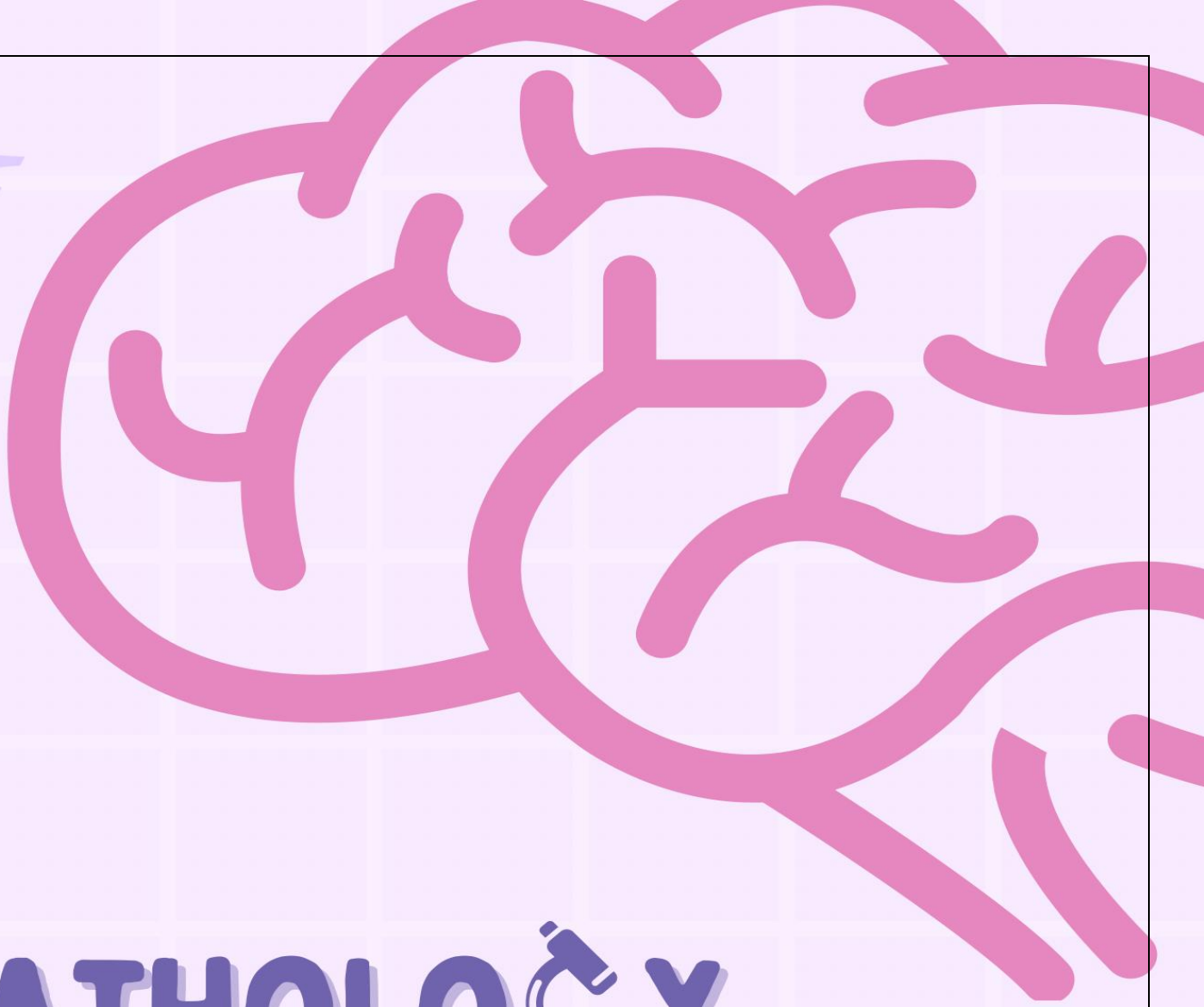

PATHOLOGY

SHEET NO. 7

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CNS TUMORS (1)

Lecture outline

- ✓ Introduction
- ✓ Epidemiology
- ✓ Characteristic features of CNS tumors
- ✓ Histologic grading of CNS tumors
  - Histologic criteria
  - CNS tumors grades
- ✓ Pediatric CNS tumors
- ✓ Development of WHO classification of CNS tumors
- ✓ Genetic alterations in gliomas
- ✓ Our textbook classification
  - Gliomas classification
  - Glial cells histology
  - Astrocytomas
    1. Diffuse astrocytoma (grade 2 / grade 3 / grade 4)
    2. Circumscribed astrocytic gliomas (pilocytic astrocytoma)

INTRODUCTION

- ✓ CNS tumors can involve the brain or spinal cord.
- ✓ CNS tumors are divided into:

1- PRIMARY CNS TUMORS

- May arise from the **cells of the coverings** (meningothelial (arachnoidal) cells in meningiomas), **the brain cells** (gliomas, neuronal tumors), or **other CNS cell populations** **(**primary CNS lymphoma, germ cell tumors).
- Primary tumors account for about 50 to 75 % of CNS tumors.

