CNS
Doctor 2021

Pathology

Modified ( )

Writer: عبد الله الطعّاني
Corrector:
Doctor: مرام عبد الجليل

CENTRAL NERVOUS SYSTEM TUMORS(1)

Maram Abdaljaleel, MD

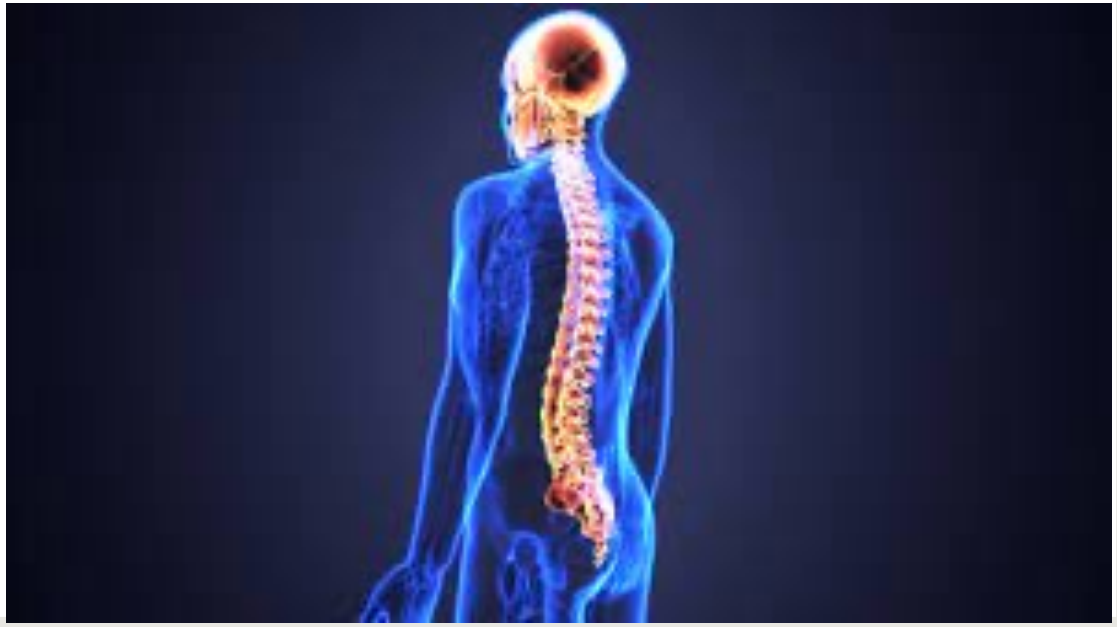
Dermatopathologist & Neuropathologist

CNS TUMORS:

(The brain parenchyma)

- may arise from the **cells of the coverings** (meningiomas), **the brain cells** (gliomas, neuronal tumors), or **other CNS cell populations** (primary CNS lymphoma, germ cell tumors), or they may originate elsewhere in the body (**metastases**).

- Can involve the **brain or spinal cord**



https://answers.childrenshospital.org/spinal-cord-injury/

EPIDEMIOLOGY:

They are not that common but they are important because they have characteristics that set them apart from any neoplastic process happening elsewhere in the body

- **INCIDENCE**:
  - The annual incidence of CNS tumors in the U.S →
    - 24 /100,000 for intracranial tumors , 1/3 malignant
    - 1-2/100,000 for intraspinal tumors

- **Metastases are more common than primary brain tumors.**

  So the brain is a common site of metastasis.
  The most common tumors that metastasize to the brain are in slide 30

Characteristic features of CNS tumors:

- **Premalignant stage: NO** premalignant or in situ lesions.

- **Metastasis is rare!**
  - 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.

So TNM staging system isn't applicable here because it depends on 3 main factors:

1. tumor size (it can be measured here)
2. regional lymph node involvement (which isn't available here)
3. metastasis (is rare here)

So you can't determine the managment plan and the prognosis of your patient based on the TNM staging of these tumors

But remember that brain is a common site for metastasis from other primary sites

Characteristic features of CNS tumors:

- **Growth pattern (infiltrative or not) and tumor location strongly influence the prognosis:** +management + outcome
  - Even low-grade lesions may infiltrate large regions of the brain, leading to serious clinical deficits, inability to be resected, and poor prognosis. Surgical excision is hard because it's infiltrative
  - The anatomic site of the neoplasm can influence outcome independent of tumor type or grade due to local effects

Growth patterns for tumors

Tumors in CNS are described either circumscribed or infiltrative / diffuse.

1. When tumors are infiltrative: they invade beyond the gross surgically evident margin & between the normal cells
2. When tumor is circumscribed: The tumor forms a discreet mass which is amenable for complete surgical excision.

Regarding the tumor location

Let's Say that we have a grade 1 tumor like meningioma (a benign tumor of meningothelial cells), it is known that it is circumscribed, grade 1 tumor, but if it was located:

1. Near the frontal cortex = good outcome, complete surgical excision is possible even if the tumor was a little big (2-3 cm).

2. At the posterior cranial fossa, just adjacent to the medulla near the cardiorespiratory centers, this is critical and an excision attempt may lead to cardiorespiratory failure and the patient might die, even if the tumor were only 0.5 cm.

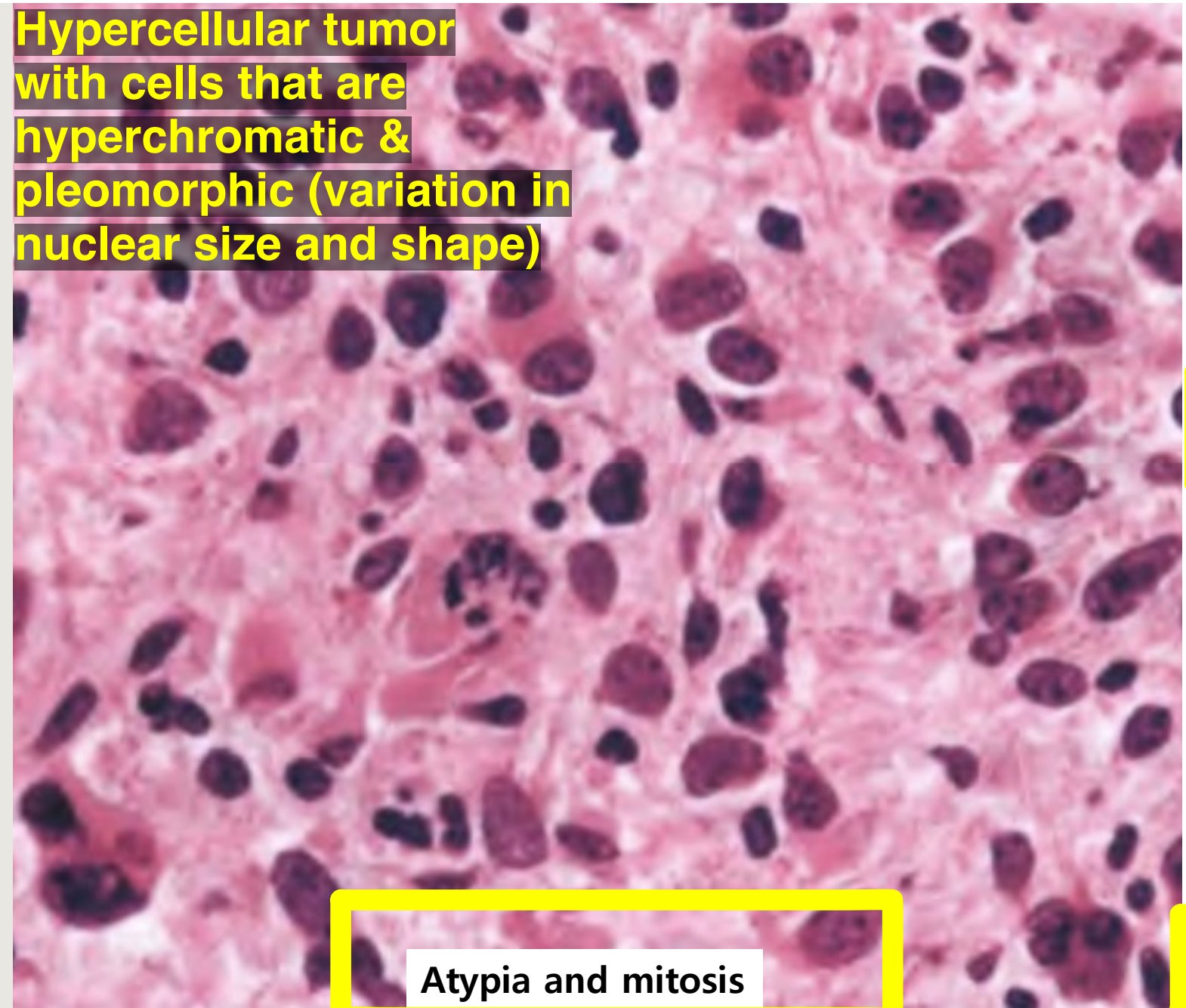
Tumor location & growth patter are almost everything in

