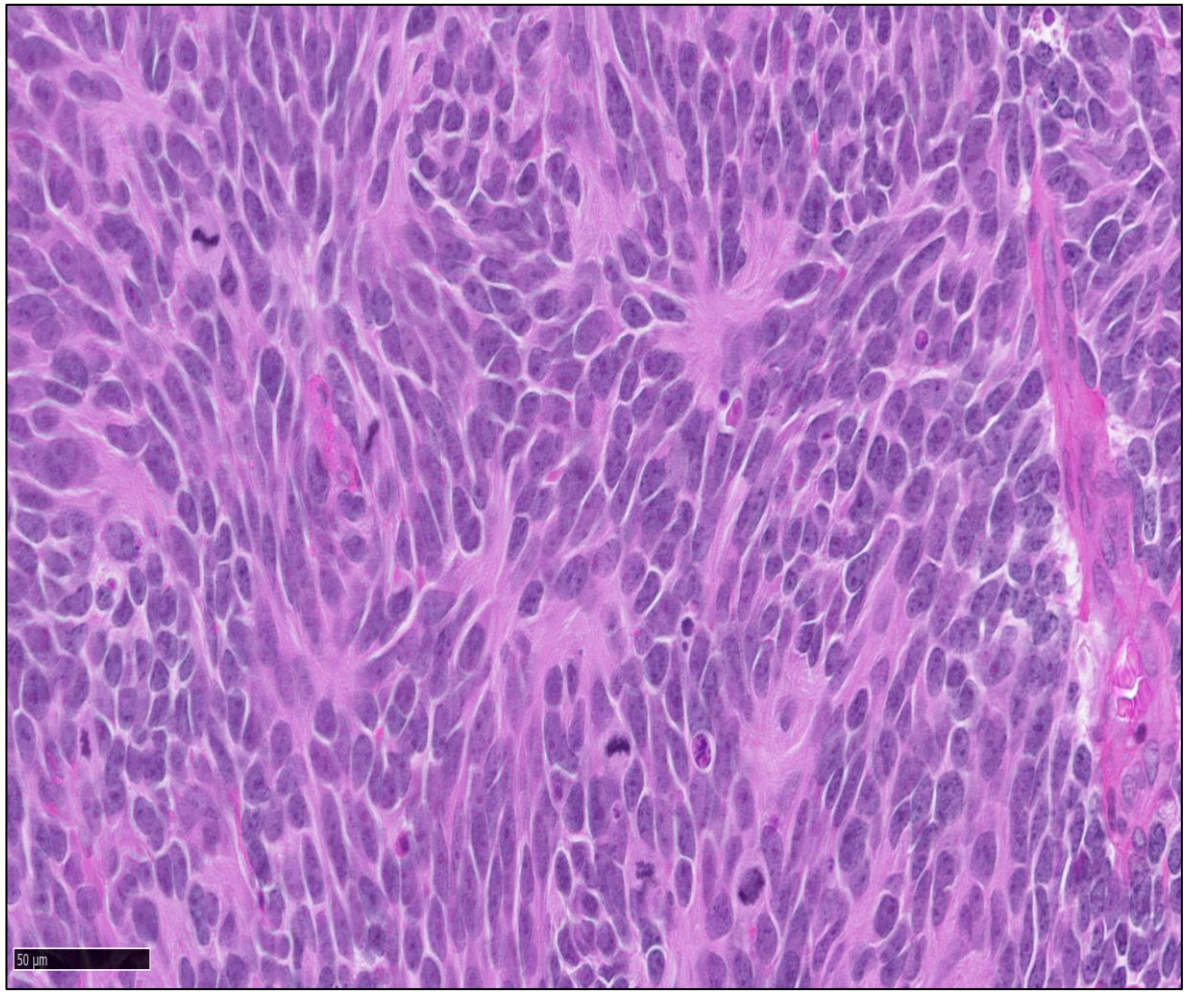
-Tumor cells are small, with little cytoplasm and hyperchromatic nuclei; mitoses are abundant.

- Often, focal neuronal differentiation is seen in the form of **Homer Wright Rosettes** (primitive tumor cells surrounding central neuropil (pink material formed by neuronal processes).

