بسم الله الرحمن الرحيم

DOPAMINE SCIENTIFIC TEAM

CNS Tumors (Pt.3)

Final | Lecture 3

﴿ إِنِّي تَوَكَّلْتُ عَلَى ٱللَّهِ رَبِّي وَرَبِّكُمْ ۚ مَّا مِن دَآبَّةٍ إِلَّا هُوَ ءَاخِذٌۢ بِنَاصِيَتِهَآ ۚ إِنَّ رَبِّي عَلَىٰ صِرَٰطٍ مُّسْتَقِيمٍ ﴾

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PATHOLOGY

رحلة اليقين مع سورة يس

ٱلۡيَوۡمَ نَخۡتِمُ عَلَىٰٓ أَفۡوَٰهِهِمۡ وَتُكَلِّمُنَآ أَيۡدِيهِمۡ وَتَشۡهَدُ
أَرۡجُلُهُم بِمَا كَانُواْ يَكۡسِبُونَ ٦٥

قال الله تعالى في بيان وصفهم الفظيع في دار الشقاء: {الْيَوْمَ نَخْتِمُ عَلَى أَفْوَاهِهِمْ} بأن نجعلهم خرسا فلا يتكلمون، فلا يقدرون على إنكار ما عملوه من الكفر والتكذيب. {وَتُكَلِّمُنَا أَيْدِيهِمْ وَتَشْهَدُ أَرْجُلُهُمْ بِمَا كَانُوا يَكْسِبُونَ} أي: تشهد عليهم أعضاؤهم بما عملوه، وينطقها الذي أنطق كل شيء.

CENTRAL NERVOUS SYTEM TUMORS(3)

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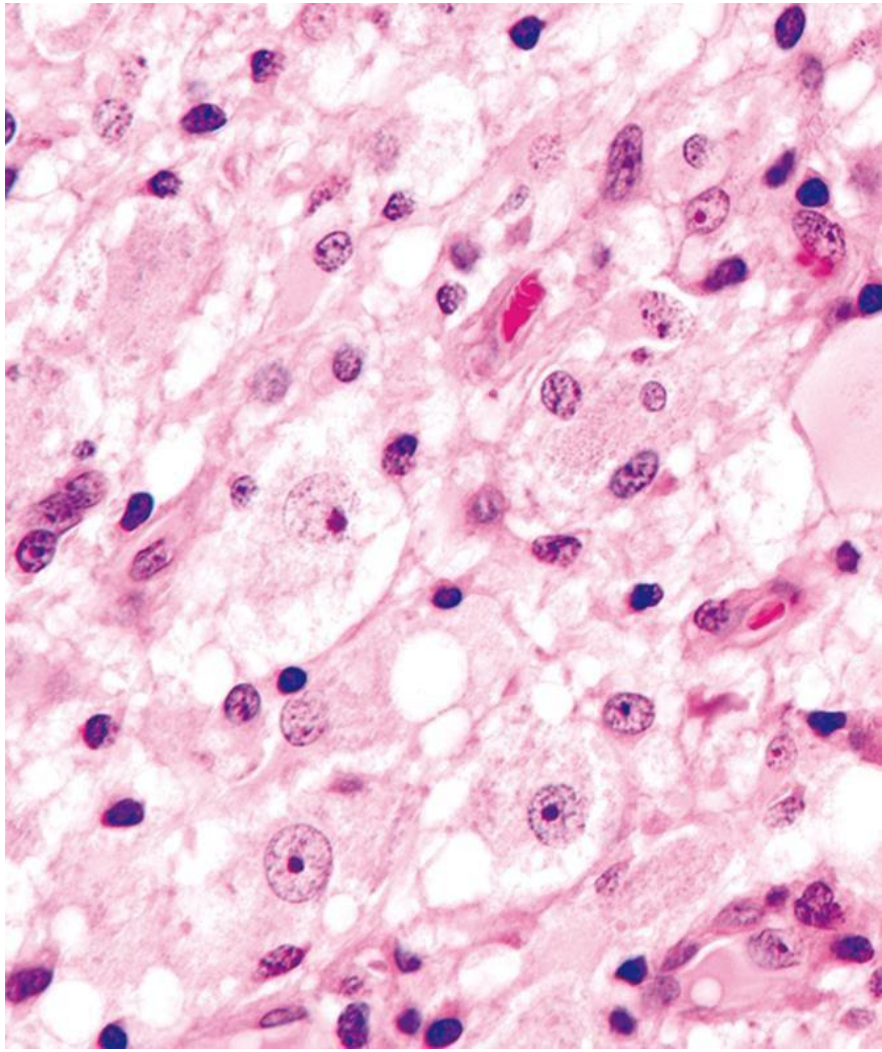
Neuronal Tumors

- **less** frequent than gliomas among the primary tumors of the CNS
- composed of cells with **neuronal characteristics and express neuronal** immunohistochemical **markers**, such as synaptophysin, neurofilaments, and NeuN
- typically, **lower-grade** lesions and they tend to have a relatively indolent biological behavior.

- Clinically, they often involve the cerebral cortex and often present with **seizures** particularly in children and young adults.