2- SECONDARY (METASTATIC) CNS TUMORS

- They originate elsewhere in the body and involve the CNS.
- They account for about 25 to 50 % of CNS tumors.

EPIDEMIOLOGY

- We can say that CNS tumors are common, especially if we compare them with lung or breast cancer.
- **INCIDENCE**:

- The annual incidence of CNS tumors --->
  - 10 - 17/100,000 for intracranial tumors.
  - 1-2/100,000 for intraspinal tumors.

CHARACTERISTIC FEATURES OF CNS TUMORS

1. NO PREMALIGNANT OR IN SITU STAGES

- This is different from other tumors, like:
  - lung adenocarcinoma can be preceded by atypical adenomatous hyperplasia.
  - Squamous cell carcinoma can be preceded by squamous dysplasia.

2. METASTASIS IS RARE

- When we were trying to determine the outcome or the prognosis for other tumors in the body system, we were looking to the histological grade and the TNM staging system.
  - T ----> primary size of the initial tumor.
  - N----> number of nearby lymph nodes that have cancer.
  - M ----> whether the cancer has metastasized.
- This isn't applicable here because there is no lymph node metastasis or distant metastasis.
- Even the most highly malignant gliomas **rarely spread** outside of the CNS.
- But the brain is **not comparably protected** against the spread of distant tumors.

3. The prognosis for CNS tumors is highly affected by two important factors: GROWTH PATTERN AND LOCATION.

- **Growth pattern----** > the tumor being infiltrative, diffused **OR** circumscribed (you can draw the boundary between the tumor and adjacent uninvolved brain parts).
  - Even low-grade lesions may infiltrate large regions of the brain, leading to serious clinical deficits, inability to be resected and poor prognosis.

- **Example:** if we have low grade glioma (grade 2 astrocytoma), but this tumor is infiltrative. This means it involves larger areas of the brain, so your patient come with more neurologic deficits, and even if you can do surgery , the surgery will end up removing large parts of the brain , which mean more neurological deficits.

  - *It is not about the grading, it is about the growth pattern of the tumor.*

- **Tumor location** --> very important factor

- The anatomic site of the neoplasm can influence outcome independent of histologic type or grade.
- Some tumors can be lethal only because they are present in critical locations.

- Example: Meningioma grade 1 (benign) that involves the posterior fossa near the vital centers in the medulla. If this tumor causes pressure on the cardio respiratory centre, this will result in cardio respiratory arrest, and can be lethal regardless of the grade and the classification.

Why the location is almost everything?

- The location is going to determine the neurologic deficit that is associated with the presence of this tumor and can determine the ability for this tumor to be surgically resected.

- If it was in critical area, it can't be resected.

- And also it is going to guide your diagnosis in the classification of the tumor because certain tumors tend to happen in certain locations.

- The prognosis also depends on age because CNS tumors are classified into adult tumors and pediatric tumors

4. RADIO IMAGING ---> this will guide your diagnosis and management plan.

- Example: If you find calcifications, you may think of oligodendroglioma.

HISTOLOGIC GRADING OF CNS TUMORS

- This classification is based on 4 histologic criteria:

1- Presence of atypia.

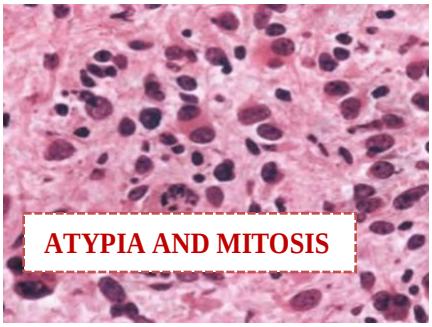
2- Mitotic count.

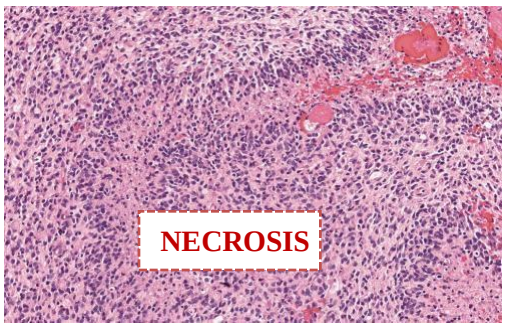
3- The presence or absence of microvascular proliferation.
- **Microvascular proliferation:** the presence of abnormal vessels (irregular in shape, lined by at least two layers of endothelial cells and sometimes these cells are mitotically active).