Sheets of undifferentiated cells

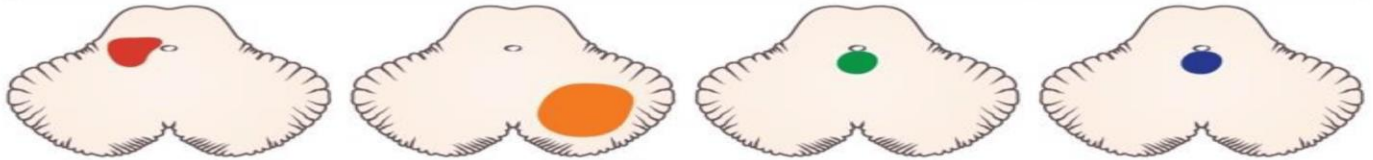


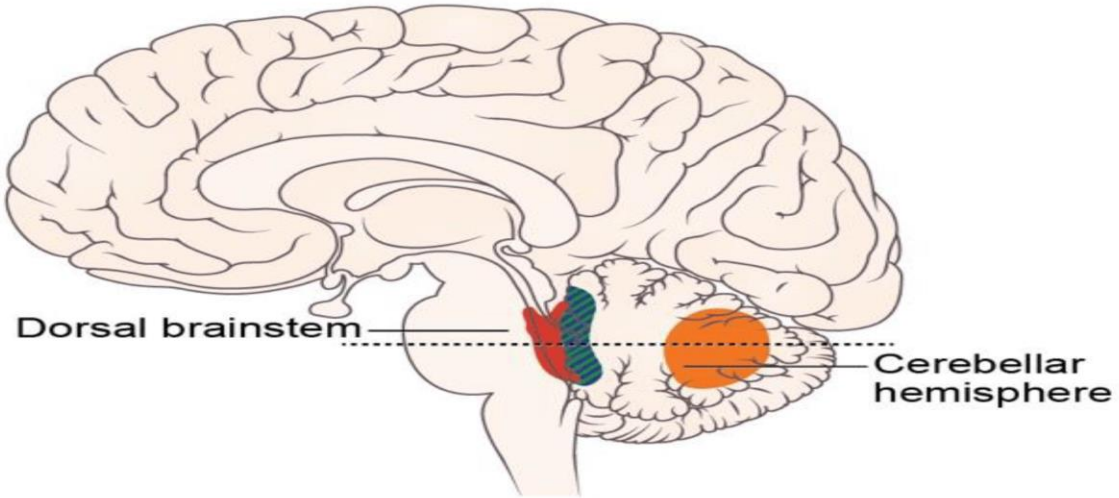
Homer Wright Rosettes



Meduloblastoma subtypes

	Wnt	Shh	Group 3	Group 4
Molecular features	• CTNNB1 • Monosomy 6	• GL1 • SUFU • PTCH1 • TP53 • SMO	• FSTL5 • MYC • VEGFA	• KDM6A • MYC • OTX
5-year survival rate	95-100%	40% (p53 mutant) & 80% (p53 wildtype)	~30-60%	75%
Anatomical location	Dorsal brainstem	Cerebellar hemisphere	Midline	Midline





4. Other Parenchymal Tumors

1. Primary Central Nervous System Lymphoma

- Mostly as diffuse large B-cell lymphomas.

- It is the most common CNS neoplasm in immunosuppressed individuals (nearly always positive for EBV).

- It is an aggressive disease with a relatively poor response to chemotherapy as compared with peripheral lymphomas.

- Primary brain lymphoma is often found as multiple tumor nodules within the brain parenchyma, yet the involvement of sites outside of the CNS is uncommon.

- Lymphoma originating outside the CNS rarely spreads to the brain parenchyma

❑ Morphology

➢**Gross:**

-Involves deep gray structures, as well as the white matter and the cortex.

- Periventricular spread is common.

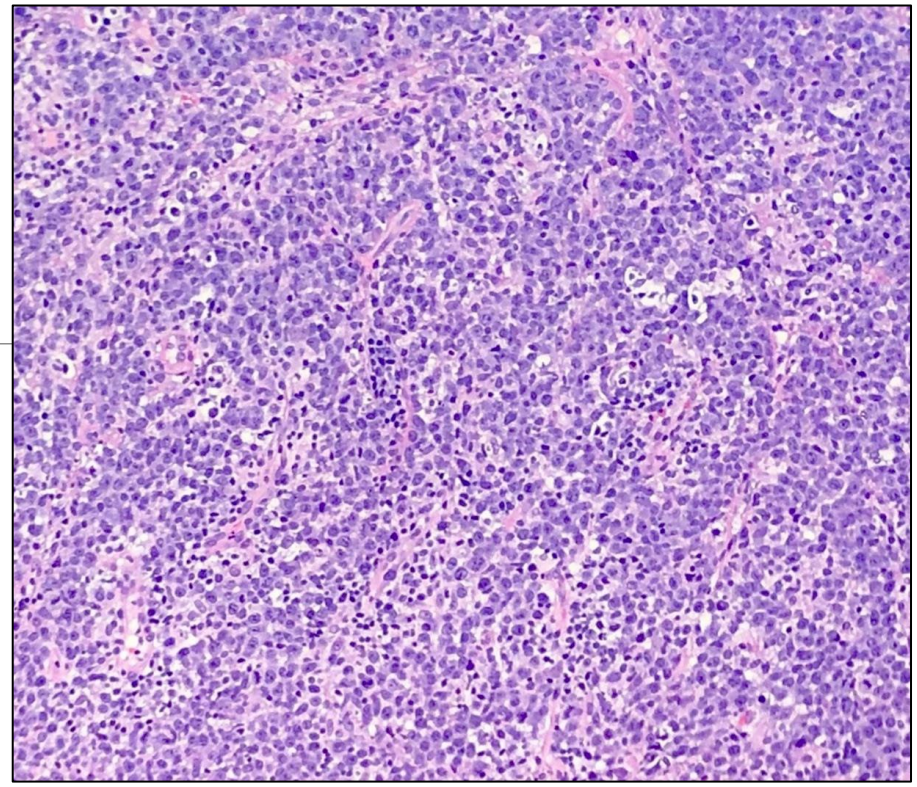
- **Well defined** as compared with glial neoplasms.

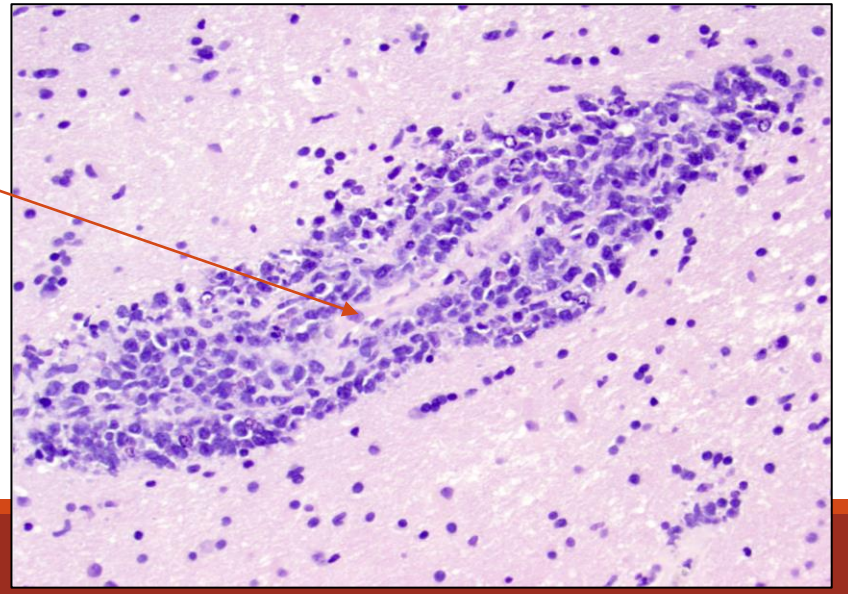
➢**Microscopic:**

- Nearly always aggressive large B-cell lymphomas.