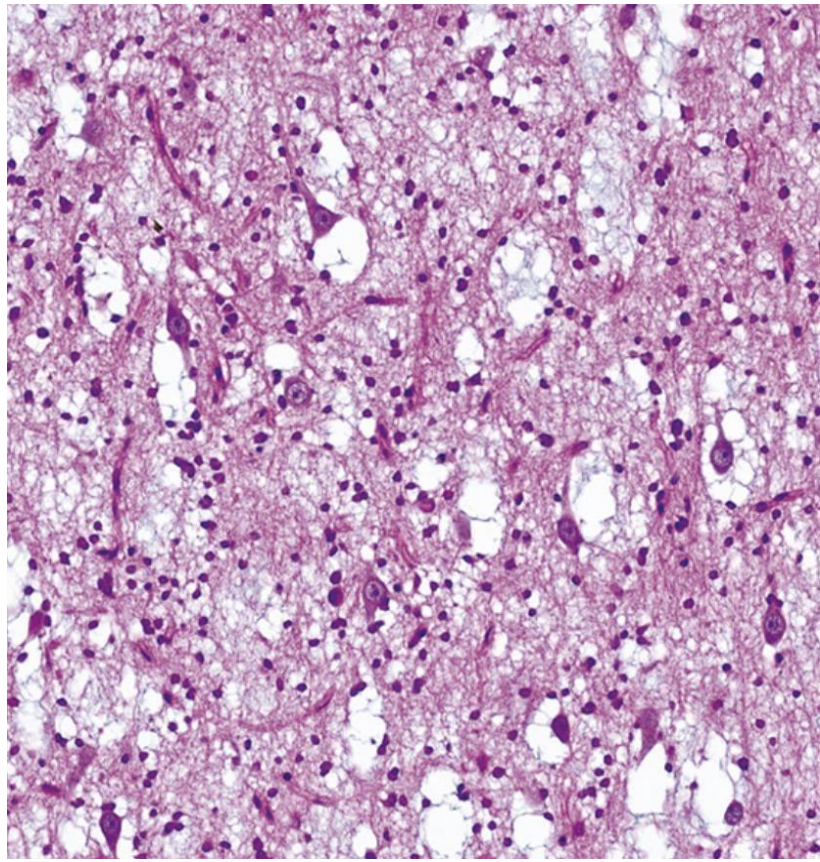
Gangliogliomas, WHO. **grade 1:**

- **Most commonly seen in children and young adults.**
- **Slow growing Glioneuronal tumor**
- composed of a mixture of **neoplastic ganglion and glial cells**
- most commonly in the **temporal lobe.**These tumors can occur anywhere in the CNS, including the cerebrum, brainstem, cerebellum, spinal cord, optic nerve, and ventricular system; however, more than 70% of the cases affect the temporal lobe.
- The tumor is associated with genetic alterations that lead to activation of the MAP kinase (MAPK) pathway, which is associated with 20-50% have mutations in BRAF gene



Dysembryoplastic neuroepithelial tumor (DNT), **WHO grade 1** Glioneuronal neoplasm

- Rare
- children and young adults
- DNT is Slow growing tumor, despite their indolent course, they are strongly associated with epilepsy.
- Many patients Present with chronic, drug-resistant seizure
- most commonly in the **superficial temporal lobe**.
  - An important characteristic of this tumor is its typical cortical location, most commonly involving the superficial temporal lobe, which explains its strong association with seizure disorders.



Embryonal (Primitive) Neoplasms:

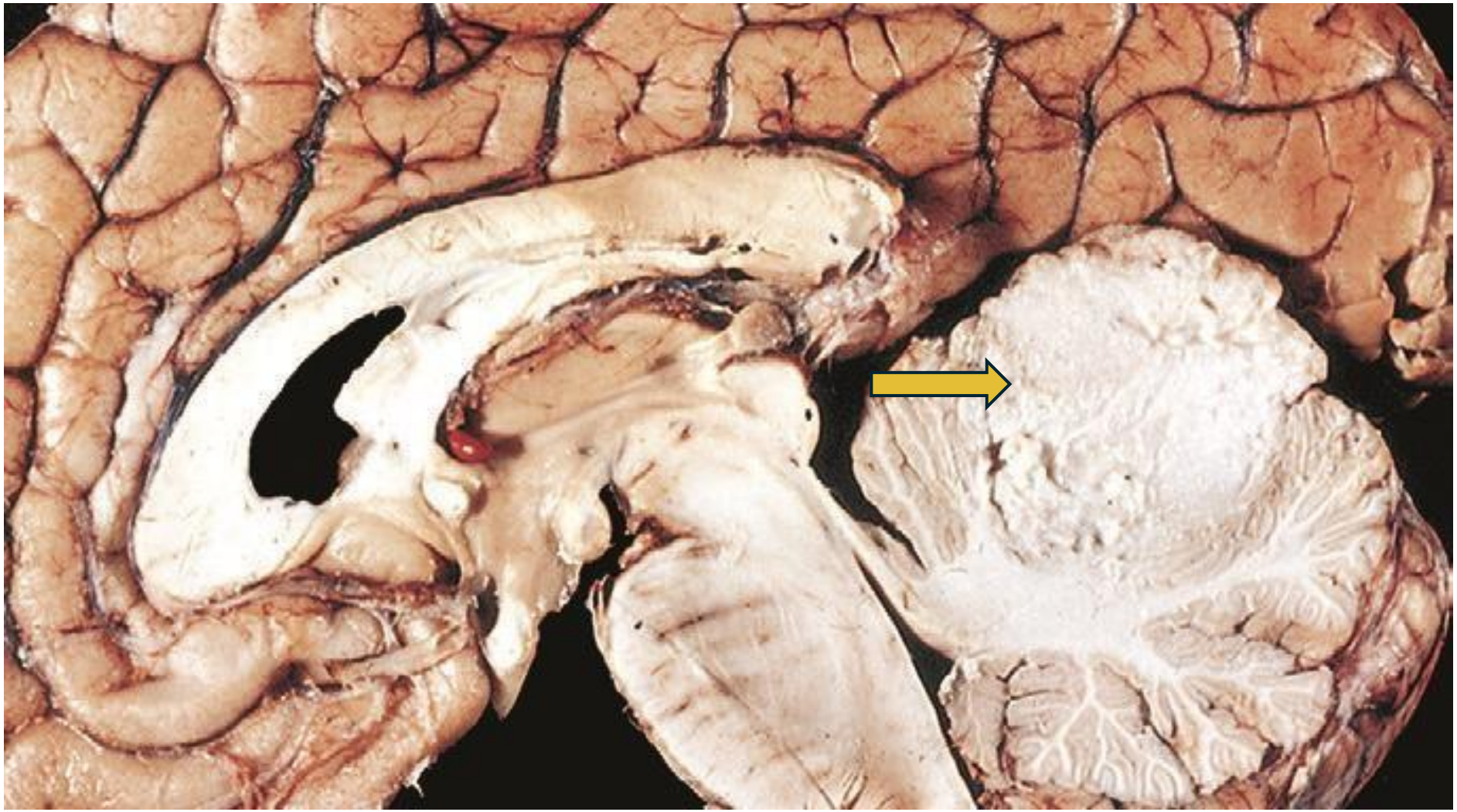
- Primitive or undifferentiated small round cell tumor of neuroectodermal origin resembling normal progenitor cells in the developing CNS.
- **Because of their primitive nature, cellular differentiation is usually limited in these tumors; however, some may show partial differentiation along neuronal, glial, or other neural lineages.**
- The most common CNS embryonal tumor is **Medulloblastoma** accounting for 20% of pediatric brain tumors. other tumors in this group include embryonal tumors with multilayered rosettes, CNS neuroblastoma, and atypical teratoid/rhabdoid tumor (AT/RT).