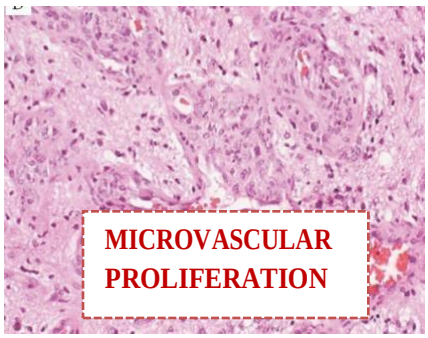
**Note : The normal vessels are regular in shape , and lined by single layer of endothelial cells

4- Necrosis.

- CNS tumors are classified into 4 types:







- **Grade 1 lesions (benign)**

- low proliferative activity

- Can be cured after surgical resection alone.

- Examples: pilocytic astrocytoma (PA), subependymal giant cell astrocytoma (SEGA), choroid plexus papilloma, myxopapillary ependymoma.

Grade 2 lesions (low grade)

- Low proliferative activity.
- Usually infiltrative and often recur.
- Some grade II entities tend to progress to higher grades of malignancy.

- Examples: Diffuse astrocytoma, oligodendroglioma, neurocytoma, some types of ependymoma.

Grade 3 lesions (anaplastic)

- Clear histological evidence of malignancy (nuclear atypia and higher proliferative activity---> mitosis).
- In most settings, patients receive radiation and/or chemotherapy.
- **Examples:** Anaplastic astrocytoma, anaplastic oligodendroglioma.

Grade 4 lesions (high grade)

- Cytologically malignant, mitotically active, rapid proliferation, necrosis-prone neoplasms.
- Associated with rapid pre- and postoperative disease evolution and fatal outcome.
- **Examples:** Glioblastoma, medulloblastoma, pineoblastoma, and most embryonal neoplasms.

PEDIATRIC CNS TUMORS

- 20% of all pediatric tumors.
- Childhood CNS tumors differ from those in adults in:

➢ LOCATION:

- 2/3 infratentorial in kids (posterior fossa) ---> cerebellum, brain stem, fourth ventricle.
- 2/3 supratentorial in adults (cerebral hemispheres above tentorium).

➢ HISTOLOGIC TYPE:

- **Kids:** medulloblastoma, pilocytic astrocytoma, ependymoma
- **Adults:** glioblastoma, metastases, meningiomas, diffuse gliomas constitute most gliomas in adults (including diffuse astrocytomas and oligodendrogliomas).

DEVELOPMENT OF WHO CLASSIFICATION OF CNS TUMORS

- For nearly a century (1979-2007), the classification of brain tumors has been done according to their **microscopic similarities.**
  - (based on the light microscopic appearance, the immunohistochemical expression of proteins, and the electron microscopic assessment of ultra structural features**)**.
- The 2000 and 2007 WHO classifications were based on the described classification and unfortunately your pathology textbook is outdated.
- The 2016 classification breaks with this nearly century-old tradition and **incorporates well-established molecular parameters into the classification.**
- The classification includes diagnostic categories that depend on **genotype.**
- The 2016 WHO classification implemented **the combined phenotypic-genotypic diagnostics** based on tumor genetic profile and histologic features (integrated diagnoses).
- The 2016 classification helped improving treatment protocols and predicting prognosis
- So for example, this tumor by **histology** (phenotype) is astrocytoma. By **genotype** (molecular) idh1 mutants tumor.

❖ **The final diagnosis** (integrated diagnosis) astrocytoma idh1 mutant grade2.

GENETIC ALTERATIONS IN GLIOMAS

1- Mutations in isocitrate dehydrogenase (IDH) genes:

- observed in astrocytomas and oligodendrogliomas may occur in IDH1 or IDH2 genes.
- Can be detected by immunohistochemical stains and molecular studies:
    - IDH1-R132H immune stain / IDH2 doesn't have immune stain
    - IDH sequencing for IDH1 codon 132 and IDH2 codon 172

- lead to increased production of 2-hydroxyglutarate -----> interferes with the activity of several enzymes that regulate gene expression----> maintaining the cells in stem cell-like physiological states --- > self- renewal and tumorigenesis.

2- Co-deletion of 1p (short arm of chromosome 1) and 19q (long arm of chromosome 19) chromosomal segments:

- present in oligodendrogliomas.