- Malignant lymphoid cells **accumulate around blood vessels** and infiltrate the surrounding brain parenchyma.

- Positive for B cell markers such as CD20





2. Germ Cell Tumors

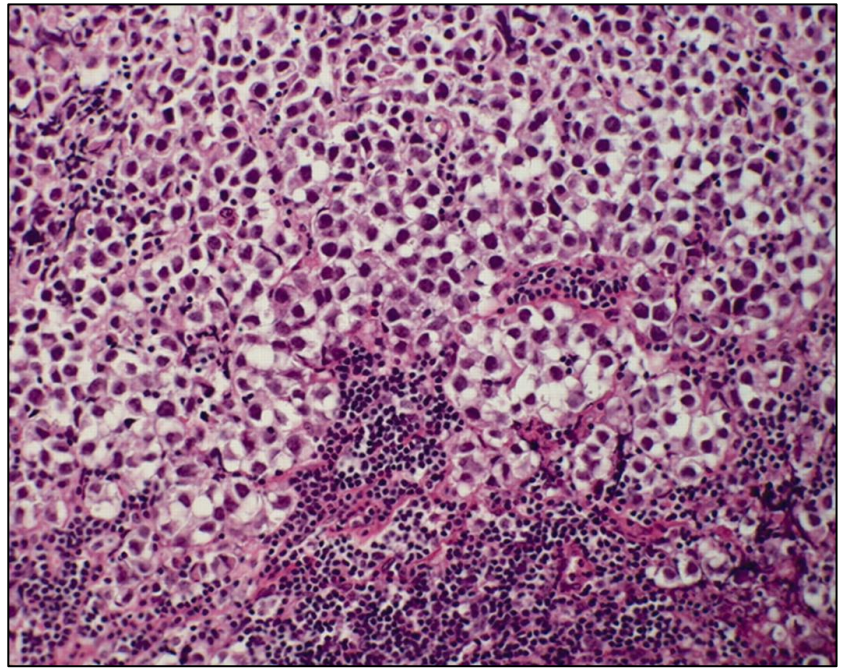
- Occurs along the midline (most commonly in the **pineal** and the **suprasellar regions**)

- They are a tumor of **the young**

- In the pineal region show a strong male predominance.

- **The most common primary CNS germ cell tumor is germinoma** **(**resembles testicular seminoma)

- Secondary CNS involvement by metastatic gonadal germ cell tumors also occurs.



5. Meningiomas (WHO grade I-III)

- Benign tumors arise from arachnoid meningothelial cells.
- Usually in adults and are often attached to the dura.
- Most in adult females, Tumor cells contain PROGESTERON receptors
- May be found along any of the external surfaces of the brain
- Presents with vague Sx or focal findings due to compression of the adjacent brain.
- Most are easily separable from the underlying brain, but some are infiltrative

- The overall prognosis is determined by the lesion size and location, surgical accessibility, and histologic grade

- Multiple meningiomas are associated with neurofibromatosis type 2 (NF2).

- About half of meningiomas not associated with NF2 have mutations in the NF2 tumor suppressor gene (in all grades).

❑ Morphology

WHO grade I:

- Grows as dura-based masses that may compress the brain, but No brain invasion.
- Extension into the overlying bone may be present.
- Histologic patterns include:
  - **Meningothelial** (whorled clusters of cells without visible cell membranes)
  - **Fibroblastic (**elongated cells and abundant collagen deposition)
  - **Transitional** (features of the meningothelial and fibroblastic types)
  - **Psammomatous** (numerous psammoma bodies)
  - **Secretory** (glandlike spaces containing PAS-positive eosinophilic material)

Atypical meningiomas (WHO grade II):

- These tumors demonstrate more aggressive local growth and a higher rate of recurrence.

- The presence of either an **increased mitotic rate OR prominent nucleoli**, **increased cellularity, patternless growth, high nucleus-to-cytoplasm ratio, or necrosis**)