Embryonal (Primitive) Neoplasms continued :

- predominantly in **children**
- Mainly in **cerebellum** **but it had been diagnosed in the brain stem**
- **All are highly malignant, WHO grade 4**
- **radiosensitive**. Despite their aggressive biological behavior, these tumors are generally radiosensitive, which is an important feature that helps the patients in the management plan
- the prognosis for untreated patients is **dismal**
- **5-year survival rate may be as high as 75%** with total excision followed by chemotherapy, and irradiation

Macroscopic appearance

- Grossly, classic medulloblastoma appears as a friable pink mass and may occasionally show macroscopic foci of necrosis; however, extensive necrosis is rare.
- In children (seen in the midline) while in adults (laterally located)
- well circumscribed lesion (often)
- may extend to the cerebellar surface and involve the Leptomeninges
- **complication:**
  - Medulloblastomas have tendency to spread to the subarachnoid space→ Dissemination through the CSF and this may result in the formation of discrete tumor nodules elsewhere.



- This picture shows a sagittal section through the brain.
  The yellow arrow points the gross appearance of medulloblastoma, seen here destroying the superior midline cerebellum.
  Here we have a relatively well-circumscribed tumor representing medulloblastoma within the cerebellum.

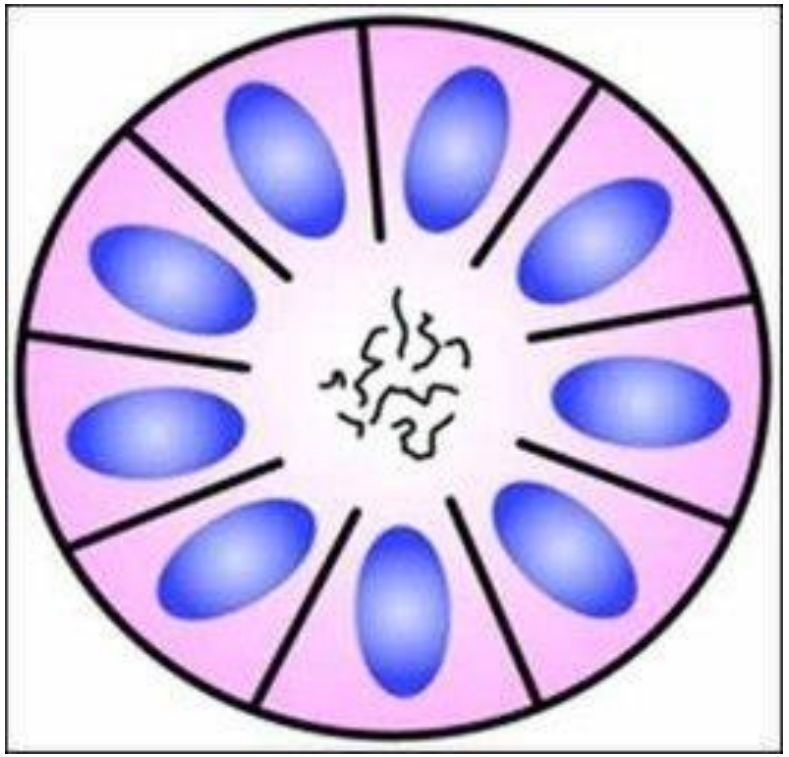
Morphology

- Very Cellular under the microscope in comparison with other tumors discussed in this lecture
- sheets of small primitive cells ("small blue"), Each cell with little cytoplasm and hyperchromatic elongated or crescent-shaped nuclei.
- The tumor is composed of densely packed, poorly differentiated embryonal cells with hyperchromatic nuclei of variable sizes and shapes; some nuclei are elongated, while others show crescent-shaped morphology.
- mitoses are abundant and apoptotic bodies will be seen
- often express neuronal markers such as synaptophysin, however expression of glial markers (GFAP) is **less common**.

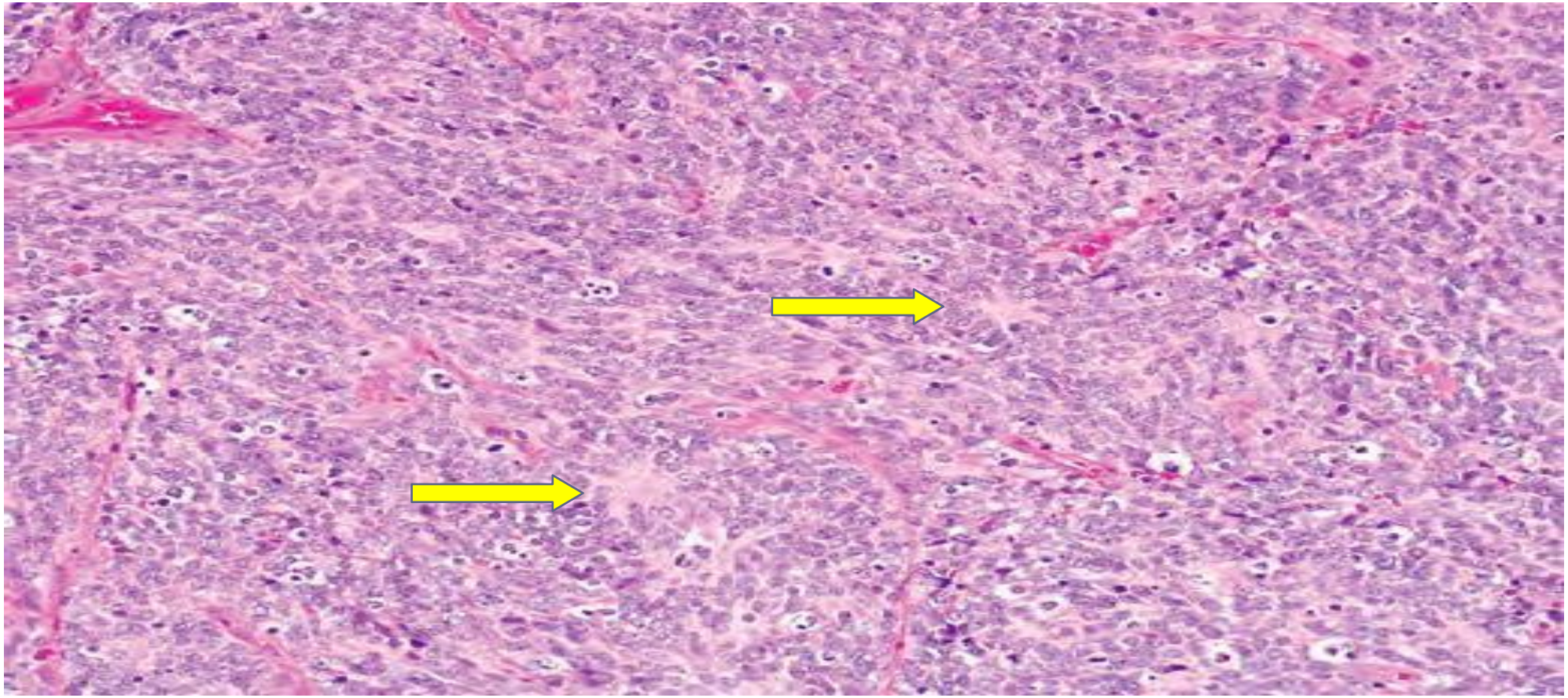
Morphology

- **Homer Wright Rosettes:**
  - primitive tumor cells surrounding central neuropil (delicate pink material formed by neuronal processes).
  - Represents focal neuronal differentiation