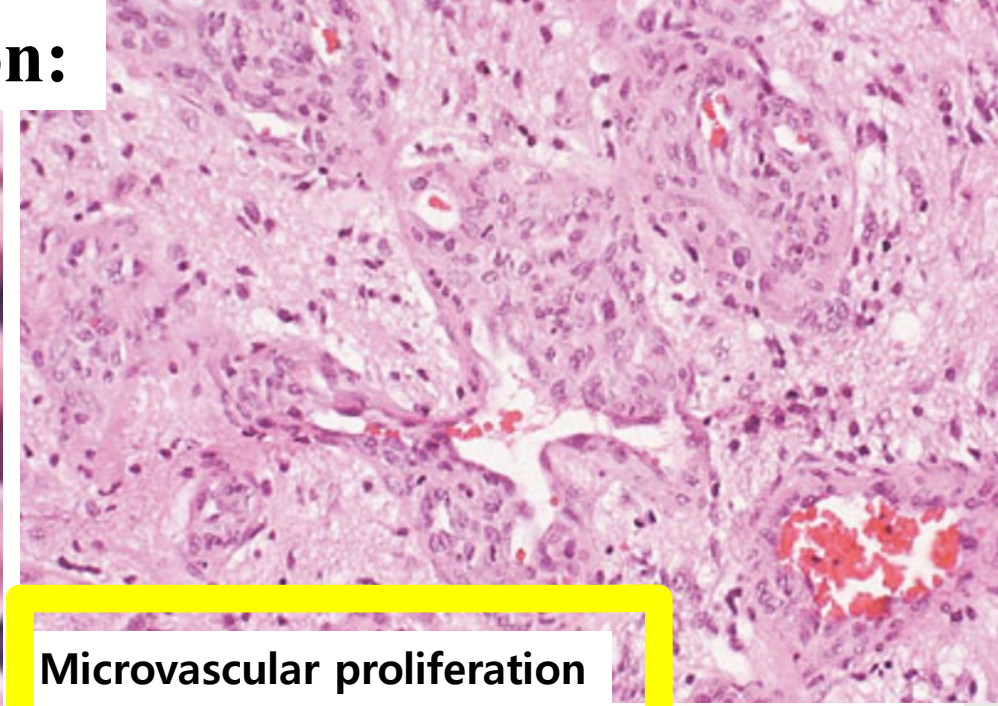
Location is very important in brain tumors just like real estate

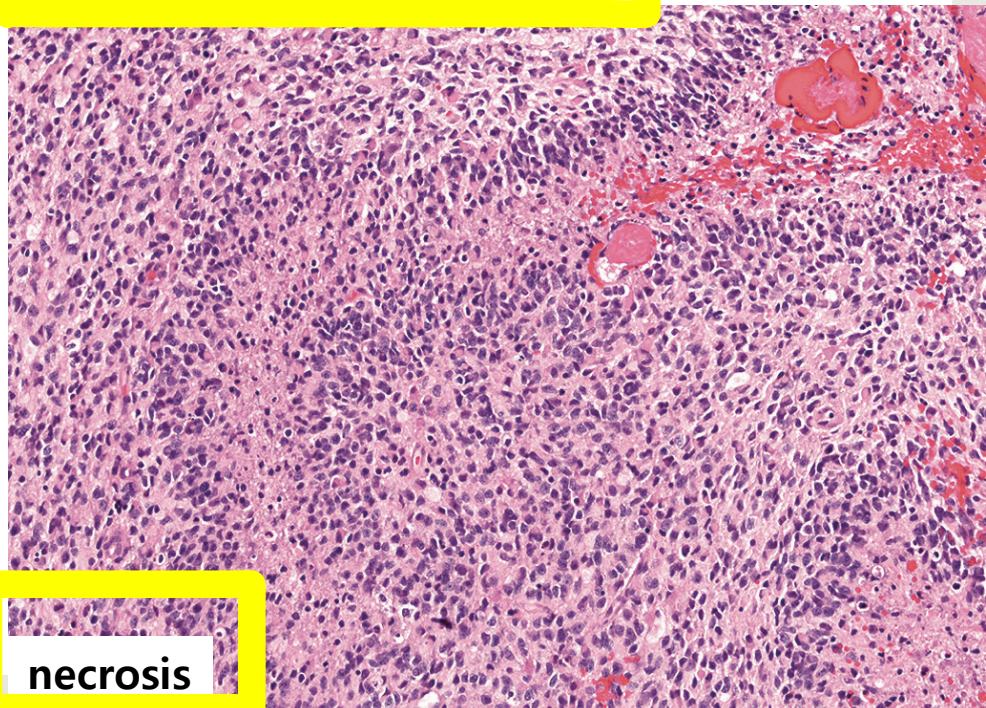
LOCATION
LOCATION
LOCATION
LOCATION
LOCATION

Histologic grading of CNS tumors

The histologic grading of CNS tumors depends on:







- **Grade 1 lesions:**
  - low proliferative activity Usually circumscribed
  - Can be cured after surgical resection alone. Which is treatment of choice

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

- **Grade 2 lesions:**
  - low proliferative activity
  - usually infiltrative and often recur
  - Some grade II entities tend to progress to higher grades of malignancy.

Here the patient will have sudden deterioration and neurologic deficit

Examples: astrocytoma, IDH- mutant, grade 2, oligodendroglioma, IDH- mutant and 1p/19q-codeleted, grade 2

- **grade 3 lesions:**
  - clear histological evidence of malignancy(nuclear atypia and Higher proliferative activity (mitosis)).
  - In most settings, patients receive radiation and/or chemotherapy.

The degree of mitosis differentiates
Between grade 2 and 3 (higher in 3)

Examples: astrocytoma, IDH- mutant, grade 3, oligodendroglioma, IDH-mutant and 1p/19q-codeleted, grade 3.

The highest grade

- **grade 4 lesions**: atypia, pleomorphism, bizarre cells & brisk mitotic activity
  - cytologically malignant, mitotically active, rapid proliferation, necrosis-prone neoplasms
    There is necrosis or microvascular proliferation
  - associated with rapid pre- and postoperative disease evolution and fatal outcome.
  - Widespread infiltration of surrounding tissue and a risk of craniospinal dissemination.

examples: Glioblastoma, IDH-wildtype, medulloblastoma, pineoblastoma, and most embryonal neoplasms

Not for Memorization

WHO grades of select CNS tumours

Diffuse astrocytic and oligodendroglial tumours	
Diffuse astrocytoma, IDH-mutant	II
Anaplastic astrocytoma, IDH-mutant	III
Glioblastoma, IDH-wildtype	IV
Glioblastoma, IDH-mutant	IV
Diffuse midline glioma, H3 K27M-mutant	IV
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	II
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	III
Other astrocytic tumours	
Pilocytic astrocytoma	I
Subependymal giant cell astrocytoma	I
Pleomorphic xanthoastrocytoma	II
Anaplastic pleomorphic xanthoastrocytoma	III
Ependymal tumours	
Subependymoma	I
Myxopapillary ependymoma	I
Ependymoma	II
Ependymoma, *RELA* fusion-positive	II or III
Anaplastic ependymoma	III
Other gliomas	
Angiocentric glioma	I
Chordoid glioma of third ventricle	II
Choroid plexus tumours	
Choroid plexus papilloma	I
Atypical choroid plexus papilloma	II
Choroid plexus carcinoma	III
Neuronal and mixed neuronal-glial tumours	
Dysembryoplastic neuroepithelial tumour	I
Gangliocytoma	I
Ganglioglioma	I
Anaplastic ganglioglioma	III
Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos)	I
Desmoplastic infantile astrocytoma and ganglioglioma	I
Papillary glioneuronal tumour	I
Rosette-forming glioneuronal tumour	I
Central neurocytoma	II
Extraventricular neurocytoma	II
Cerebellar liponeurocytoma	II
Tumours of the pineal region	I
Pineocytoma	II or III
Pineal parenchymal tumour of intermediate differentiation	
Pineoblastoma	IV
Papillary tumour of the pineal region	II or III
Embryonal tumours	
Medulloblastoma (all subtypes)	IV
Embryonal tumour with multilayered rosettes, C19MC-altered	IV
Medulloepithelioma	IV
CNS embryonal tumour, NOS	IV
Atypical teratoid/rhabdoid tumour	IV
CNS embryonal tumour with rhabdoid features	IV
Tumours of the cranial and paraspinal nerves	
Schwannoma	I
Neurofibroma	I
Perineurioma	I
Malignant peripheral nerve sheath tumour (MPNST) I	I, III or IV
Meningiomas	
Meningioma	I
Atypical meningioma	II
Anaplastic (malignant) meningioma	III
Mesenchymal, non-meningothelial tumours	
Solitary fibrous tumour / haemangiopericytoma	I, II or III
Haemangioblastoma	I
Tumours of the sellar region	I
Craniopharyngioma	I
Granular cell tumour	I
Pituicytoma	I
Spindle cell oncocytoma	I

Pediatric CNS tumors:

70% of pediatric CNS tumors are infratentorial in the posterior fossa

70% of adult CNS tumors are supratentorial

- 20% of all pediatric tumors.
- Childhood CNS tumors differ from those in adults in:
  - **Location:**
    - 2/3 infratentorial in kids (posterior fossa)
    - 2/3 supratentorial in adults (cerebral hemispheres above tentorium)
  - **Mutation profile & histologic subtype:**
    - Kids: medulloblastoma, pilocytic astrocytoma, ependymoma
    - Adults: glioblastoma, metastases, meningiomas, diffuse gliomas constitute most gliomas in adults(including astrocytomas and oligodendrogliomas).