- Some histologic patterns—**clear cell and chordoid**

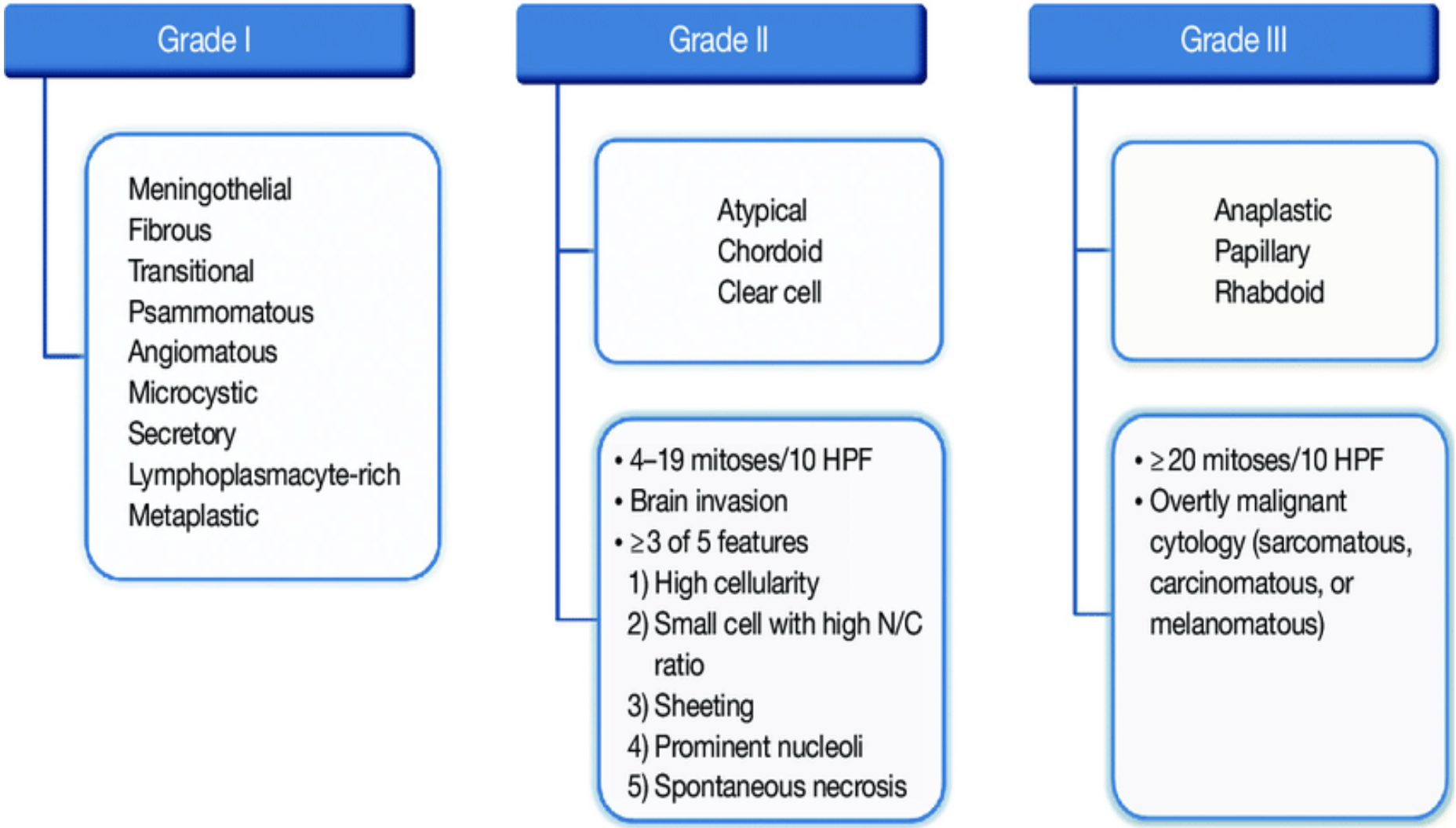
- **The presence of brain invasion.**

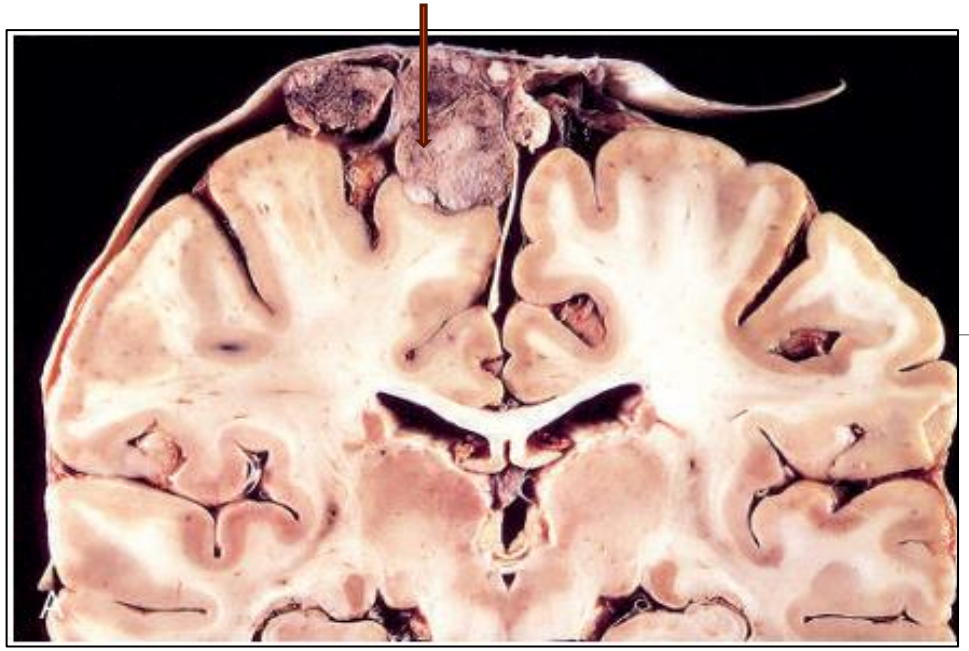
Anaplastic (malignant) meningiomas (WHO grade III)

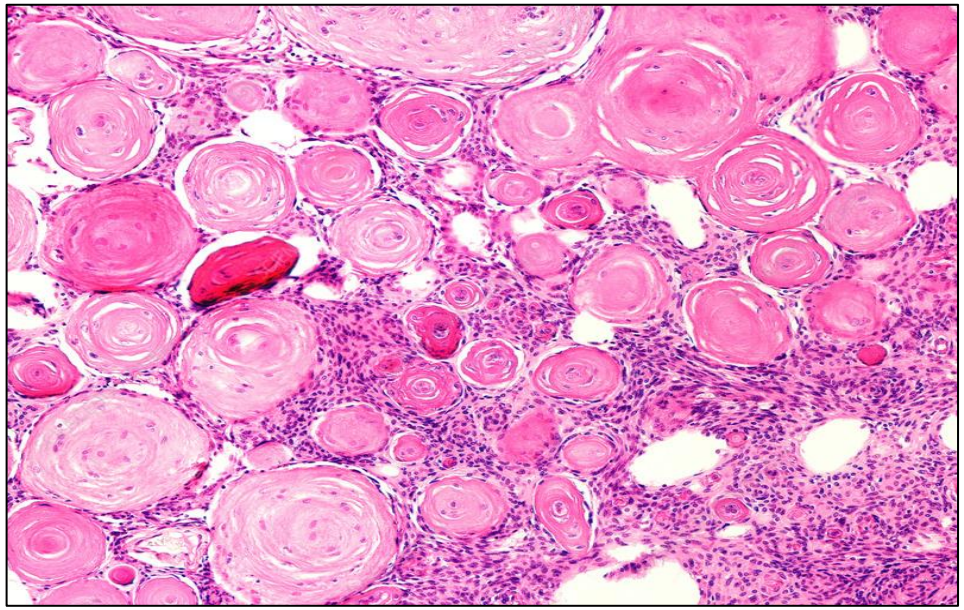
-Highly aggressive tumors that may resemble a high-grade sarcoma or carcinoma morphologically.