  - **Not specific**; seen also in neuroblastoma and pineoblastoma and other neuroectodermal tumors



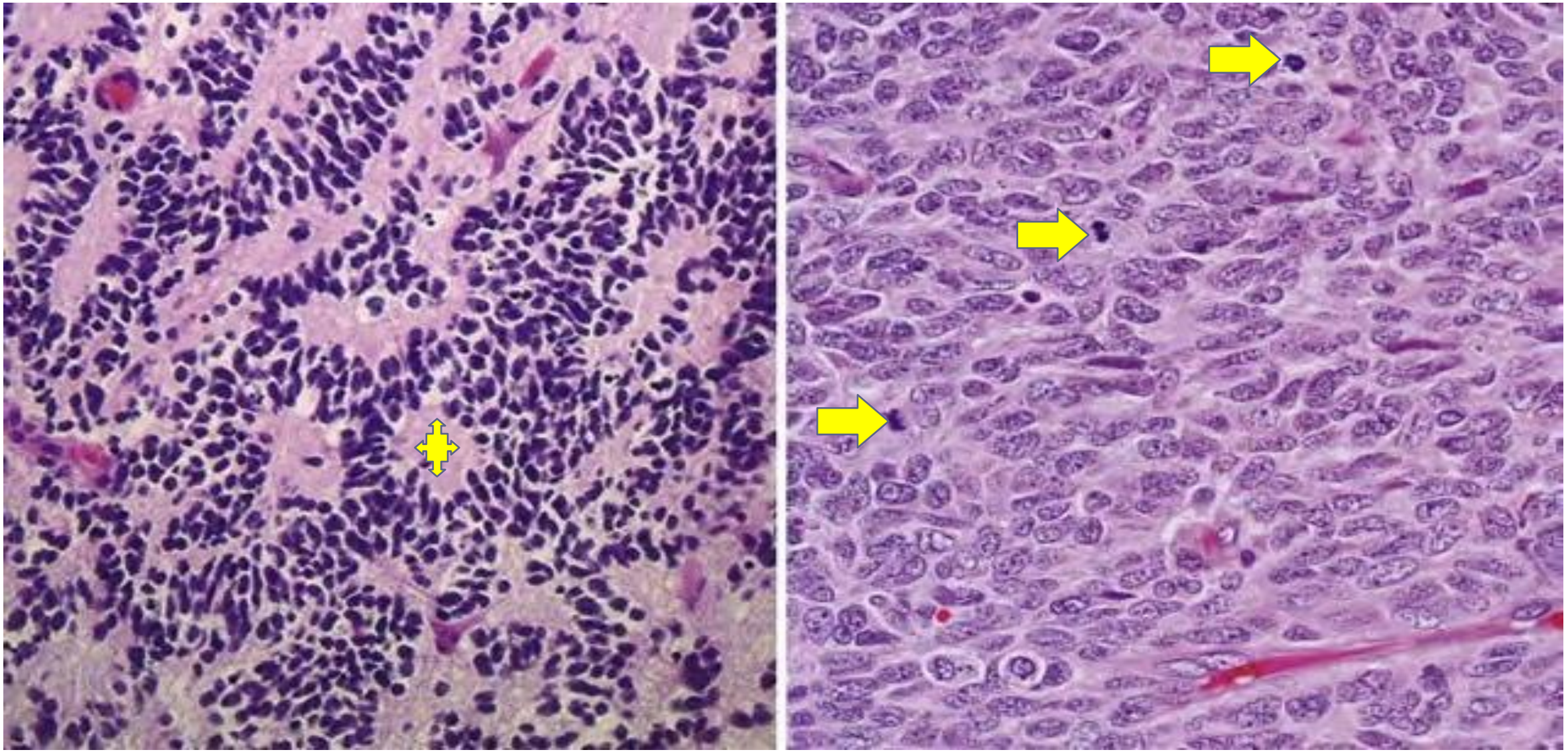
Sheets of primitive small blue cells that form Homer Wright rosettes with central neuropil (arrows).



