CENTRAL NERVOUS SYTEM TUMORS(1)

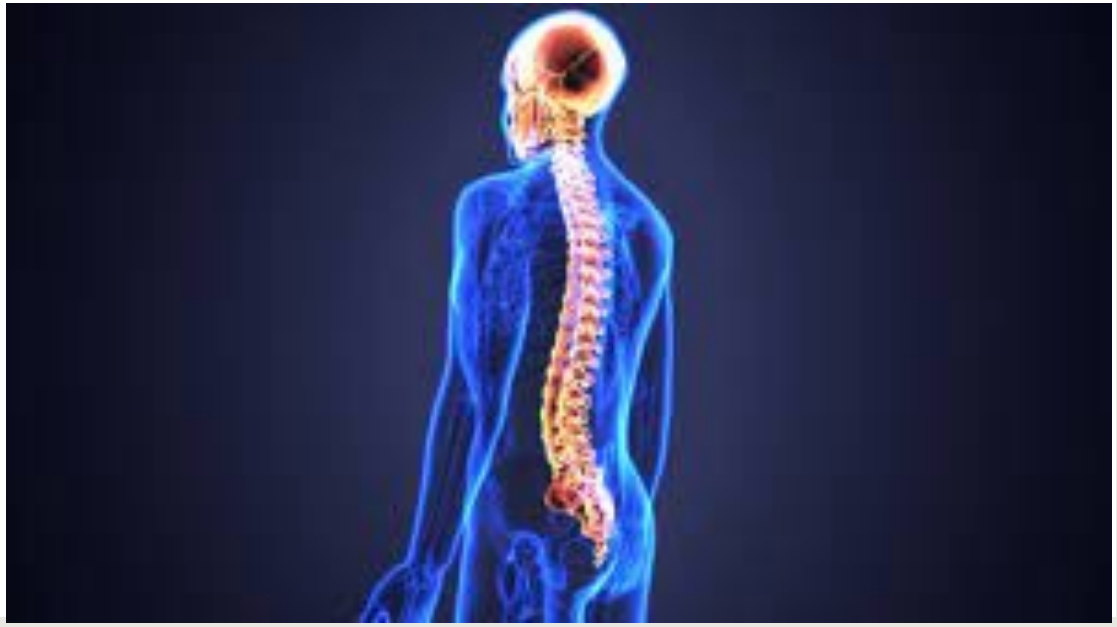
Maram Abdaljaleel, MD

Dermatopathologist & Neuropathologist

CNS TUMORS:

- 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:

- **INCIDENCE**:
  - The annual incidence of CNS tumors →
    - 10 - 17/100,000 for intracranial tumors
    - 1-2/100,000 for intraspinal tumors

- **50-75% are primary tumors, and the rest are metastatic (secondary).**

Characteristic features of CNS tumors:

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

- **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.

Characteristic features of CNS tumors:

- **Growth pattern (infiltrative or not) and tumor location strongly influence the prognosis:**
  - 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 outcome independent of histologic type or grade