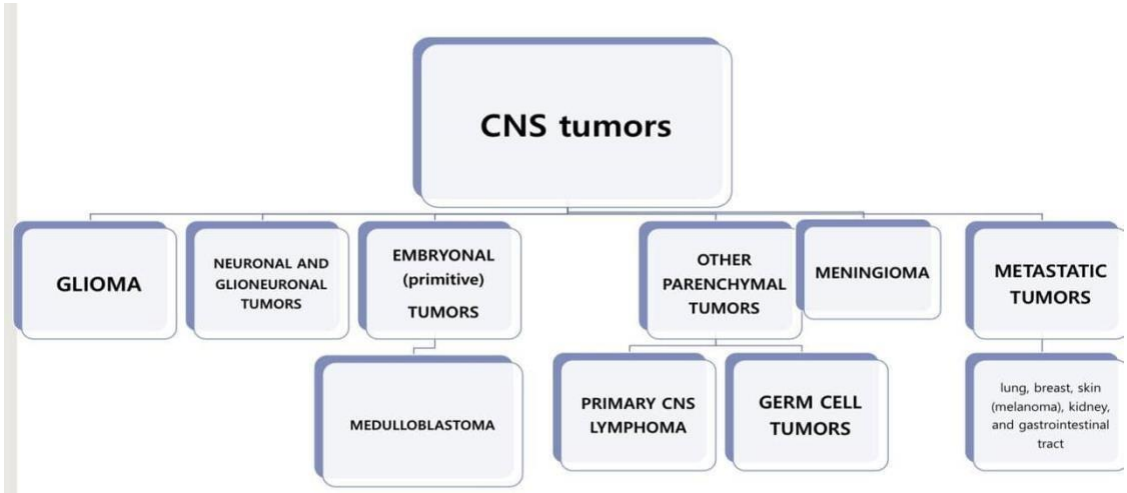
3- Mutations in the promoter for telomerase:

- Immortalization of tumor cells, eg. glioblastomas.

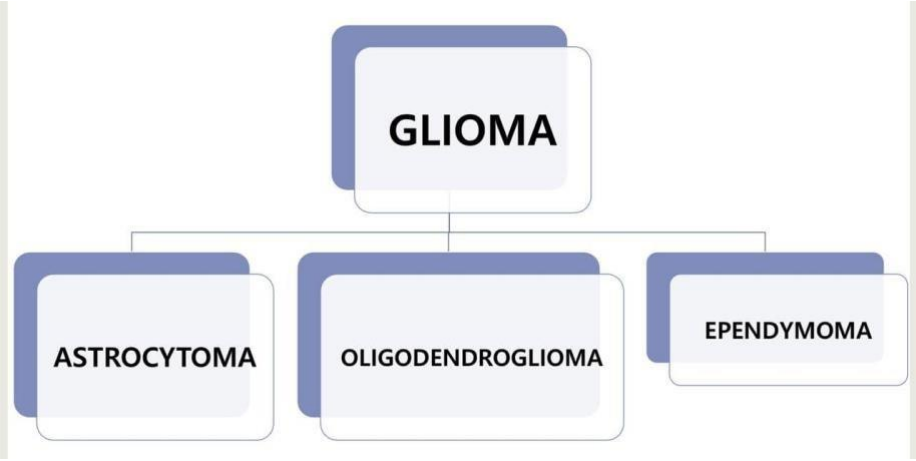
4- Other genetic alterations:

- include mutations that lead to overexpression of the **EGF receptor** and other **receptor tyrosine kinases** or disable **p53 or RB.**

OUR TEXTBOOK CLASSIFICATION



Glioma --> tumors of brain parenchyma, classified according to morphologic similarities to the glial cells

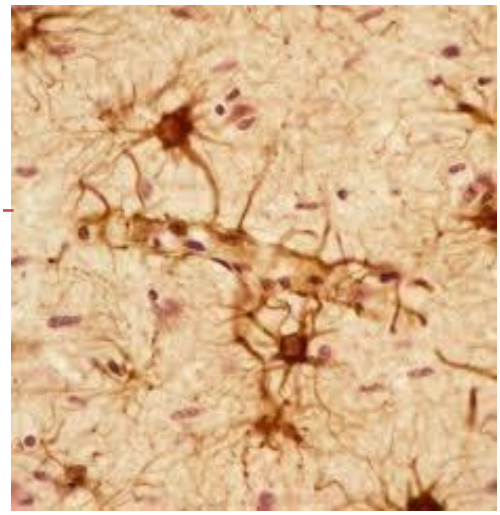


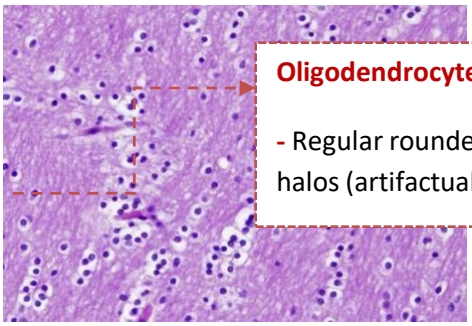
GLIAL CELLS HISTOLOGY

Astrocyte

- Round nucleus with many cell processes. If you stain the cell with GFAB (the glial fibrillary acidic protein) ---> star shape with cell body and processes lightened by brown stain---- > GFAB positive.