CLASSIFICATION OF CENTRAL NERVOUS SYSTEM TUMORS

- For nearly a century, the classification of brain tumors has been done according to their **microscopic similarities** with what's thought to be their cell of origin (based on the light microscopic appearance, the immunohistochemical expression of proteins, and the electron microscopic assessment of ultrastructural features).

- 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 histologic features & tumor genetic profile (integrated diagnoses)** → It's composed of 2 parts Phenotype and genotype

- The 2016 classification helped **improving treatment protocols and predicting prognosis.**

genetic alterations in gliomas:

1- Mutations in isocitrate dehydrogenase (IDH) genes:

- observed as an early event in gliomagenesis
- Seen in astrocytomas and oligodendrogliomas

If it's not present it can't be astrocytomas or oligodendrogliomas

- Gain of function Mutation affection IDH1 codon 132 or IDH2 codon 172.
- The most frequent is IDH1 R132H mutation (83-91%) of IDH mutant gliomas

The most common mutation in IDH 1

- IDH2 mutation: R172K is the most frequent IDH2 mutation

The most common mutation in IDH 2

- ✓ Can be detected by immunohistochemical stains and molecular studies:
  - IDH1-R132H immune stain The only available stain
  - IDH sequencing for IDH1 codon 132 and IDH2 codon 172

    If the immunohistochemical stain was negative we will send it for sequencing
    The sequencing will tell me if it is mutant or wildtype (opposite of mutant)
- ✓ Gain of function mutation→ lead to increased production of 2-hydroxyglutarate (oncometabolite)→interferes with the activity of several enzymes that regulate gene expression→ DNA hypermethylation & maintaining the cells in stem cell-like physiological states→ self- renewal and tumorigenesis

p= short arm q= long arm

2- **whole arm Co-deletion of 1p and 19q chromosomal segments:** Complete loss of them

- Diagnostic of oligodendrogliomas in the presence of IDH mutation.

- The vast majority of IDH mutant and 1p/19q co-deleted oligodendroglioma →carry TERT promotor hotspot mutations

- **TERT promotor hotspot mutations**: telomerase stabilization, cellular immortalization and proliferation

Tolemerase maintains the tolemers which are certain DNA sequences present at the end of the chromosome, it protects DNA and it's important for the cell devision

3- **ATRX and P53 loss of function mutation:**

- Both occur in IDH mutant astrocytomas
- **ATRX mutation** induces abnormal telomeres maintenance mechanism known as **"alternative lengthening of telomeres"** It makes the cell
- **ATRX mutation is Mutual exclusive with the activating promoter mutation of the TERT gene+1p/19q codeletion)** Mutual exclusive ralation between 3 mutations means if one happened the other won't
- **P53 mutation:** enable tumor cell survival

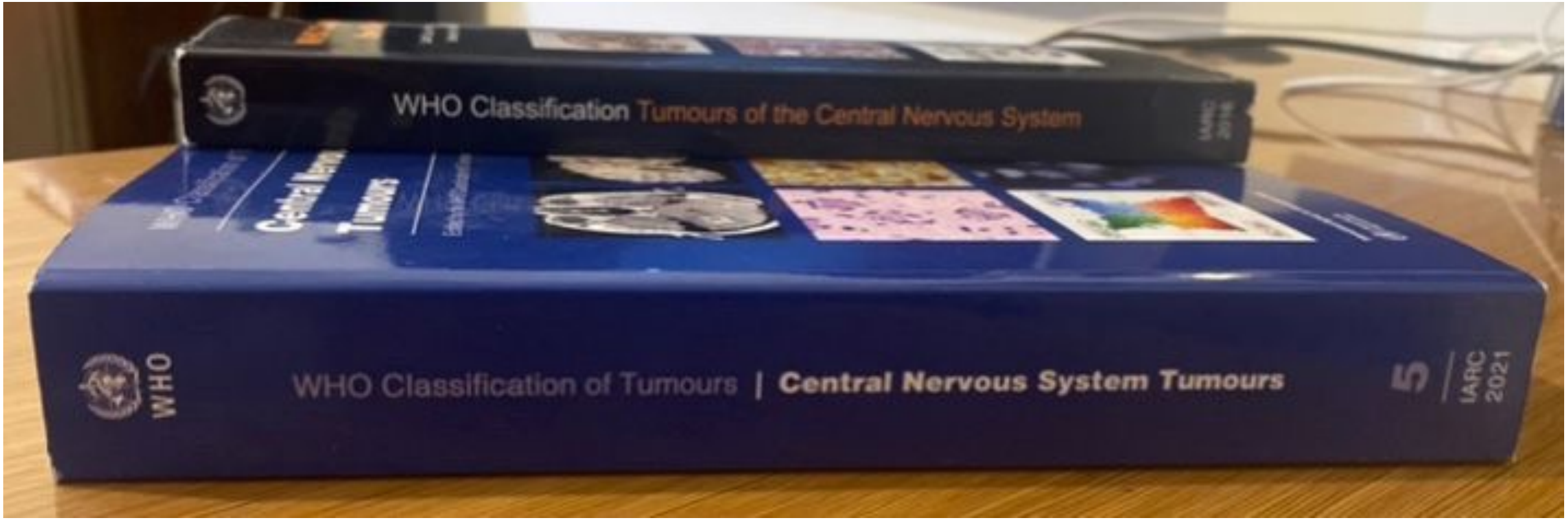
It's present in 90% of ATRX cases

- ATRX → associated with genomic instability → induces P53 dependent cell death→ mutation in P53 helps these cells to survive.

So for an IDH-mutant astrocytoma diagnosis, we need IDH mutation, ATRX mutation and P53 mutation, the first is a gain of function mutation and the last 2 are loss of function mutation. Remember that 1p/19q-codeleted are for oligodendrogliomas not astrocytomas


2021


Great event.
Now what?


WHO Classification Tumours of the Central Nervous System
Central Nervous System Tumours
WHO
WHO Classification of Tumours | Central Nervous System Tumours
5
IARC
2021

Diffuse astrocytoma, *MYB* or *MYBL1*-altered

22 New Entities

Astrocytoma, IDH-mutant
Diffuse midline glioma, H3 K27-altered
Chordoid glioma
Astroblastoma, MN1-altered
Supratentorial ependymoma, ~~C11orf95~~ ZFTA fusion-positive
Embryonal tumor with multilayered rosettes
Malignant melanotic nerve sheath tumor
Solitary fibrous tumor
Mesenchymal chondrosarcoma (formerly a subtype)
Adamantinomatous craniopharyngioma (formerly a subtype)
Papillary craniopharyngioma (formerly a subtype)
Pituicytoma, granular cell tumor of the sellar region, and spindle cell oncocytoma (grouped
Pituitary adenoma / PitNET

13 with Revised Terminology

Primary intracranial sarcoma, *DICER1*-mutant
Pituitary blastoma

1 Pituitary

UPDATE

Gliomas

WHO 2016

2.1: Diffuse astrocytic and oligodendroglial tumours

- 2.1.1: Introduction
- 2.1.2: Diffuse astrocytoma, IDH-mutant
  - 2.1.2.1: Gemistocytic astrocytoma, IDH-mutant
- 2.1.3: Diffuse astrocytoma, IDH-wildtype
- 2.1.4: Diffuse astrocytoma, NOS
- 2.1.5: Anaplastic astrocytoma, IDH-mutant
- 2.1.6: Anaplastic astrocytoma, IDH-wildtype
- 2.1.7: Anaplastic astrocytoma, NOS
- 2.1.8: Glioblastoma, IDH-wildtype
  - 2.1.8.1: Giant cell glioblastoma
  - 2.1.8.2: Gliosarcoma
  - 2.1.8.3: Epithelioid glioblastoma
- 2.1.9: Glioblastoma, IDH-mutant
- 2.1.10: Glioblastoma, NOS
- 2.1.11: Diffuse midline glioma, H3 K27M mutant
- 2.2.1: Oligodendroglioma, IDH-mutant and 1p/19q-codeleted
- 2.2.2: Oligodendroglioma, NOS
- 2.2.3: Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codel
- 2.2.4: Anaplastic oligodendroglioma, NOS
- 2.2.5: Oligoastrocytoma, NOS
- 2.2.6: Anaplastic oligoastrocytoma, NOS