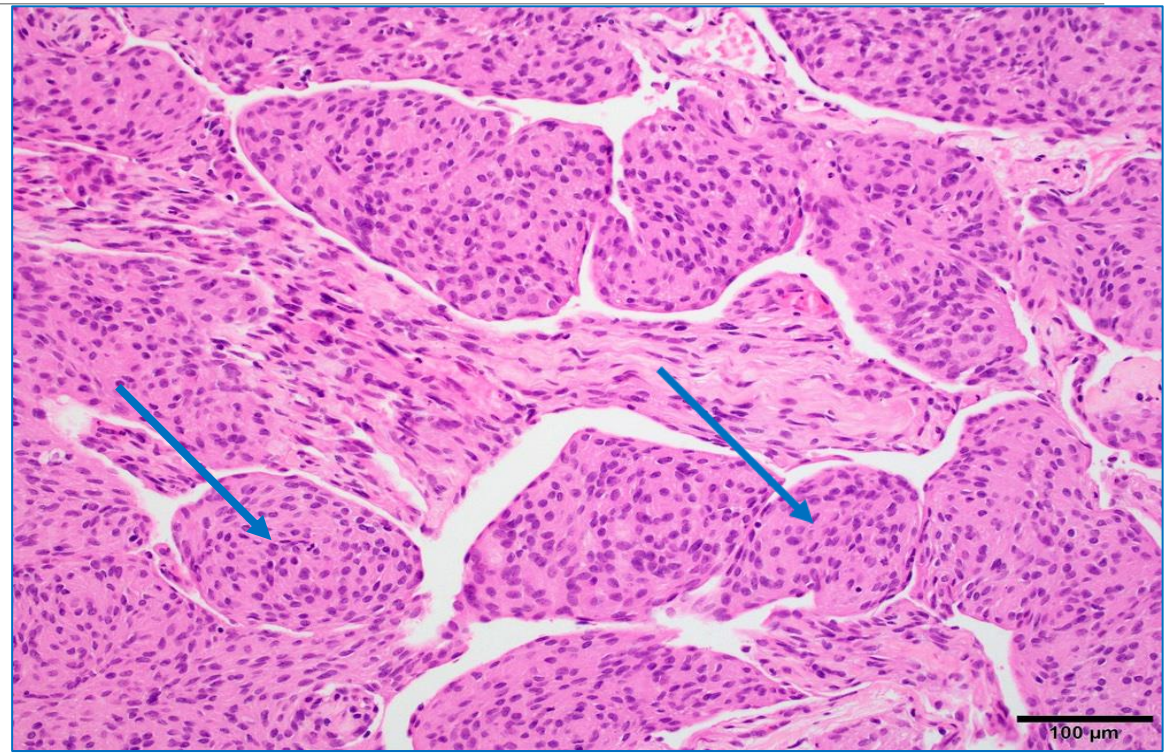
- Mitotic rates are typically much higher than in atypical meningiomas.

- **Papillary** or **Rhabdoid** morphology


Grade I
Meningothelial
Fibrous
Transitional
Psammomatous
Angiomatous
Microcystic
Secretory
Lymphoplasmacyte-rich
Metaplastic
Grade II
Atypical
Chordoid
Clear cell
• 4–19 mitoses/10 HPF
• Brain invasion
• ≥3 of 5 features
1) High cellularity
2) Small cell with high N/C ratio
3) Sheeting
4) Prominent nucleoli
5) Spontaneous necrosis
Grade III
Anaplastic
Papillary
Rhabdoid
• ≥20 mitoses/10 HPF
• Overtly malignant cytology (sarcomatous, carcinomatous, or melanomatous)






100 µm

5. Metastatic Tumors

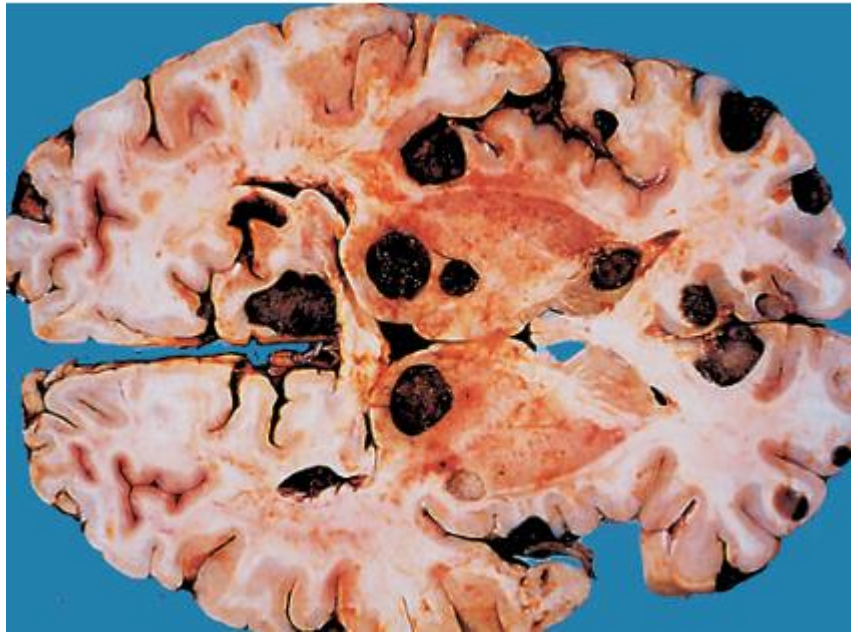
- Mostly carcinomas.