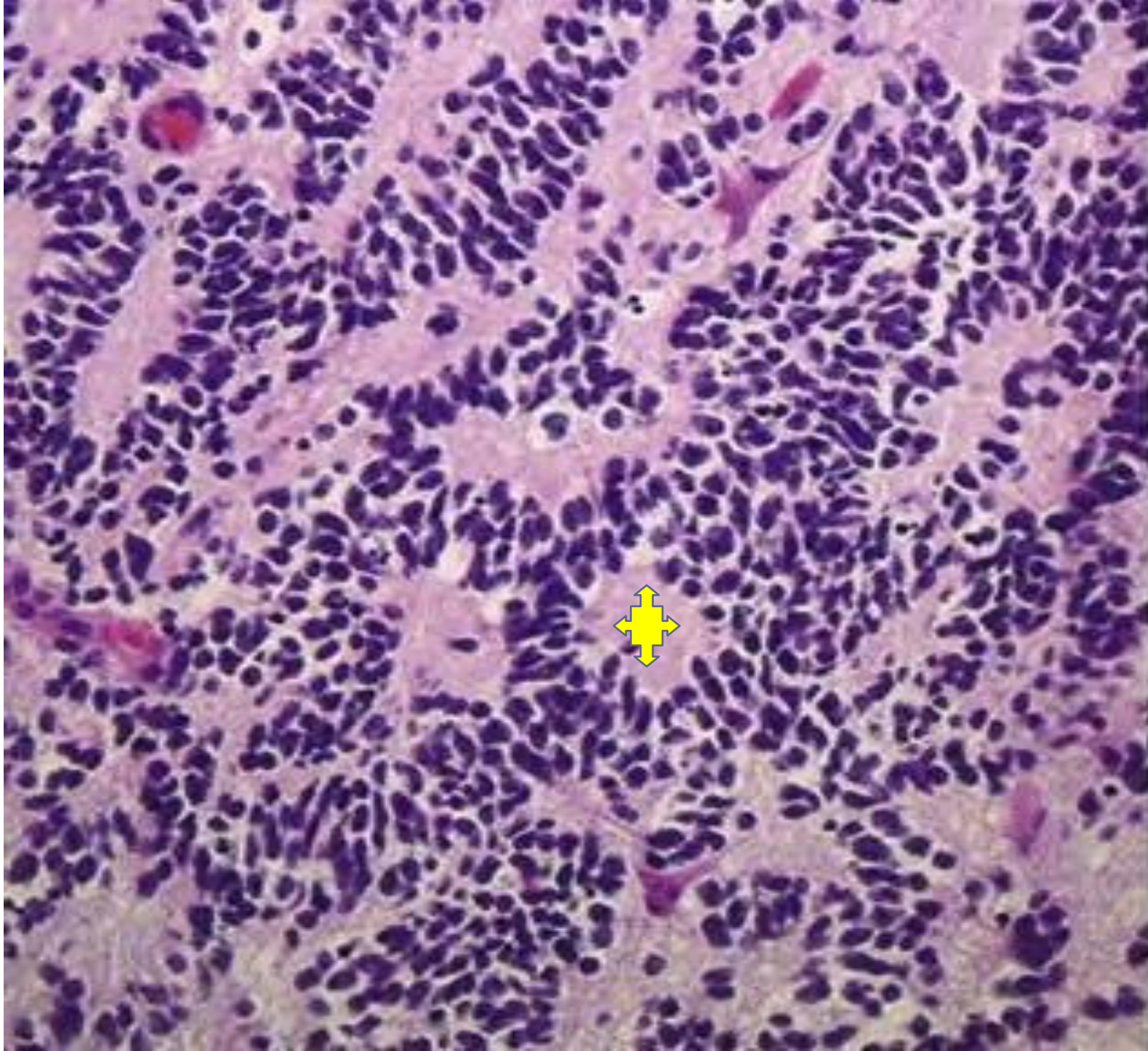
- The picture shows the microscopic findings of medulloblastoma. There is a cellular proliferation of densely packed small round blue cells. These cells have elongated, hyperchromatic nuclei, and frequent apoptotic bodies may be seen.

- The yellow arrows indicate Homer Wright rosettes, where primitive tumor cells surround the central neuropil or central pink material.

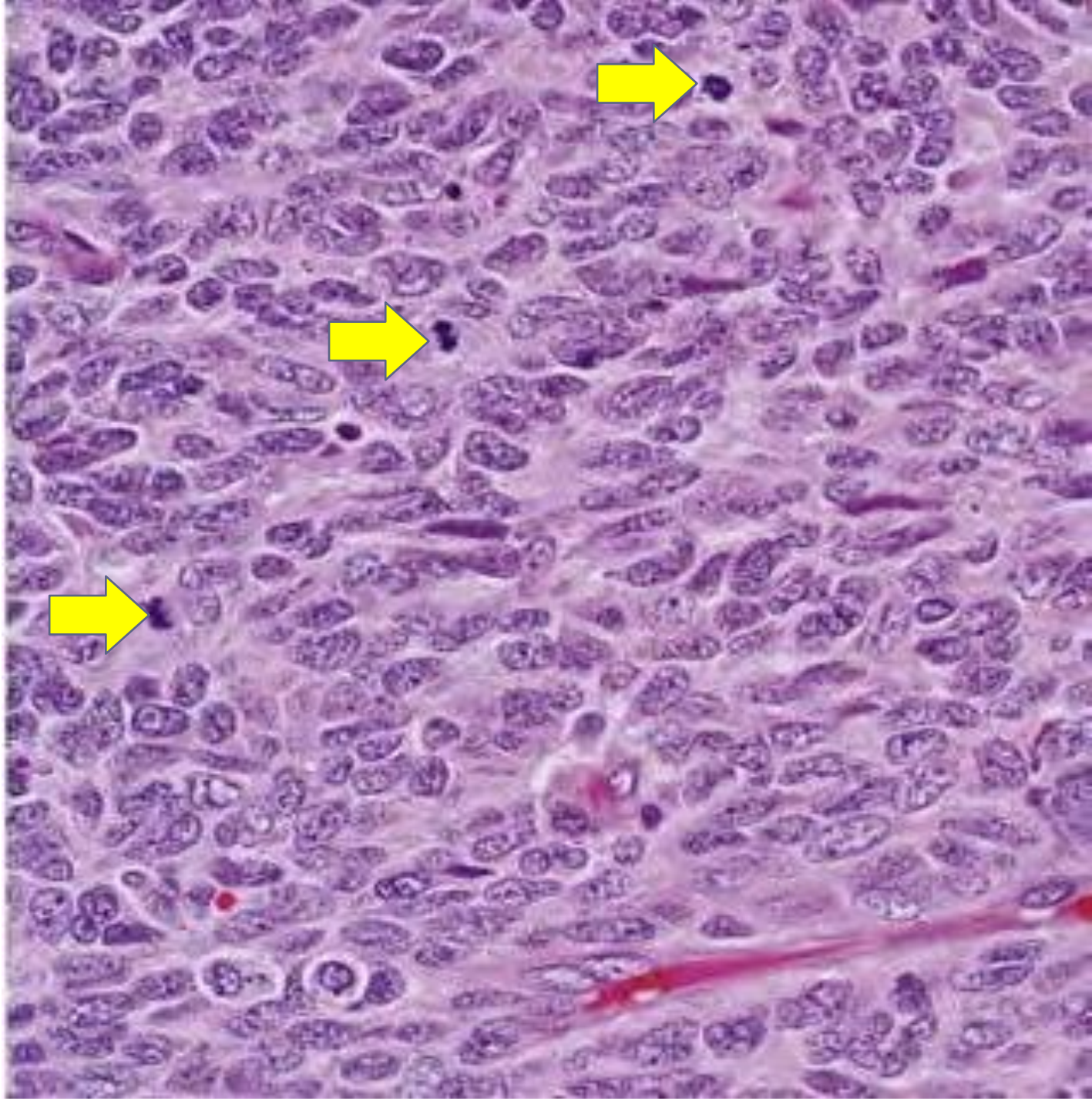
- This figure shows medulloblastoma, which is composed of poorly differentiated small round blue cells with skin cytoplasm and hyperchromatic, pleomorphic nuclei, including elongated and crescent-shaped nuclei.



- The yellow arrows in the figure indicate Homer Wright rosettes, where tumor cells surround eosinophilic material (neuropil).



- This figure shows frequent mitotic figures, as indicated by the arrows pointing to three mitotic figures in this field.