2.3: Other astrocytic tumours

- 2.3.1: Pilocytic astrocytoma
  - 2.3.1.1: Pilomyxoid astrocytoma
- 2.3.2: Subependymal giant cell astrocytoma
- 2.3.3: Pleomorphic xanthoastrocytoma

Gliomas, Glioneuronal and Neuronal Tumours

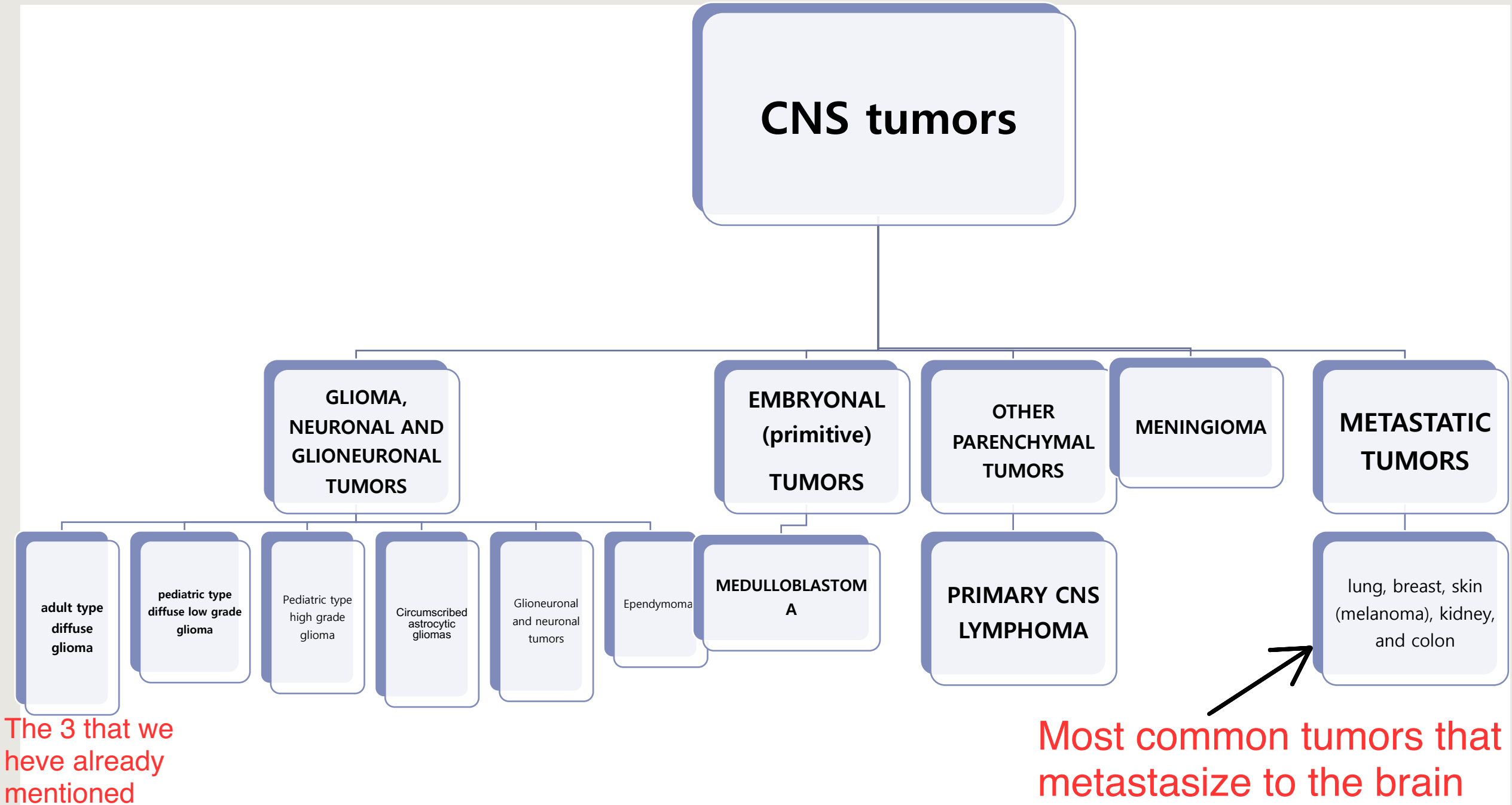
WHO 2021

- 2.0.0.1: Introduction to gliomas, glioneuronal tumours, and neuronal tumours

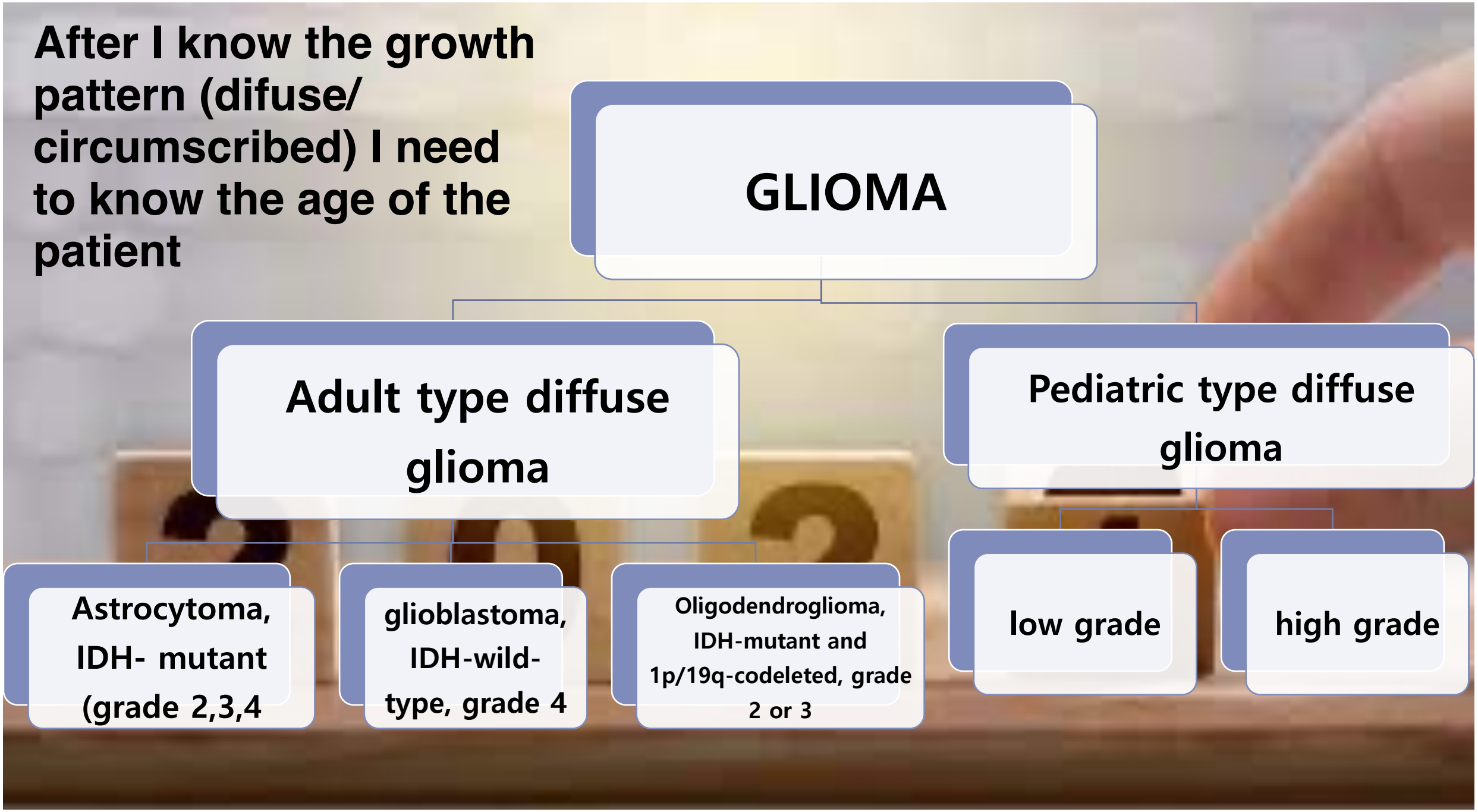
2.1: Gliomas, Glioneuronal and Neuronal Tumours