- The most common primary sites are the **lung, breast, skin (melanoma), kidney, and gastrointestinal tract**, which together account for about 80% of cases.

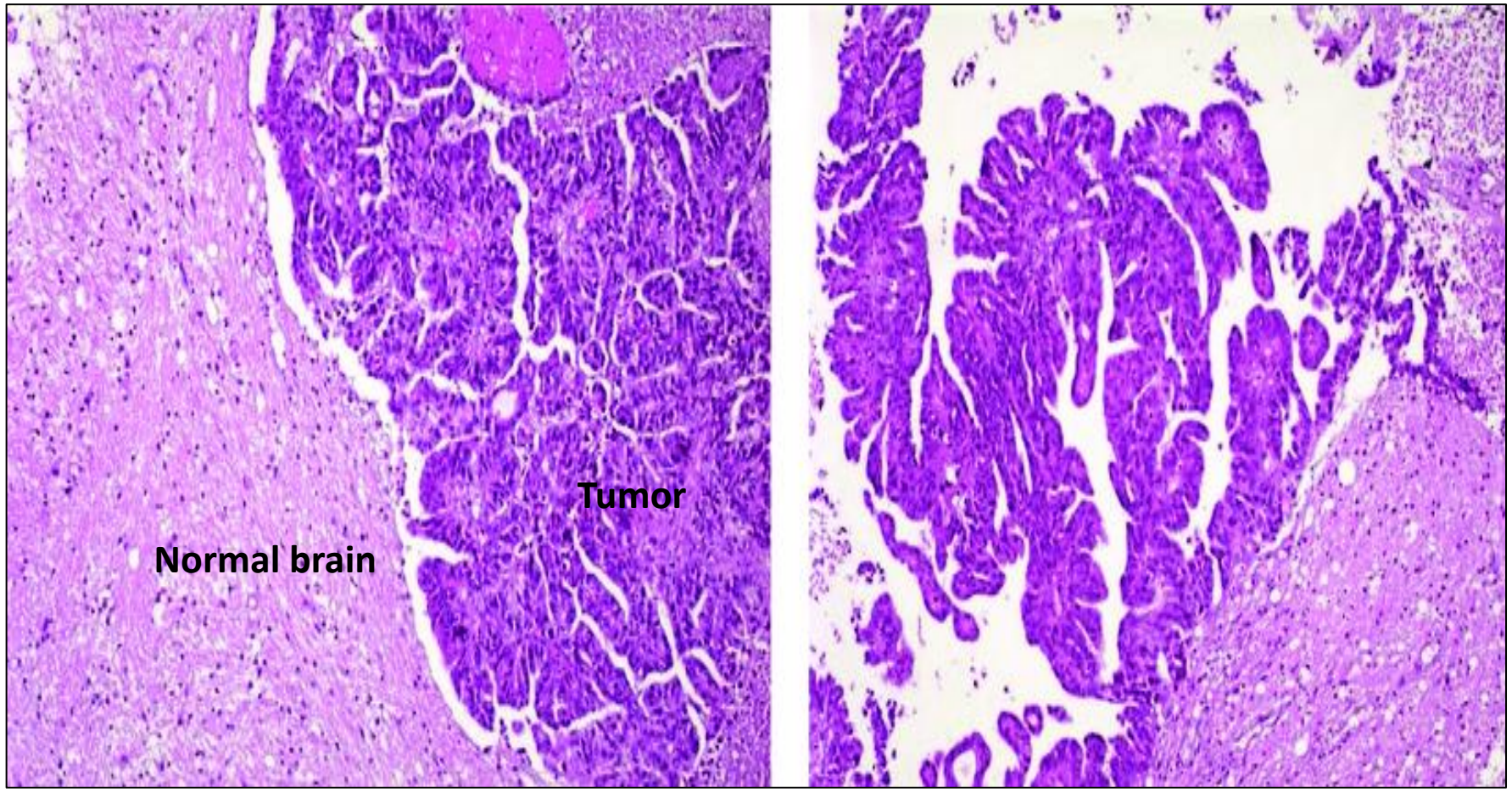
➢ **Gross:**

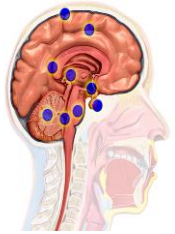
- Form sharply demarcated masses (usually multiple), often at the grey-white matter junction.

- The boundary between tumor and brain parenchyma is sharp at the microscopic level as well, with surrounding reactive gliosis



Brain Metastasis





Familial Tumor Syndromes

1. Tuberous Sclerosis:

- An autosomal dominant syndrome

-Results from disruption of TSC1 tumor suppressor genes, which encodes hamartin, or TSC2, which encodes tuberin. Proteins regulate protein synthesis & cell proliferation.

- Characterized by the development of **hamartomas and benign neoplasms** involving the brain and other tissues.

CNS hamartomas:

-Consists of **cortical tubers** and **subependymal hamartomas**, including a larger tumefactive form known as **subependymal giant cell astrocytoma.**

- Because of their proximity to the foramen of Monro, they often present acutely with obstructive hydrocephalus.

- Seizures are associated with cortical tubers.