- Astrocytes are the most common cells, they outnumber the neurons.



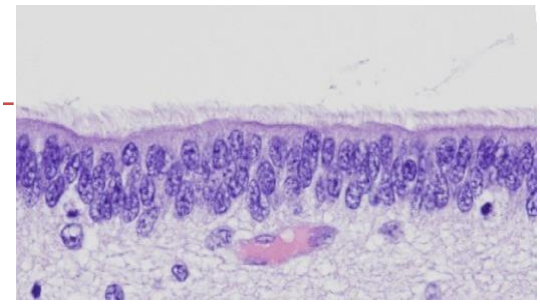


Oligodendrocyte

- Regular rounded nucleus with perinuclear halos (artifactual clear areas).

Ependymal cell

- It is like epithelial cell, cuboidal to columnar lining the ventricular system and the central canal.



ASTROCYTOMAS

- Classified into two major categories according to **their infiltrative potential**:

1- **diffuse (infiltrating) astrocytoma----** > you can't draw a line between the normal brain parenchyma and the neoplastic area.

2- **Circumscribed astrocytic gliomas:** PA, SEGA, pleomorphic xanthoastrocytoma (PXA).

➢ Diffuse (infiltrating) Astrocytoma

- **80%** of adult gliomas.
- **Age at diagnosis:** 40−60-year old.
- **Location:** cerebral hemispheres.
- **Presentation:**
  - Seizures, headaches, and focal neurologic deficits related to the anatomic site of involvement.
- **Outcome:**
  - Static or progressive
  - If the patient shows rapid clinical deterioration, it can be correlated with the appearance of higher-grade component and more rapid tumor growth.

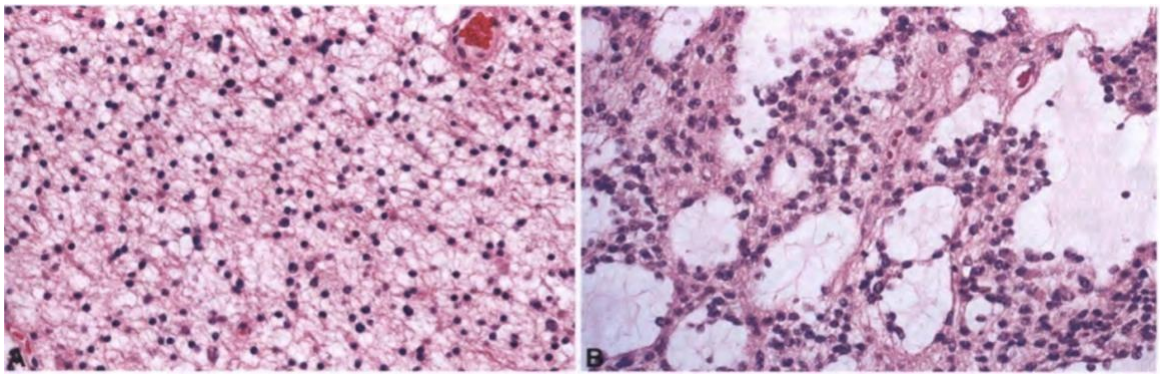
- **On the basis of histologic features astrocytomas are stratified into three groups**

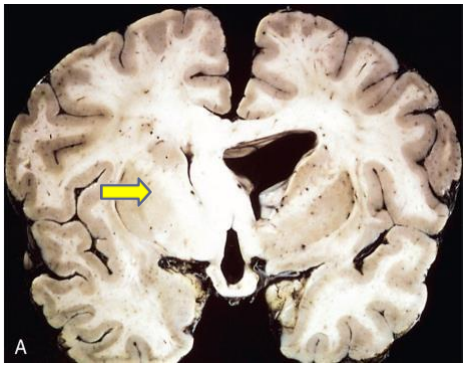
    1. Diffuse astrocytoma (grade 2), mean survival is > 5 years.
    2. anaplastic astrocytoma (grade 3), mean survival is 2-3 years
    3. Glioblastoma (grade 4), mean survival is 15 months.