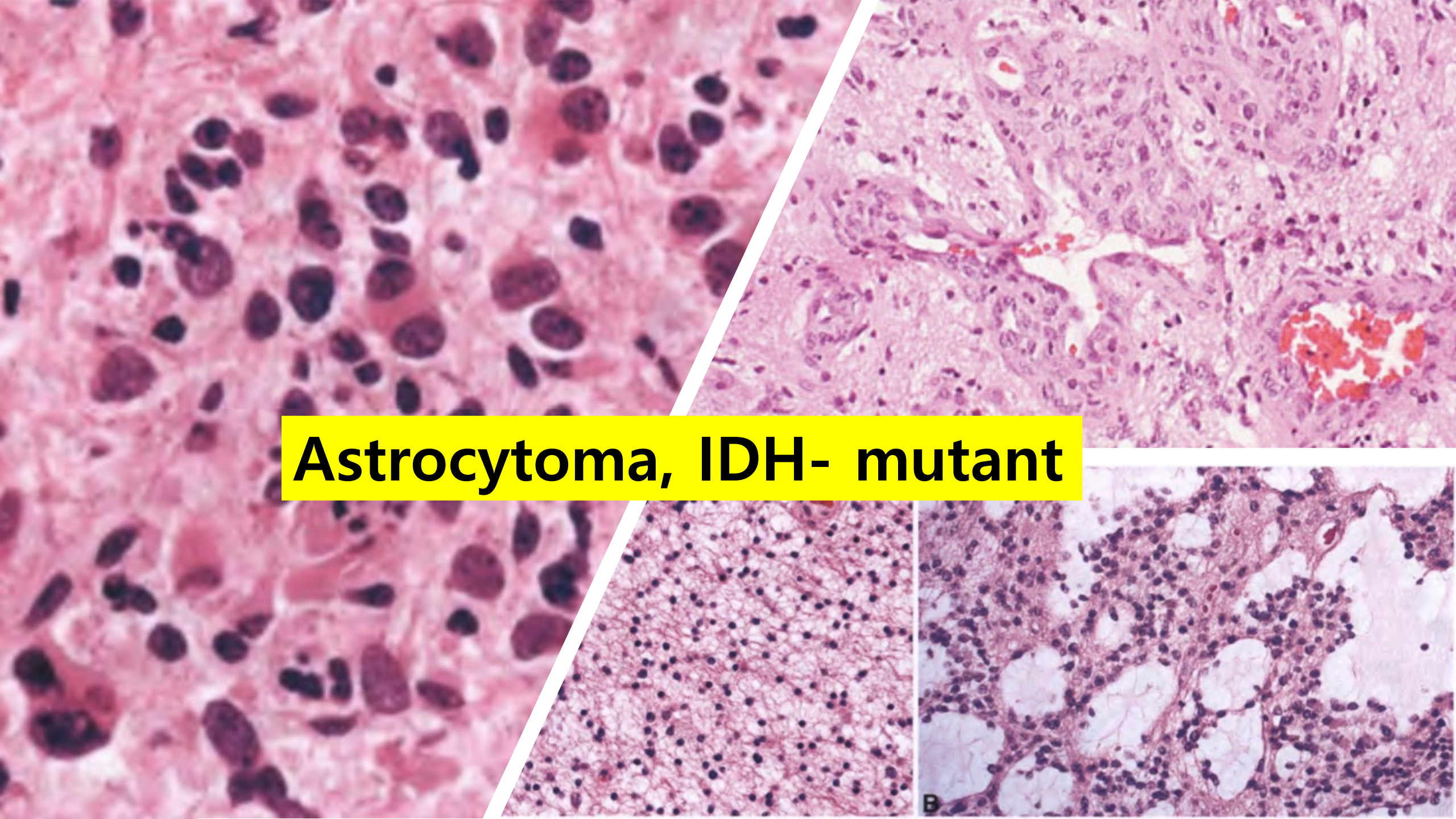
- Adult-type diffuse gliomas
  - 2.1.1.1: Astrocytoma, IDH-mutant
  - 2.1.1.2: Oligodendroglioma, IDH-mutant and 1p/19q-codeleted
  - 2.1.1.3: Glioblastoma, IDH-wildtype
- Paediatric-type diffuse low-grade gliomas
  - 2.1.4.1: Diffuse astrocytoma, MYB or MYBL1-altered
  - 2.1.4.2: Angiocentric glioma
  - 2.1.3.5: Polymorphous low-grade neuroepithelial tumour of the young
  - 2.1.5.1: Diffuse low-grade glioma, MAPK pathway-altered
- 2.1.2: Paediatric-type diffuse high grade gliomas
  - 2.1.2.1: Diffuse midline glioma, H3 K27-altered
  - 2.1.2.2: Diffuse hemispheric glioma, H3 G34-mutant
  - 2.1.2.3: Diffuse paediatric-type high grade glioma, H3 wildtype and IDH wild type
  - ~~2.1.2.4: Diffuse midline glioma, EGFR mutant (formerly Pilocytic astrocytoma, EGFR mutant)~~
  - 2.1.2.4: Infant-type hemispheric glioma
- 2.1.3: Circumscribed astrocytic gliomas
  - 2.1.3.1: Pilocytic astrocytoma
  - 2.1.3.2: High-grade astrocytoma with piloid features
  - 2.1.3.3: Pleomorphic xanthoastrocytoma
  - 2.2.0.4: Subependymal giant cell astrocytoma
  - 2.2.0.1: Chordoid glioma
  - 2.2.0.2: Astroblastoma, MN1-altered
- 2.1.4: Glioneuronal and neuronal tumours
  - 2.1.3.7: Ganglioglioma
  - 2.1.3.9: Desmoplastic infantile ganglioglioma / Desmoplastic infantile astrocytoma
  - 2.1.3.10: Dysembryoplastic neuroepithelial tumour
  - 2.2.0.3: Diffuse glioneuronal tumour with oligodendroglioma-like features and nuclear clusters
  - 2.2.0.5: Papillary glioneuronal tumour

We need to know this classification which categorizes gliomas into diffuse and circumscribed


CNS tumors
GLIOMA, NEURONAL AND GLIONEURONAL TUMORS
EMBRYONAL (primitive) TUMORS
OTHER PARENCHYMAL TUMORS
MENINGIOMA
METASTATIC TUMORS
adult type diffuse glioma
pediatric type diffuse low grade glioma
Pediatric type high grade glioma
Circumscribed astrocytic gliomas
Glioneuronal and neuronal tumors
Ependymoma
MEDULLOBLASTOMA
PRIMARY CNS LYMPHOMA
lung, breast, skin (melanoma), kidney, and colon
The 3 that we heve already mentioned
Most common tumors that metastasize to the brain

After I know the growth pattern (difuse/ circumscribed) I need to know the age of the patient




Astrocytoma, IDH- mutant
B

Definition:

Phenotype: It Is a diffusely infiltrating glioma

Genotype:

- IDH1 or less frequently IDH2 mutation.
- Inactivating mutation in TP53 and/or ATRX
- absence of 1p/19q codeletion

- **Age at diagnosis:** 40–60 year old.

Usually

- **Location:** cerebral hemispheres +/- cerebellum, brainstem, or spinal cord.

- **Presentation:** Depends on the tumor's location
  - seizures, headaches, and focal neurologic deficits related to the anatomic site of involvement.
  - Clinically: static for years or Progressive.

- **The prognosis gets poorer as the grade increases**

This will cause
Rapid deterioration
New deficits
Entering the ICU

- **On the basis of histologic features astrocytomas, IDH- mutant are stratified into three groups:**
  - **astrocytomas, IDH- mutant,** grade 2, median survival is >10 years.
  - **astrocytomas, IDH- mutant** grade 3, median survival is 5-10 years
  - **astrocytomas, IDH- mutant** grade 4, median survival is 3 years.

- **NO grade 1 astrocytoma, IDH- mutant, because by convention grade 1 implies benign behavior and all diffuse gliomas are considered malignant**

Morphology, macroscopic:

For all grades, the boundaries between neoplastic tissue & normal tissue are vague and indistinct (difficult to outline and distinguish). The tumor infiltrates even beyond any grossly evident margin.