- MORPHOLOGY

Cortical hamartomas

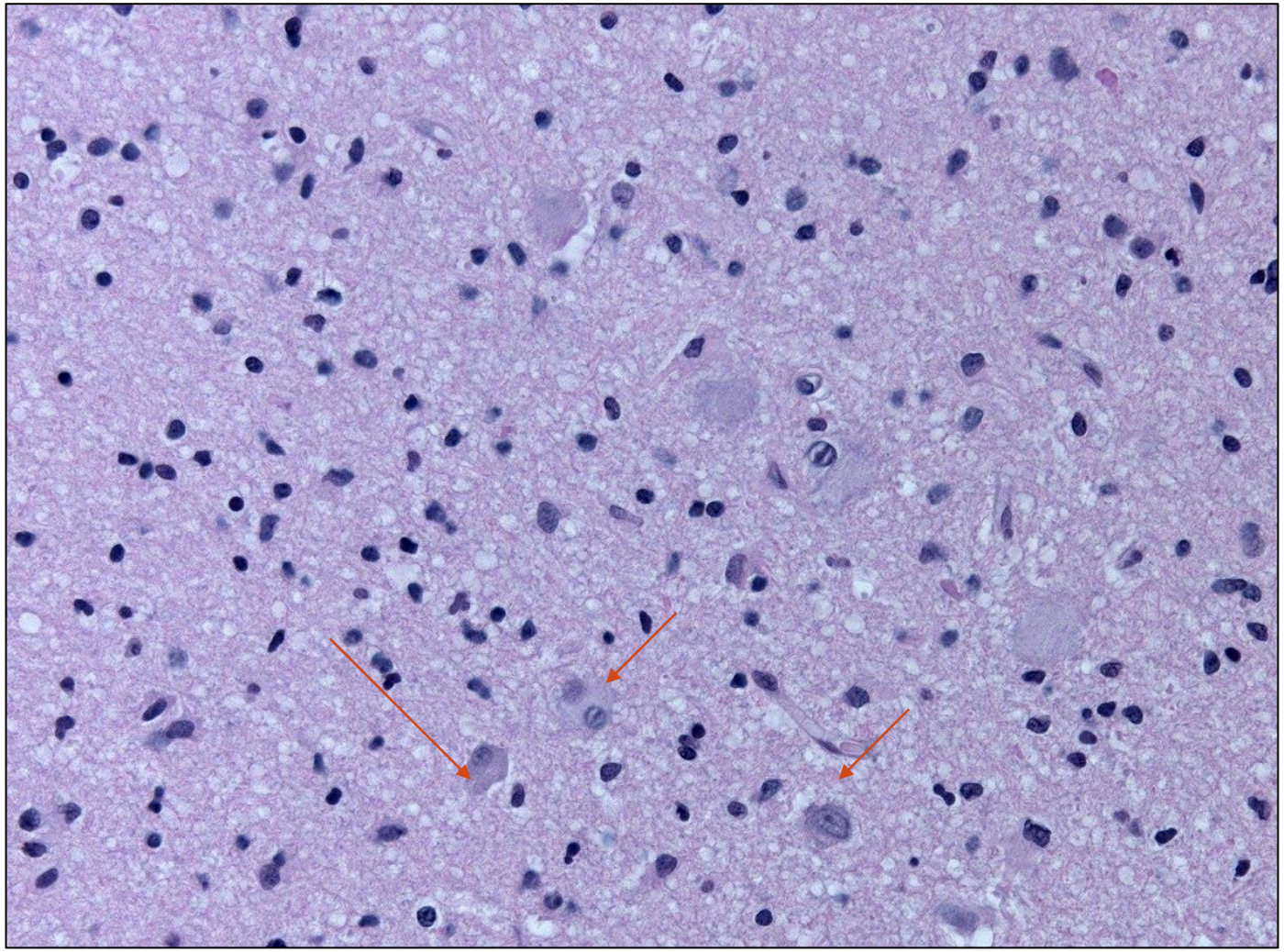
-Firmer than normal cortex and have been likened in appearance to potatoes

- Composed of haphazardly arranged large neurons that lack the normal cortical laminar architecture.

- May exhibit a mixture of glial and neuronal features

- Similar abnormal cells are present in subependymal nodules.

Cortical tuber with dysmorphic neuronal cells



Extracerebral lesions:

- Renal angiomyolipomas

- Retinal glial hamartomas

- Pulmonary lymphangiomyomatosis

- Cardiac rhabdomyomas.

- Cysts (liver, kidneys, and pancreas)

- Cutaneous lesions include angiofibroma, hypopigmented areas, and sub-ungual fibromas.

2. Von Hippel–Lindau Disease

- An autosomal dominant disorder.

- The affected gene, **the tumor suppressor VHL**, encodes a protein that degrades the transcription factor hypoxia-inducible factor (HIF).

- Tumors arising in patients with von Hippel–Lindau disease generally have lost all VHL protein function. As a result, the tumors express high levels of HIF, which drives the expression of VEGF, various growth factors, and sometimes erythropoietin.

- Individuals develop **hemangioblastomas** within the cerebellar hemispheres, retina, and, less commonly, the brain stem, spinal cord, and nerve roots.

- Patients also may have **cysts** involving the pancreas, liver, and kidneys and have an increased propensity to develop renal cell carcinoma.

- MORPHOLOGY

Hemangioblastoma:

- A highly vascular neoplasm that occurs as a mural nodule associated with a large, fluid-filled cyst.