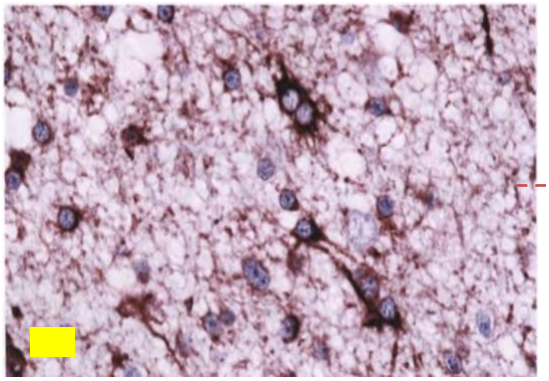
- **The prognosis gets poorer as the grade increases.**
- **NO grade 1 diffuse astrocytoma**

1. Diffuse astrocytoma (grade 2)

- **Mild to moderate** increase in the number of glial cells + fibrillary background made of fine astrocytic cell processes.
- Variable **nuclear pleomorphism**, however not prominent atypia.
- Hyper chromatic nuclei and may be elongated
- Mitotic activity is generally **absent**
- **NO** necrosis
- **NO** microvascular proliferation
- It is common to have microcyst formation







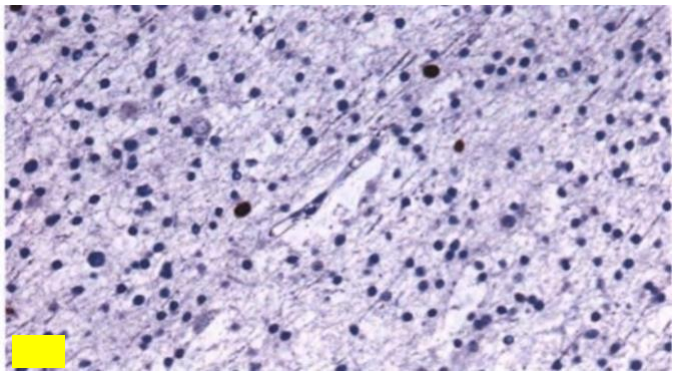
GFAP stain

- The cell body and the process are going to be GFAB positive.

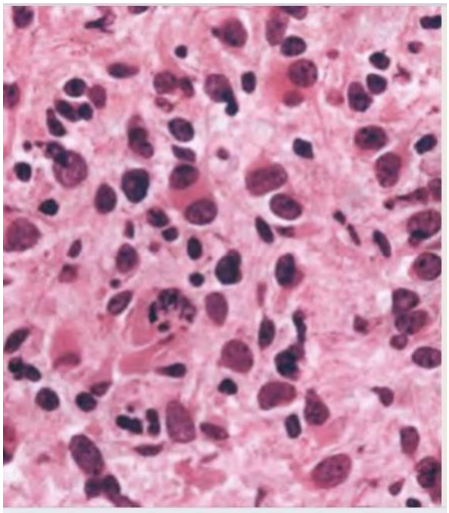
- Low proliferative activity ---> if you search for mitotic figures ---- > they are usually absent

Ki67 stain (proliferative marker)

- We have just two nuclei that are dark brown.



2. Anaplastic astrocytoma (grade 3)



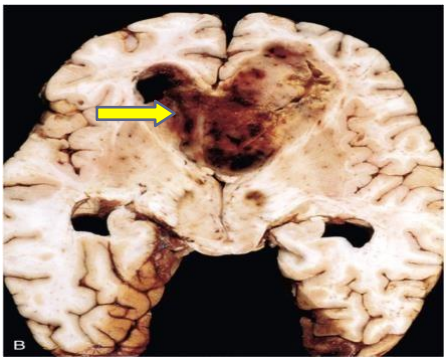
- ❖ more cellular
- ❖ greater nuclear pleomorphism
- ❖ mitotic figures are **present**
- ❖ **NO** necrosis
- ❖ **NO** microvascular proliferation

3. Glioblastomas (grade 4)

- Lesions can start as Glioblastoma from the beginning (**primary**) or progress from a previous grade 2 or 3 tumors to grade 4 (**secondary**).
- prognosis is **very poor** even with treatment (resection, radiotherapy, and chemotherapy)

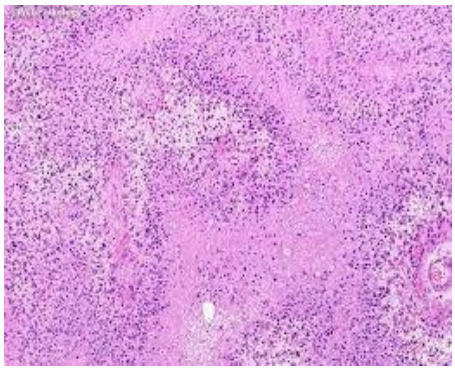
  ○ **Macroscopic**

- Variation in the gross appearance of the tumor from region to region is characteristic (was called **glioblastoma multiforme**).
- Some areas are firm and white, others are soft and yellow (due to tissue necrosis), and others show regions of cystic degeneration and hemorrhage.
- It shows multiple picture depend on where you are looking from.