Grade 2 &3:

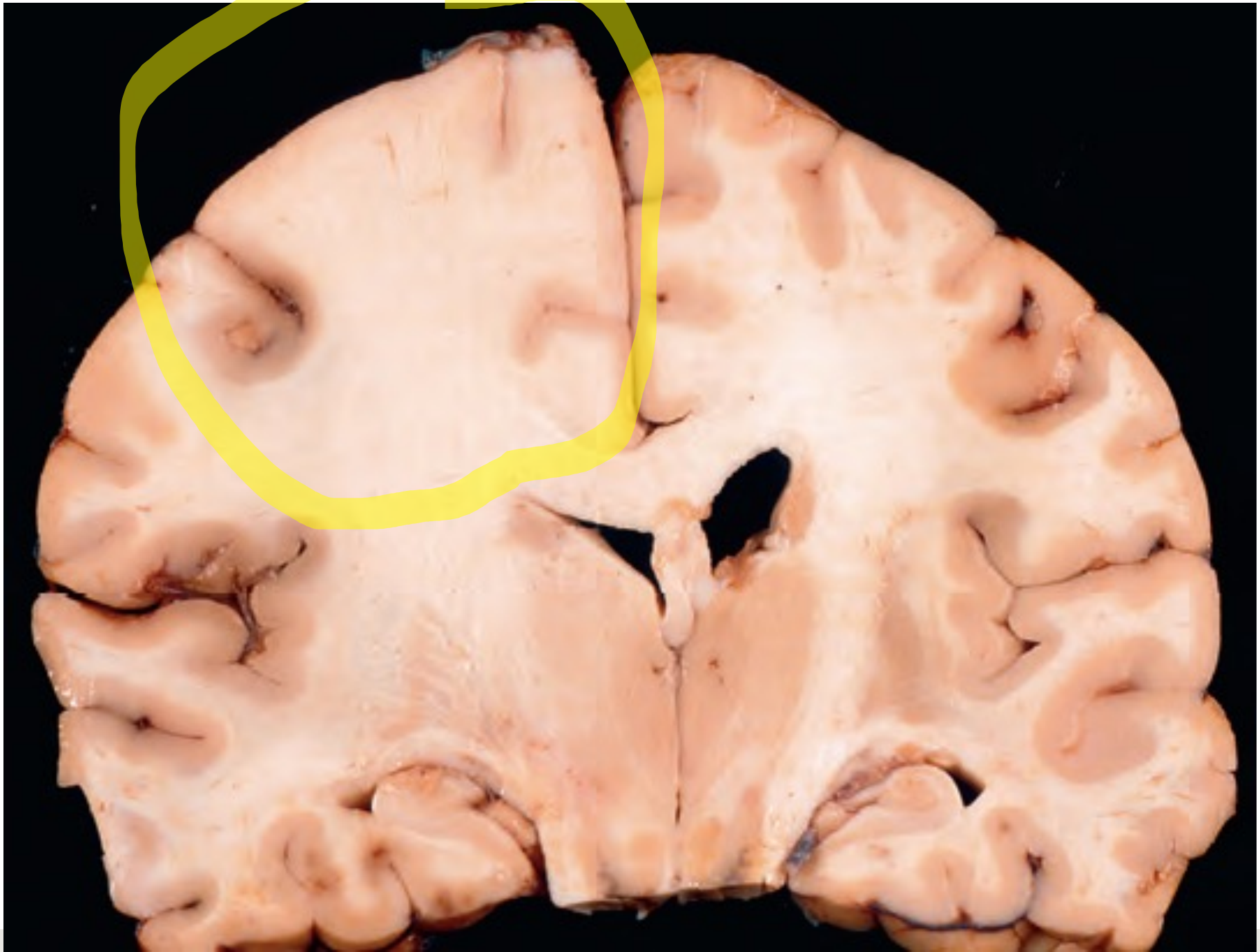
- poorly defined, infiltrative tumors
- expand and distort the invaded brain
- **NO** discrete mass, Infiltration beyond the grossly evident margins.

Grade 4:

IDH-wild-type GBM doesn't have a precursor lesion
(Starts as grade 4 and is more aggressive)

- poorly defined, infiltrative tumors
- lacks large areas of central necrosis and hemorrhage seen in IDH-wild-type GBM

But this hemorhage and necrosis aren't of the same magnitude as Glioblastoma IDH wildtype (it's magnitude in grade 4 is small)



Regarding the picture above

Note the vague boundries between the white and grey matters (it's not well defined).

You can't tell where the tumor starts and ends because it's diffused, not well defined. It extends beyond what you see!

Diffuse astrocytoma, IDH- mutant, WHO grade 2, Microscopic:

- The transition between neoplastic and normal tissue is indistinct
- tumor cells infiltrate normal tissue many centimeters from the main lesion.

- **Hypercellular** (compared to normal white matter): **mild to moderate** increase in the number of glial cell nuclei.
- **Cytologic atypia**:
  - mild
  - enlarged, elongated or irregular hyperchromatic nuclei
  - No prominent atypia

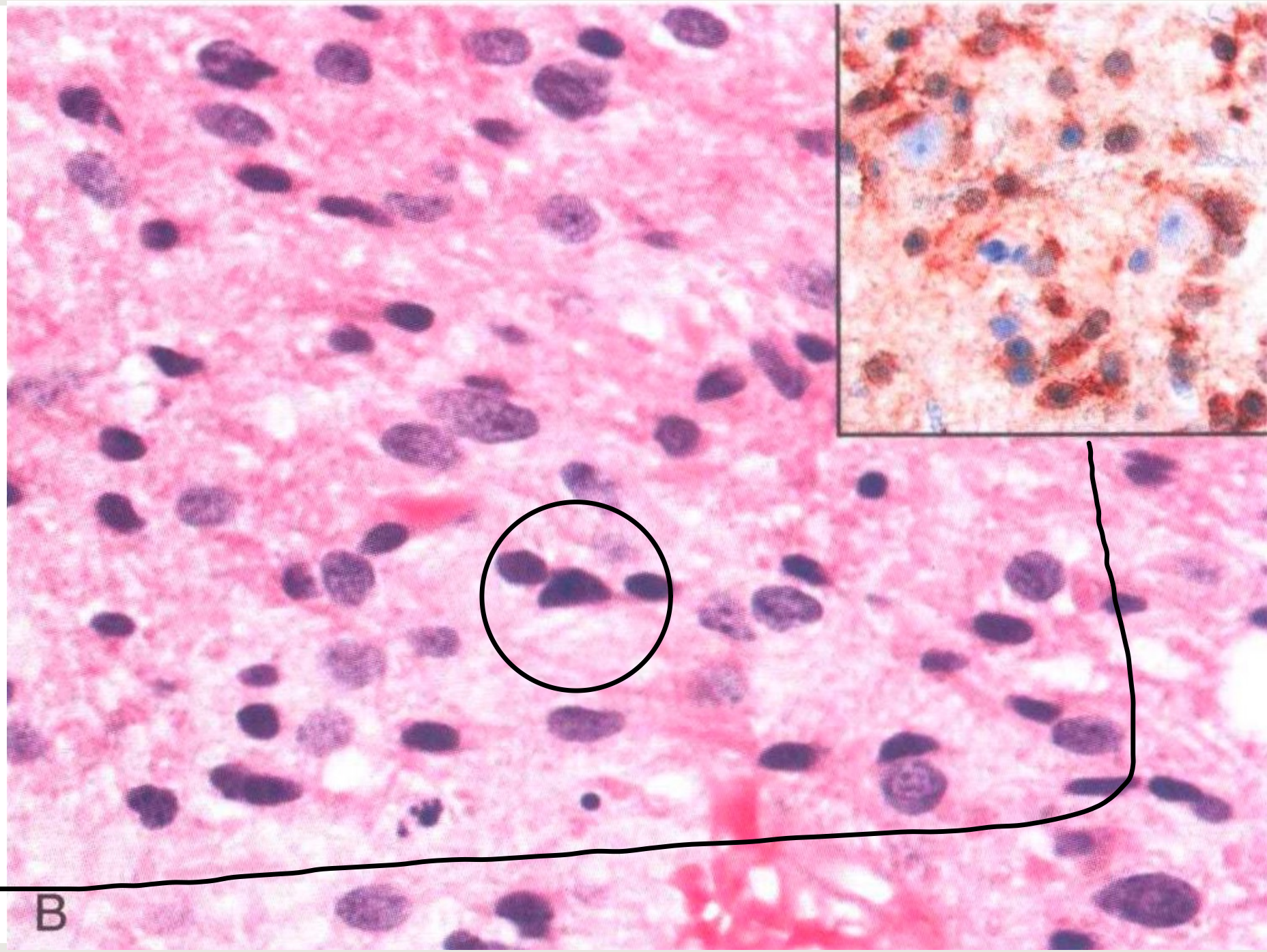
+ **fibrillary background** made of a network of fine astrocytic cell processes