Meningiomas, WHO grades 1-3

- Tumors that arise from meningothelial cells of the arachnoid matter and usually attached to the dura. They are among the most common extra axial tumors of the CNS.

- Age at presentation: adults (women>men)

- Location: any of the external surfaces of the brain, spinal cord, within the ventricular system, from the stromal arachnoid cells in the choroid plexus.

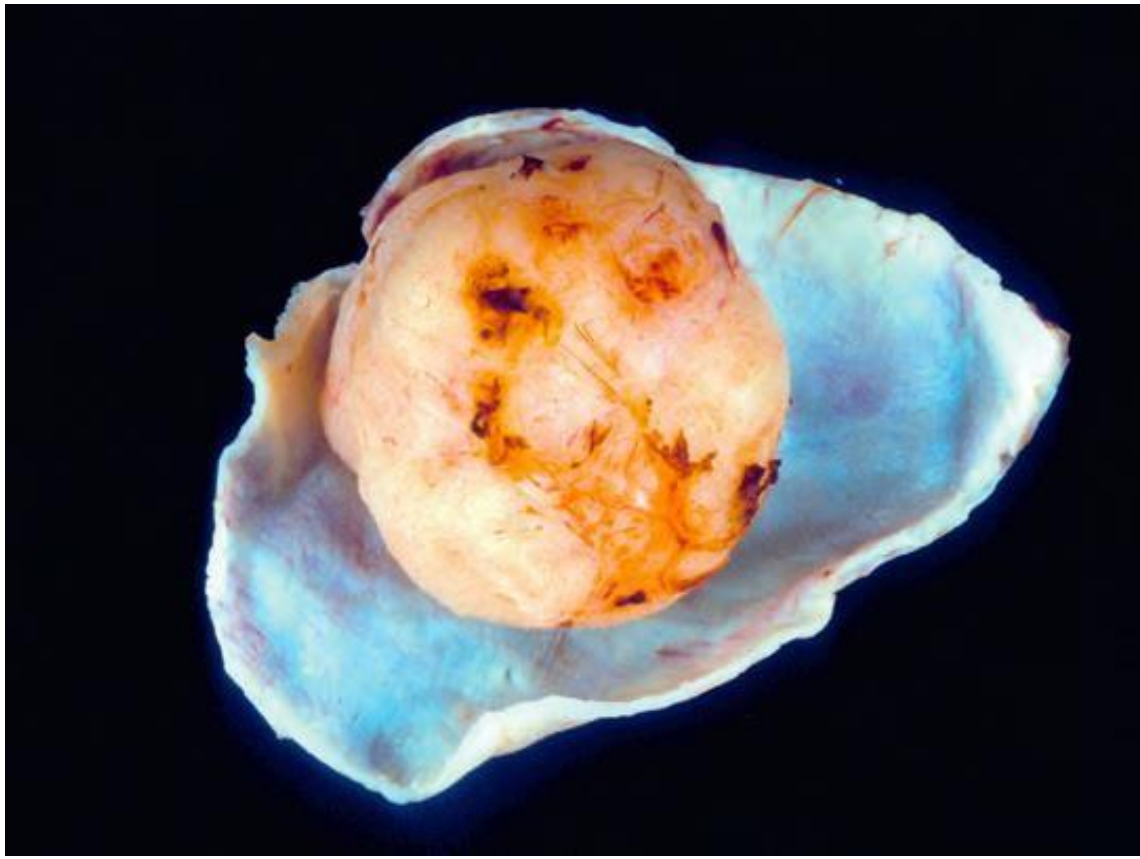
- **Presentation:** Most common headache, seizures, weakness (depends on location)
- **Prognosis:** determined by the lesion size and location, surgical accessibility, and histologic grade.
- Most meningiomas are easily separable from the underlying brain but some tumors are infiltrative (associated with increased risk of recurrence)
- Meningiomas express **progesterone receptors** and may grow more rapidly during pregnancy, only to regress after delivery.

Pathogenesis

- The most common cytogenetic abnormality is loss of chromosome 22, especially the long arm (22q).
- The deletions include the region that harbors the NF2 (Neurofibromatosis 2)gene.
- Of sporadic meningiomas, 50% to 60% harbor mutations in the NF2 gene
- Multiple meningiomas + 8th nerve schwannoma or glial tumor → common in the setting of NF2.

Macroscopic:

- Rubbery, rounded, or bosselated dural masses that compress underlying brain.
- Mostly separable from underlying brain, but some tumors are infiltrative.



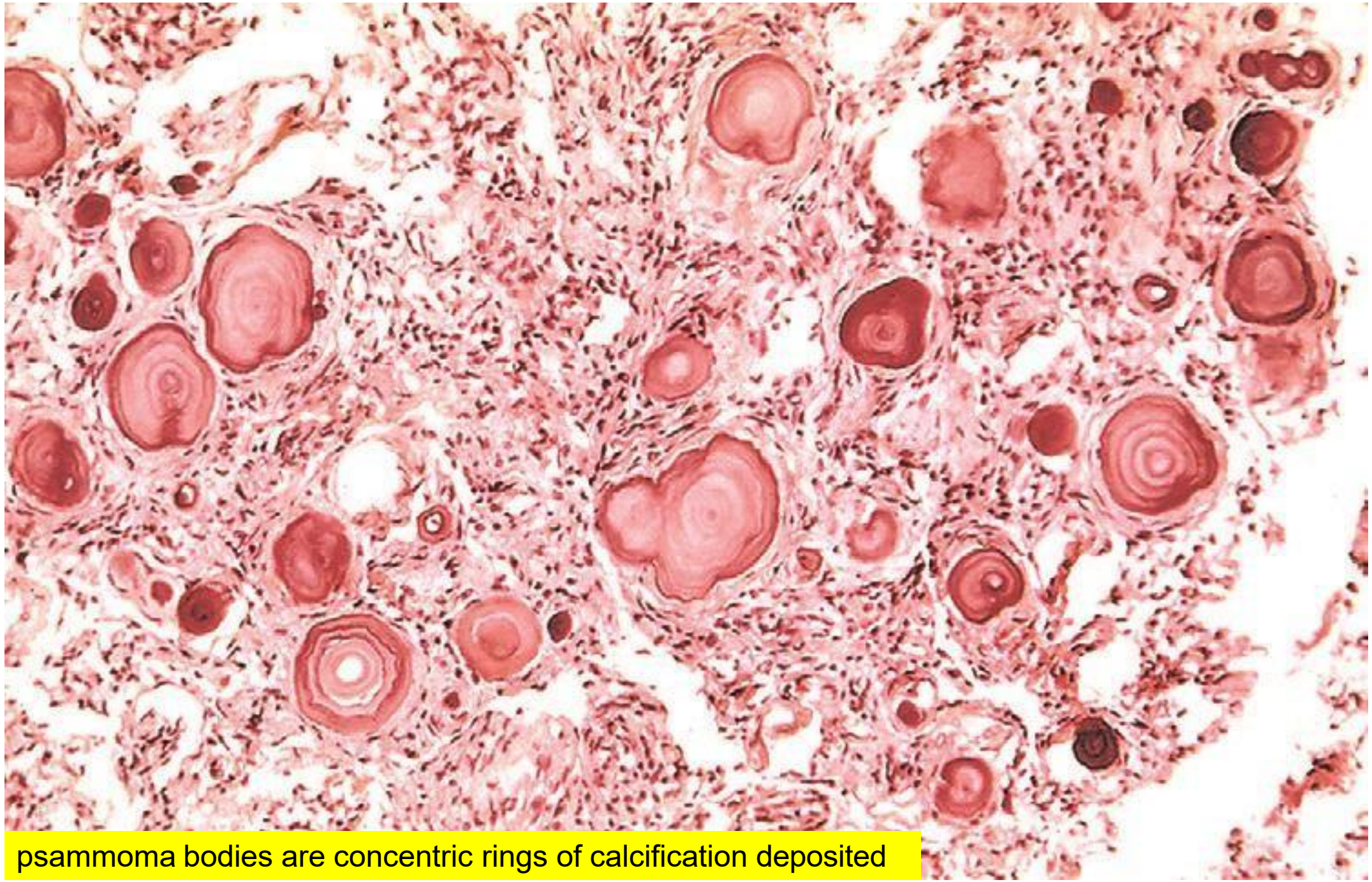
Meningiomas (WHO grade 1):