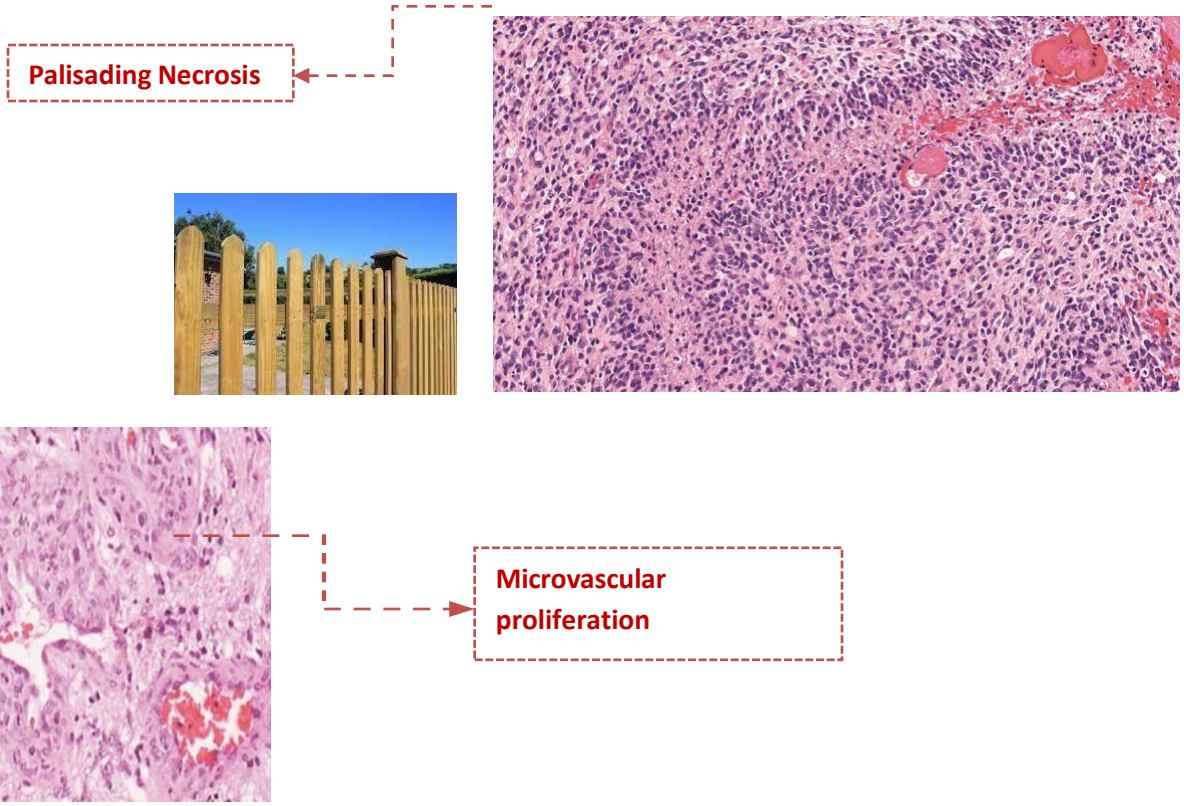
  ○ **Microscopic**

- cellular tumor with nuclear pleomorphism as in anaplastic astrocytoma with either
- **<u>Necrosis:</u>** irregular zones of necrosis surrounded by dense accumulations of tumor cells (**Palisading necrosis).**