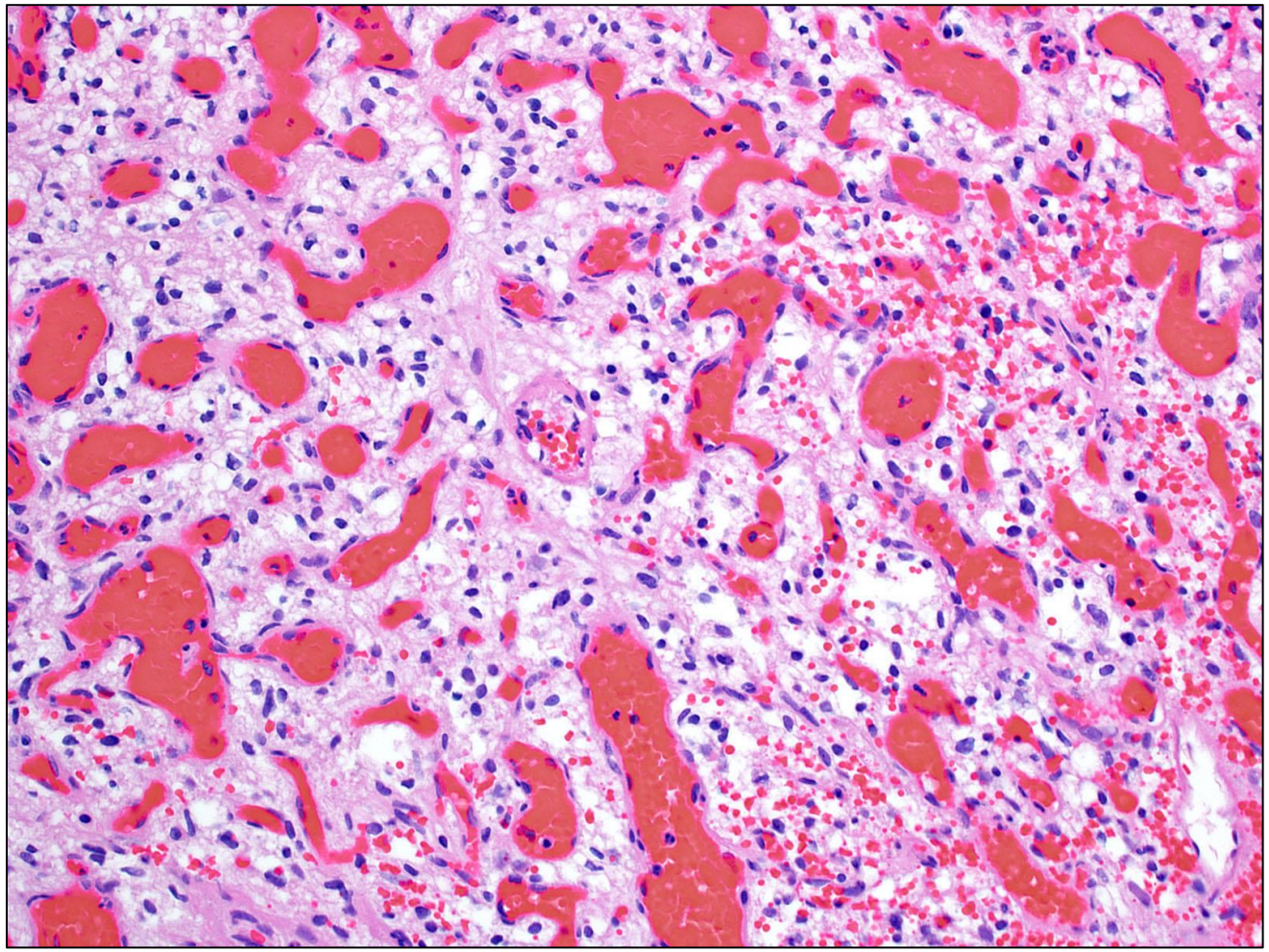
- Occurs most commonly in the **cerebellum.**

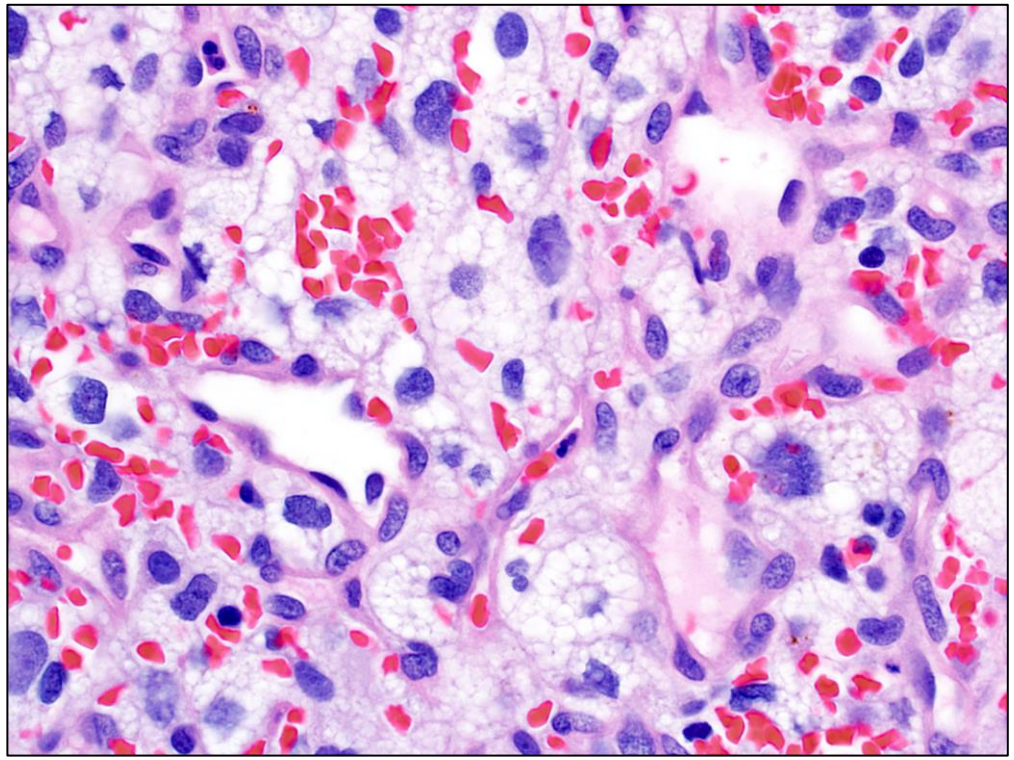
➢ **Microscopically:**

-Consists of numerous **capillary-sized or larger thin-walled vessels** separated by intervening stromal cells with a **vacuolated**, lightly PAS-positive, lipid-rich cytoplasm.

-The stromal cells express **inhibin**.

Classic hemangioblastoma features include numerous vessels and vacuolated stromal cells






Thank you