- Well-defined dura-based masses that may compress the brain but do not typically invade it +/- overlying bone extension.
- Epithelioid cells arranged in whorled (syncytial) pattern +/- psammoma bodies

Meningiomas (WHO grade 1):

- Many histologic subtype, with no prognostic difference, including:
  - **Meningothelial (most common)**→clusters of epithelioid cells with fuzzy or indiscernible cell membranes
  - Other patterns Include
    - **fibrous meningiomas**, where the tumor is fibroblastic with intersecting fascicles of spindle cells and abundant collagen deposition
    - **transitional meningiomas** with mixed meningothelial and fibroblastic features, often including many whorls, which means concentric wrapping of the tumor cells around themselves
    - **angiomatous**
    - **microcystic**
    - **lymphoplasmacytic-rich**
    - **psammomatous**, where we have abundant fibromatous bodies in the tumor;
    - as well as **secretory meningiomas and metaplastic meningiomas**.

  However, none of these histologic subtypes have significant prognostic influence.



psammoma bodies are concentric rings of calcification deposited

MENINGIOMAS, WHO grade 2

- recurrence and aggressive local growth (may require radiation & surgery)

1) **4 to 19 mitoses/10 HPF; or**
2) **3 out of 5** atypical cytological features**:** increased cellularity, small cells with a high N/C ratio, prominent nucleoli, patternless growth, or necrosis; **or**
3) **clear cell** or **chordoid subtypes of meningioma; or**
4) **unequivocal brain invasion**

MENINGIOMAS, WHO grade 3:

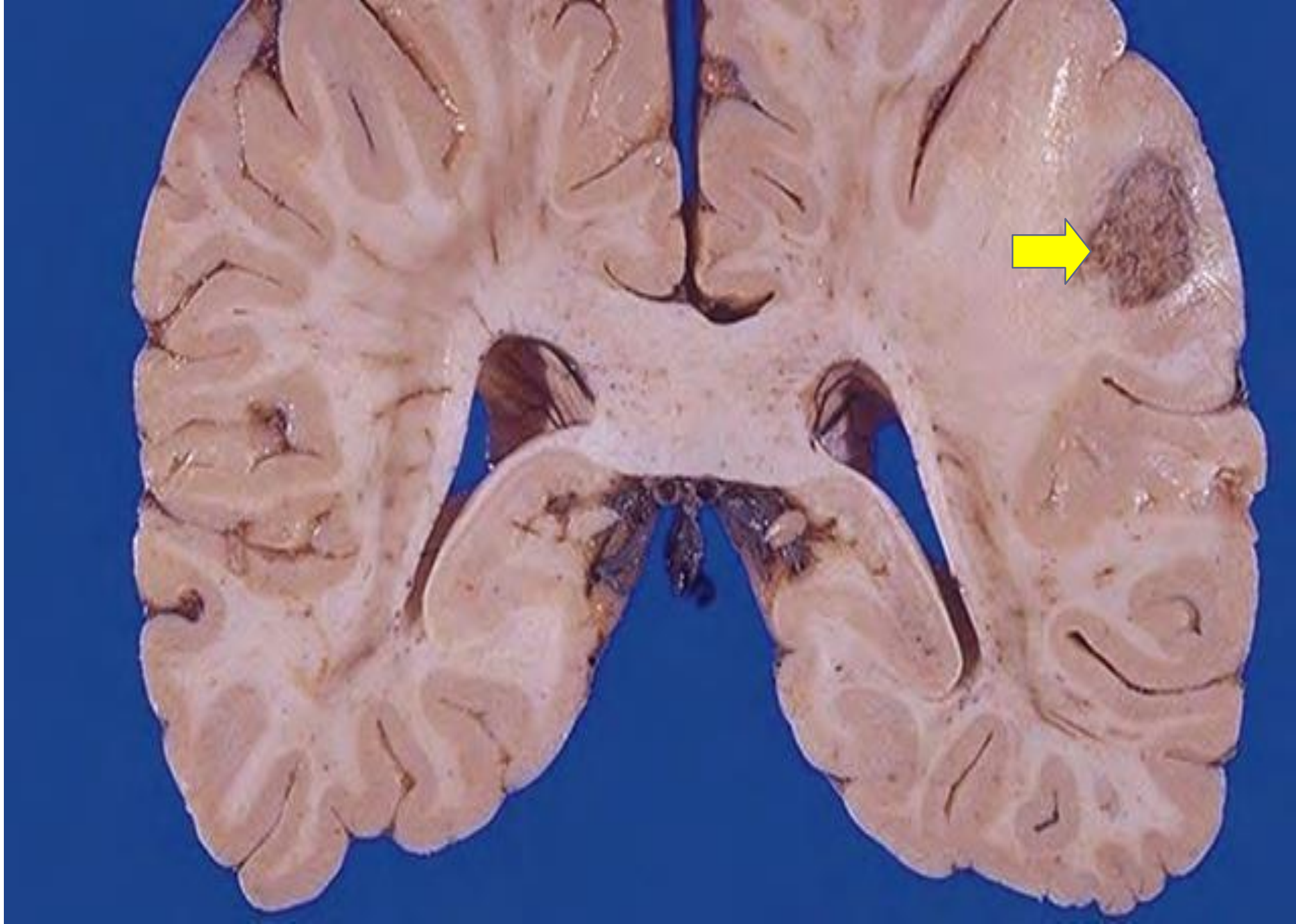
- Rare, highly aggressive, resemble a high-grade sarcoma or carcinoma or melanoma morphologically. They are classified as grade 3 meningiomas by having at least one of the following features:

1) **≥20 mitoses/ 10HPF;** or
2) Frank anaplasia (sarcoma, carcinoma or melanoma-like areas); or
3) TERT promotor mutation; or
4) Homozygous deletion of CDKN2A/B
5) **Papillary;** or **rhabdoid meningioma.**

Metastatic Tumors:

- Accounts for >50% of intracranial tumors.
- mostly **carcinomas**
- The most common primary sites are **lung, breast, skin (melanoma), kidney, and colon (**80% of cases).
- **sharply demarcated masses**, often seen at the grey-white matter junction, and elicit local edema and reactive gliosis

- The figure shows Red brown mass at the gray white matter junction from a metastatic renal cell carcinoma, appreciate that the margin is sharply demarcated



Primary Central Nervous System Lymphoma:

- Accounts for about 2% of extra nodular lymphoma and 1% of intracranial tumors
- **the most common CNS neoplasm in immunosuppressed individuals** including those with AIDS and those with transplantations.
- In non-immunosuppressed populations, the frequency increases after 60 years of age. "primary" is used to highlight the difference between these tumors and secondary involvement of the brain with lymphomas elsewhere in the body.
- Aggressive disease, poor response to chemotherapy (especially if compared with comparable histology that occur at non-CNS site)
- The most common type: **diffuse large B-cell lymphomas,** generally they are aggressive and have one of the worse prognosis profiles relatively.

Primary brain lymphoma:

- They are often multifocal
- involvement outside of the CNS (in lymph nodes or BM) is a **rare and late** complication. On the other hand, lymphoma arising outside CNS rarely involve the brain parenchyma
- relatively **well defined** as compared with glial neoplasms but not as discrete as metastases.

Familial Tumor Syndromes

- inherited syndromes caused by mutations in tumor suppressor genes and associated with increased risk of neoplasms
- tumors of the nervous system make a prominent aspect of some of these syndromes, including:
  - ✓ **Tuberous Sclerosis**
  - ✓ **Von Hippel-Lindau Disease**

Tuberous Sclerosis

- autosomal dominant neuroectodermal syndrome
- 1 in 6000 births
- characterized by:
  - **development of multiple hamartomas and benign neoplasms involving the brain and other tissues**
  - **In addition, the CNS manifestation Extracerebral lesions/tumors may happen:**
    - Renal angiomyolipomas, retinal glial hamartomas, pulmonary lymphangioleiomyomatosis, and cardiac rhabdomyomas
    - Many of these develop during childhood and adolescence.

- Cysts at various sites, including the liver, kidneys, and pancreas.
- **Cutaneous lesion** are very characteristic and often provide important diagnostic clue and these include :
  - Angiofibromas these lesions are typically seen in the central part of the face
  - localized leathery thickenings (shagreen patches)
  - hypopigmented macules areas (ash-leaf patches) They are called ash-leaf spots because of their characteristic shape.
  - subungual fibromas Which may occur around or beneath the nails and appear later in the course of the disease

CNS hamartomas

- The characteristic lesion of Tuberous Sclerosis in the CNS are hamartomas
- Hamartomas within the CNS take the form of **cortical tubers and subependymal nodules**
- **Cortical tubers** are particularly important clinically because they are epileptogenic, and surgical resection can be beneficial.
- In terms of histology, hamartomas consist of glioneuronal hamartomas and subependymal hamartomas along the ventricular walls including **subependymal giant cell astrocytomas (SEGA)** which are characteristic tumors associated with tuberous sclerosis.

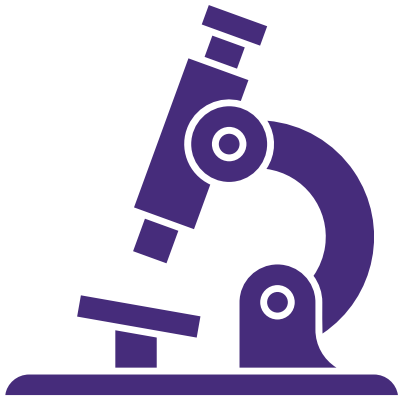
Von Hippel-Lindau Disease:

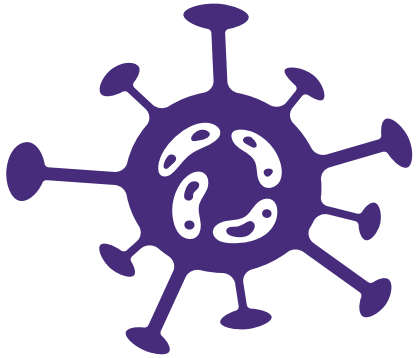
- autosomal dominant inherited disease
- 1 in 30,000 to 40,000.
- This syndrome is characterized by the development of multiple tumors and cystic lesions in different organs.
- **Associated with:**
  - hemangioblastomas of the CNS
    - which most commonly happen in the cerebellum and retina, but may happen in the brainstem, spinal cord and nerve roots.
  - cysts in several organs including pancreas, liver, and kidneys
  - Increased risk of renal cell carcinomas especially the clear cell renal cell carcinoma
  - Pheochromocytomas arising from the adrenal medulla

Hemangioblastomas

- **Hemangioblastomas are highly vascularized that commonly associated with Von Hippel-Lindau Disease**
- In terms of histology these are highly vascular neoplasms consists of numerous capillary-size or larger or thin-walled vessels with intervening neoplastic stromal cells, which represent the true tumor component. These stromal cells typically have vacuolated, lipid-rich cytoplasm, giving a clear or foamy appearance under the microscope.
- From an immunohistochemical standpoint the neoplastic stromal cells express **inhibin** (useful diagnostic marker), distinguishes hemangioblastomas from other highly vascular tumors, such as metastatic clear cell renal cell carcinoma.


thank you





PATHOLOGY QUIZ LECTURE 3

External Resources

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