LOCATION
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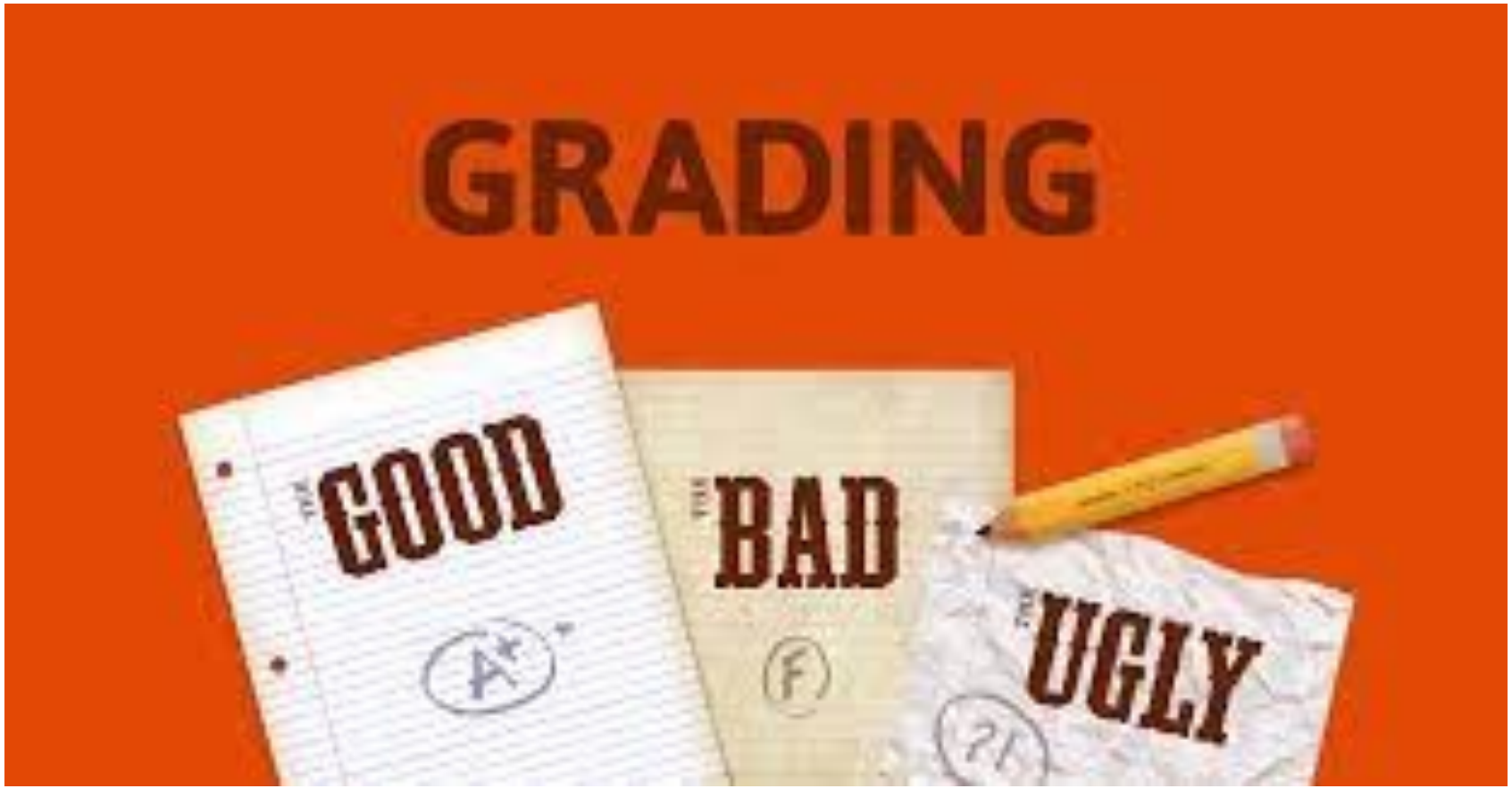
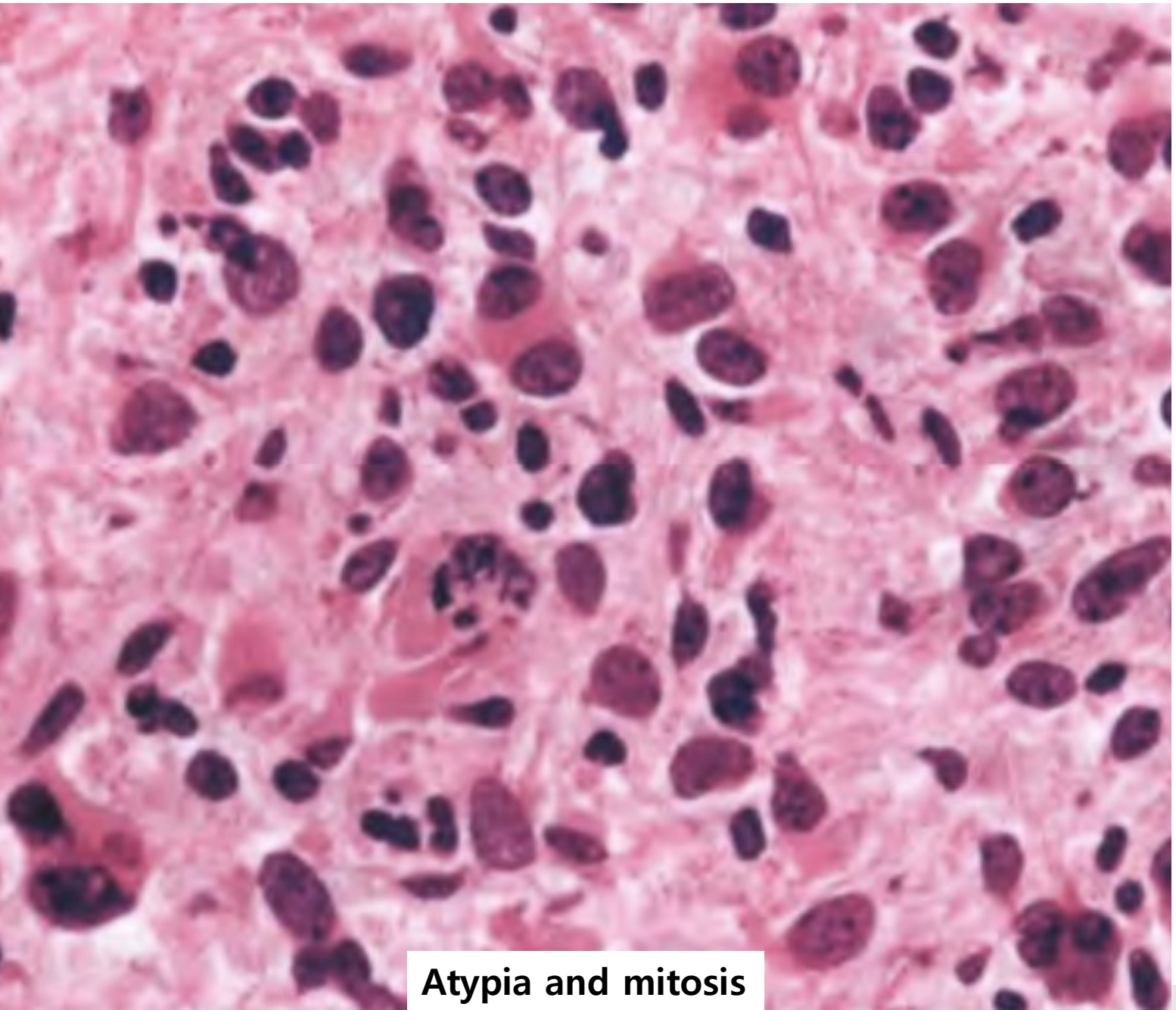
LOCATION