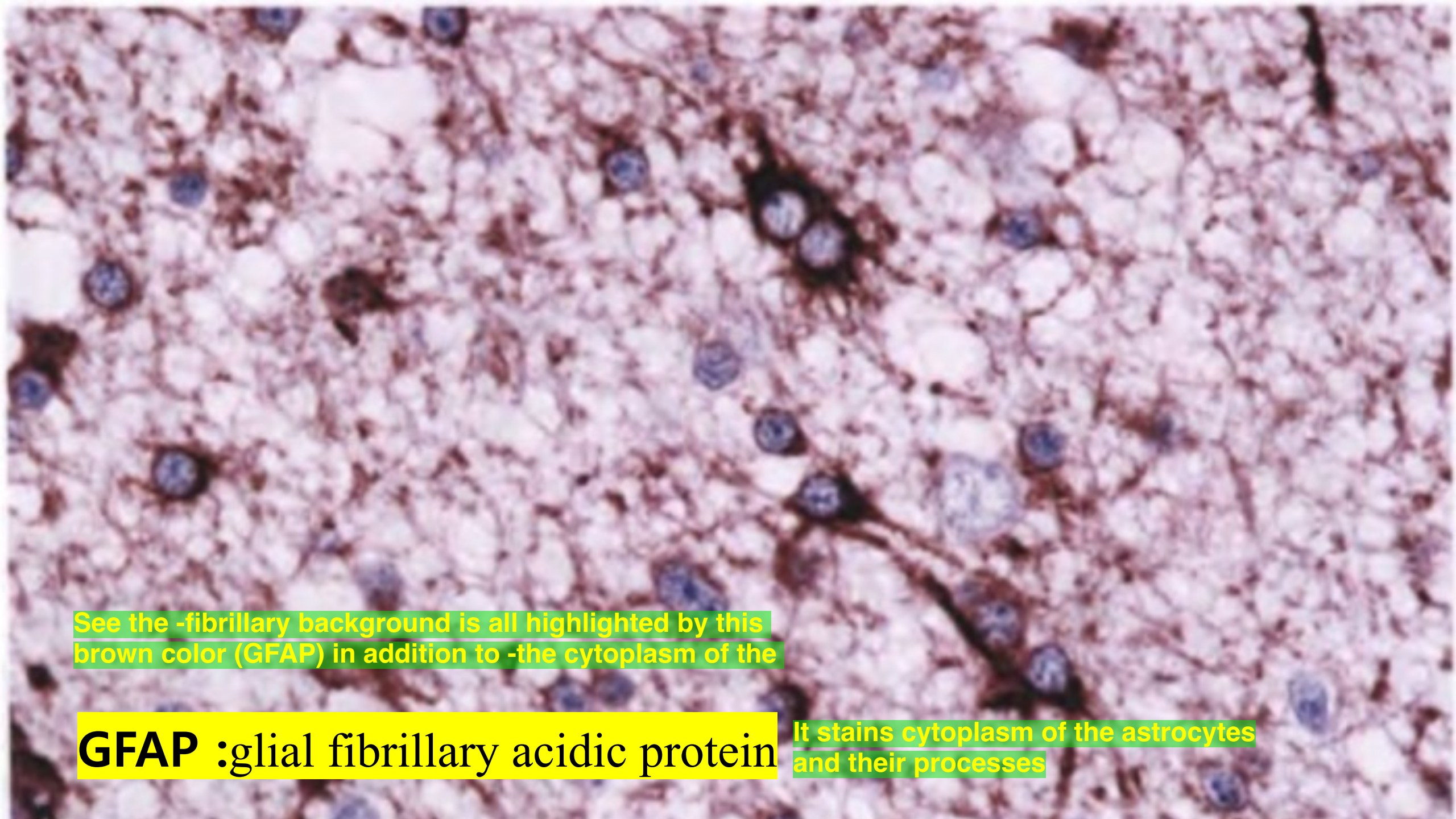
- **NO or rare** Mitotic activity
- **NO** necrosis
- **NO** microvascular proliferation

Hyperchromatic enlarged nuclie

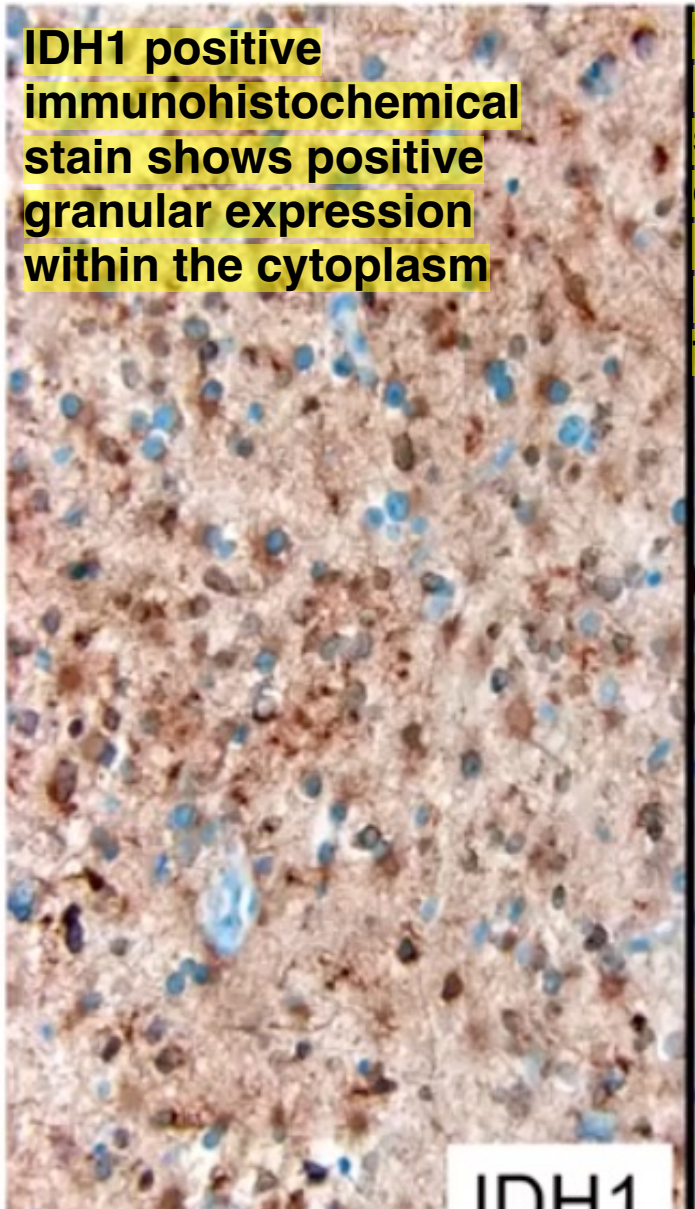
Enlarged irregular nuclei embedded within fbrillar matrix of the brain

Inset: IDH1 immune stain is positive in tumor cells

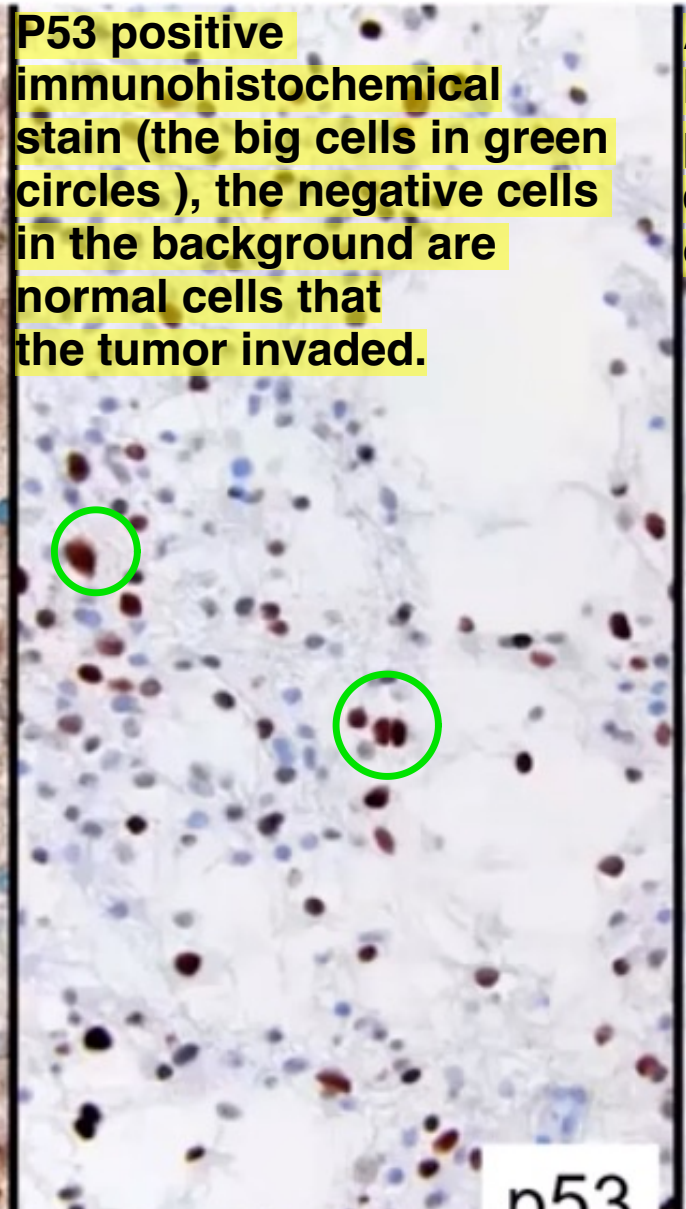



See the -fibrillary background is all highlighted by this brown color (GFAP) in addition to -the cytoplasm of the
GFAP :glial fibrillary acidic protein
It stains cytoplasm of the astrocytes and their processes