OR

- **<u>microvascular proliferation</u>**

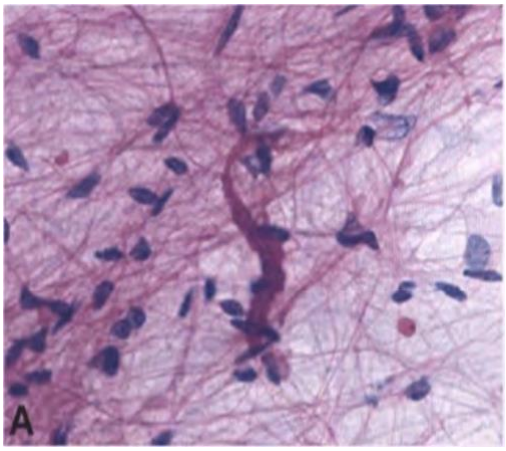


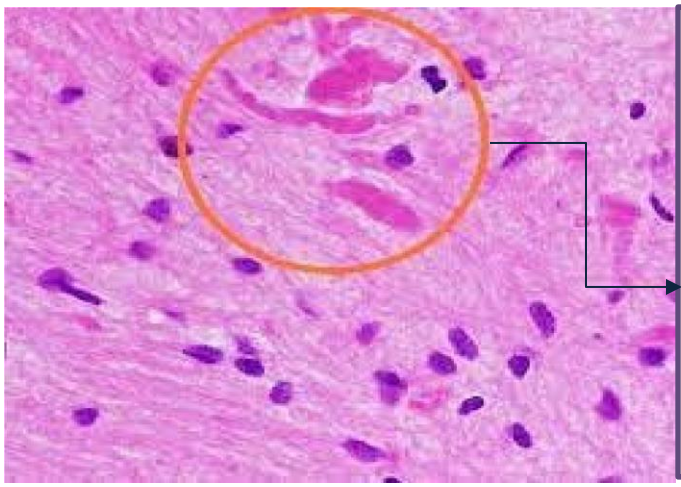
➢ **Circumscribed astrocytic gliomas:**

Pilocytic Astrocytoma

- relatively benign, Slow growing tumors, can be treated by resection
- **Age at presentation:** children and young adults.
- **Location:** cerebellum> 3rd ventricle > optic pathways> spinal cord> cerebral hemispheres.
- **Molecular profile:** activating mutations or translocations involving the gene encoding the BRAF, which result in activation of the MAPK signaling pathway.
- **Do not have mutations in IDH1 and IDH2,** supporting their distinction from the low-grade diffuse gliomas.

- **Microscopic**
  - bipolar cells with long, thin GFAP positive “hairlike” processes
  - Rosenthal fibers
  - Eosinophilic granular bodies
  - microcysts are often present
  - necrosis and mitoses are rare



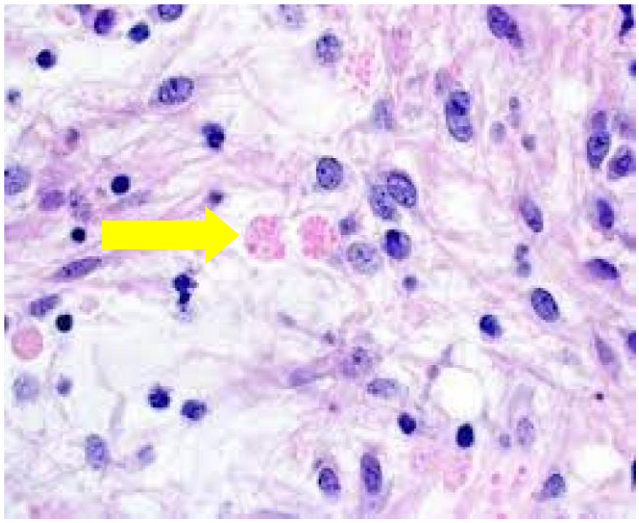


Rosenthal fibers :

• are rounded or elongated, homogenous, and brightly eosinophilic structures within the astrocytic processes.

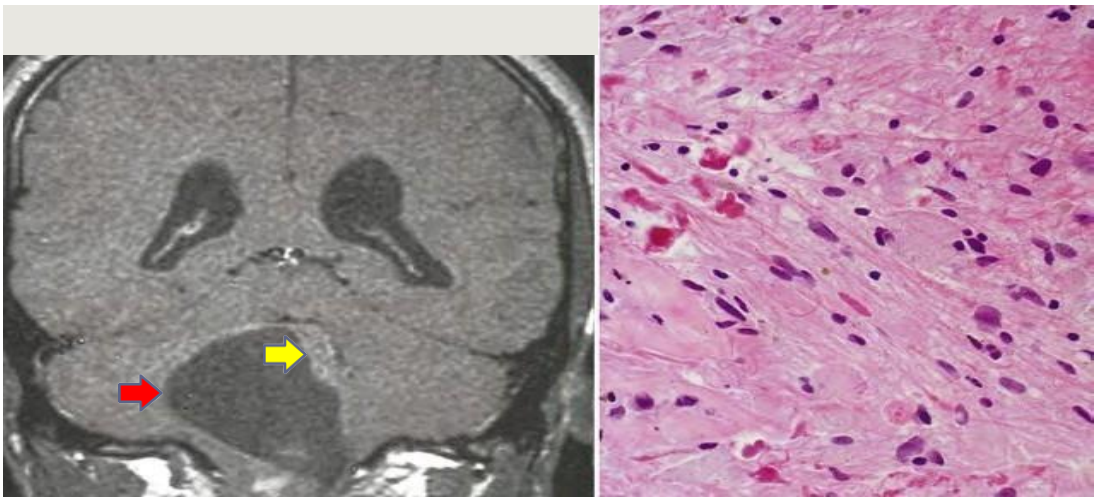
• made of clumped intermediate filament proteins, primarily glial fibrillar acidic protein(GFAP +VE) .

• Can be physiologic (gliosis) or pathologic (PA) and Alexander disease , so it is not diagnostic or exclusive for pilocytic astrocytoma



Eosinophilic granular bodies:

rounded hyaline droplets in cytoplasm of astrocytes seen in PA and ganglion-cell tumors.



- Well circumscribed, cystic with a mural nodule in the wall of the cyst or solid.
- Red arrow points to the lesion (infra tentorial tumor), usually within the midline.
- This tumor is formed by large radiolucent area which represents the cystic cavity, so the tumor has a cystic cavity with a solid area (yellow arrow).