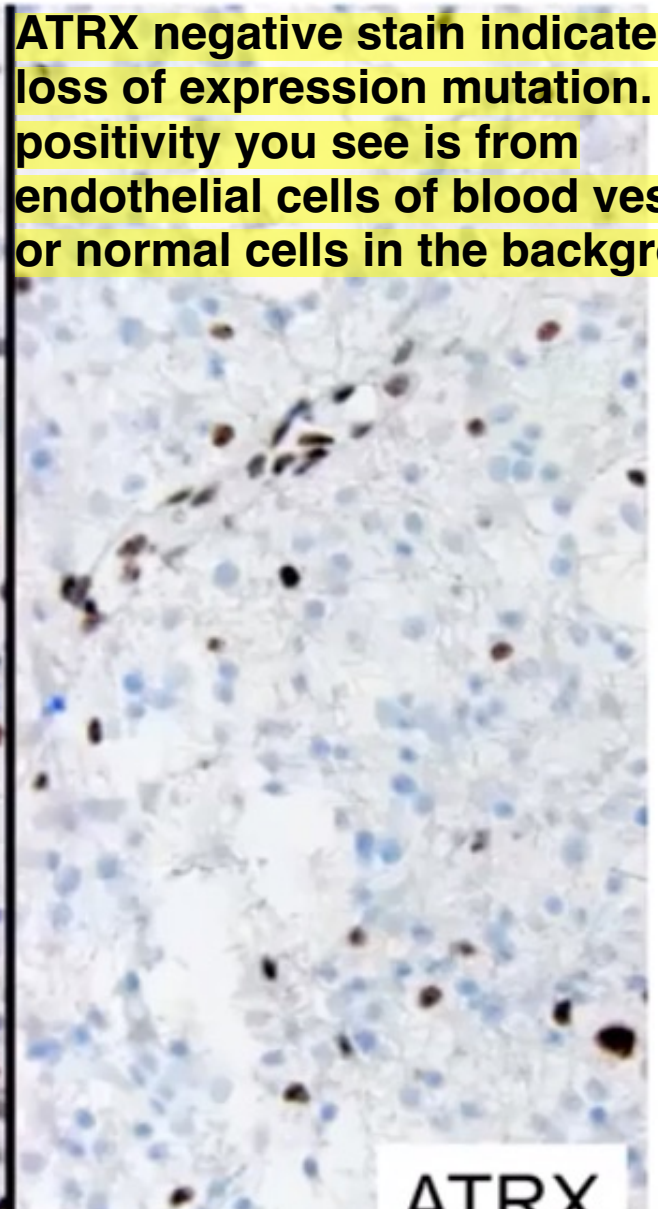
Astrocytoma, IDH-mutant, CNS WHO grades 2-4



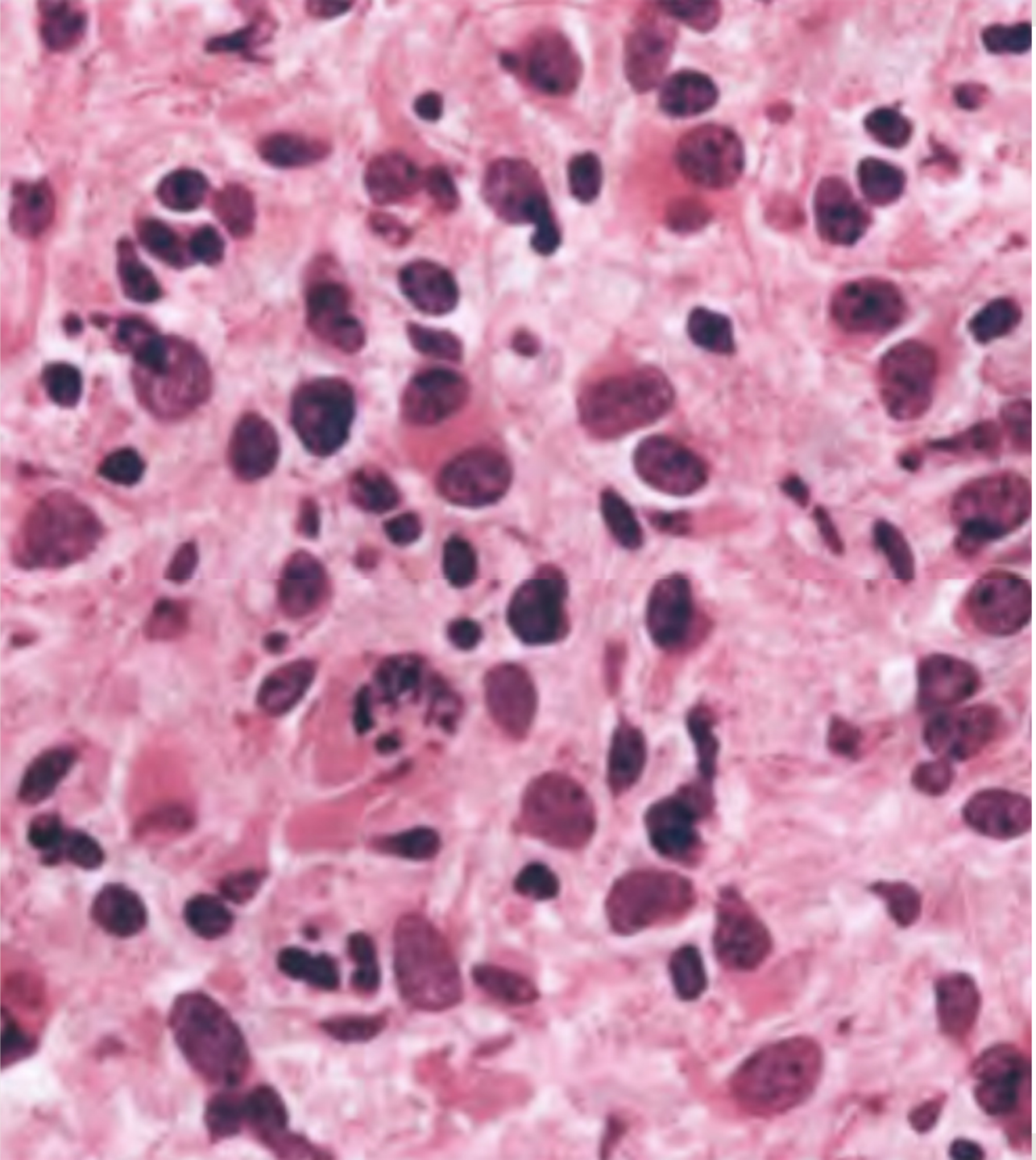
IDH1 positive immunohistochemical stain shows positive granular expression within the cytoplasm



P53 positive immunohistochemical stain (the big cells in green circles), the negative cells in the background are normal cells that the tumor invaded.



ATRX negative stain indicates loss of expression mutation. The positivity you see is from endothelial cells of blood vessels or normal cells in the background.



The mitosis separates grade 2 from 3

Astrocytoma, IDH-mutant, grade 3:

- More densely cellular
- More nuclear pleomorphism
- mitotic figures are **present**
- **NO** necrosis
- **NO** microvascular proliferation

Astrocytoma, IDH-mutant, grade 4:

- Same as grade 3 with Microvascular proliferation and/or necrosis

- The presence of homozygous deletion of CDKN2A &/or CDKN2B
  → **astrocytomas, IDH- mutant, grade 4 (EVEN IF THE HISTOLOGY SUGGESTS A LOWER GRADE).**

The presence of one of these features or more than one in an IDH & ATRX mutated astrocytoma indicates grade 4 astrocytoma, without looking at other features:

1. Microvascular proliferation
2. Necrosis
3. Homozygous deletion of CDKN2A &/or CDKN2B


thank you