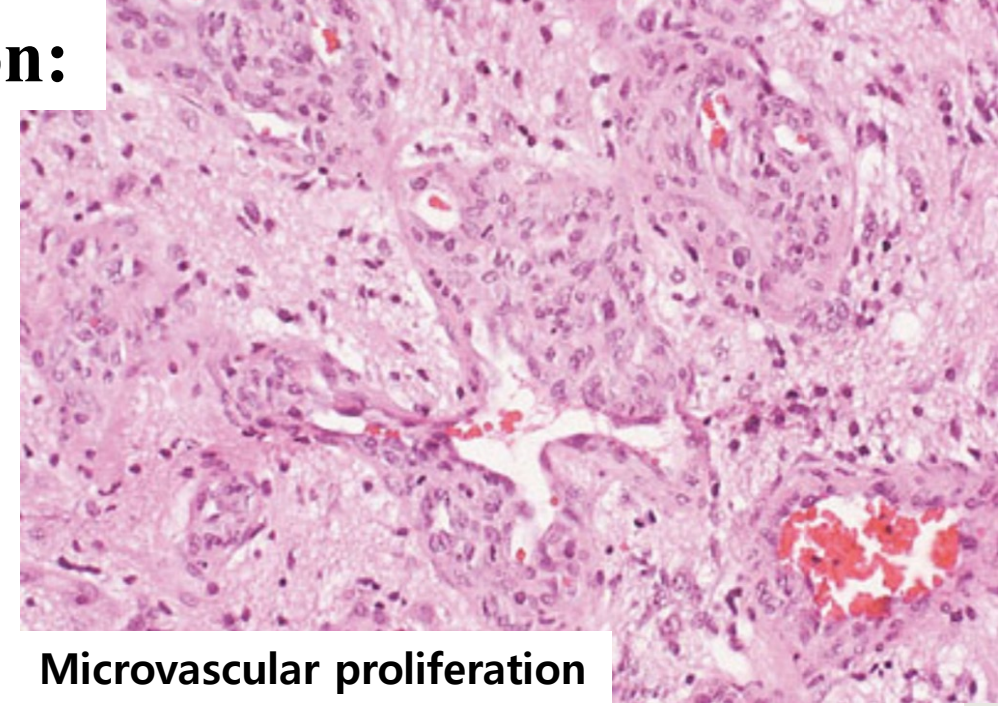
Histologic grading of CNS tumors



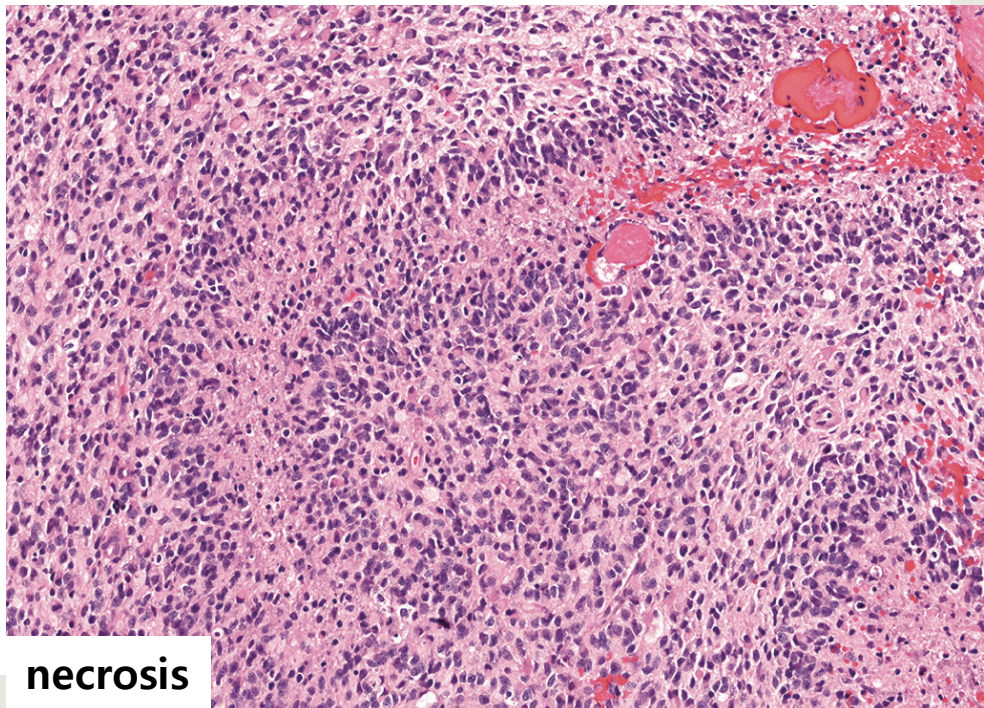
The histologic grading of CNS tumors depends on:



Atypia and mitosis



Microvascular proliferation



necrosis

- **Grade 1 lesions (benign):**

  - low proliferative activity

  - Can be cured after surgical resection alone.

Example: 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.
  - Widespread infiltration of surrounding tissue and a risk of craniospinal dissemination.
  - examples: Glioblastoma, medulloblastoma, pineoblastoma, and most embryonal neoplasms

Any slide showing this stamp at the right lower corner is NOT REQUIRED FOR YOUR TEST!

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

Pineocytoma	I
Pineal parenchymal tumour of intermediate differentiation	II or III
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, 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

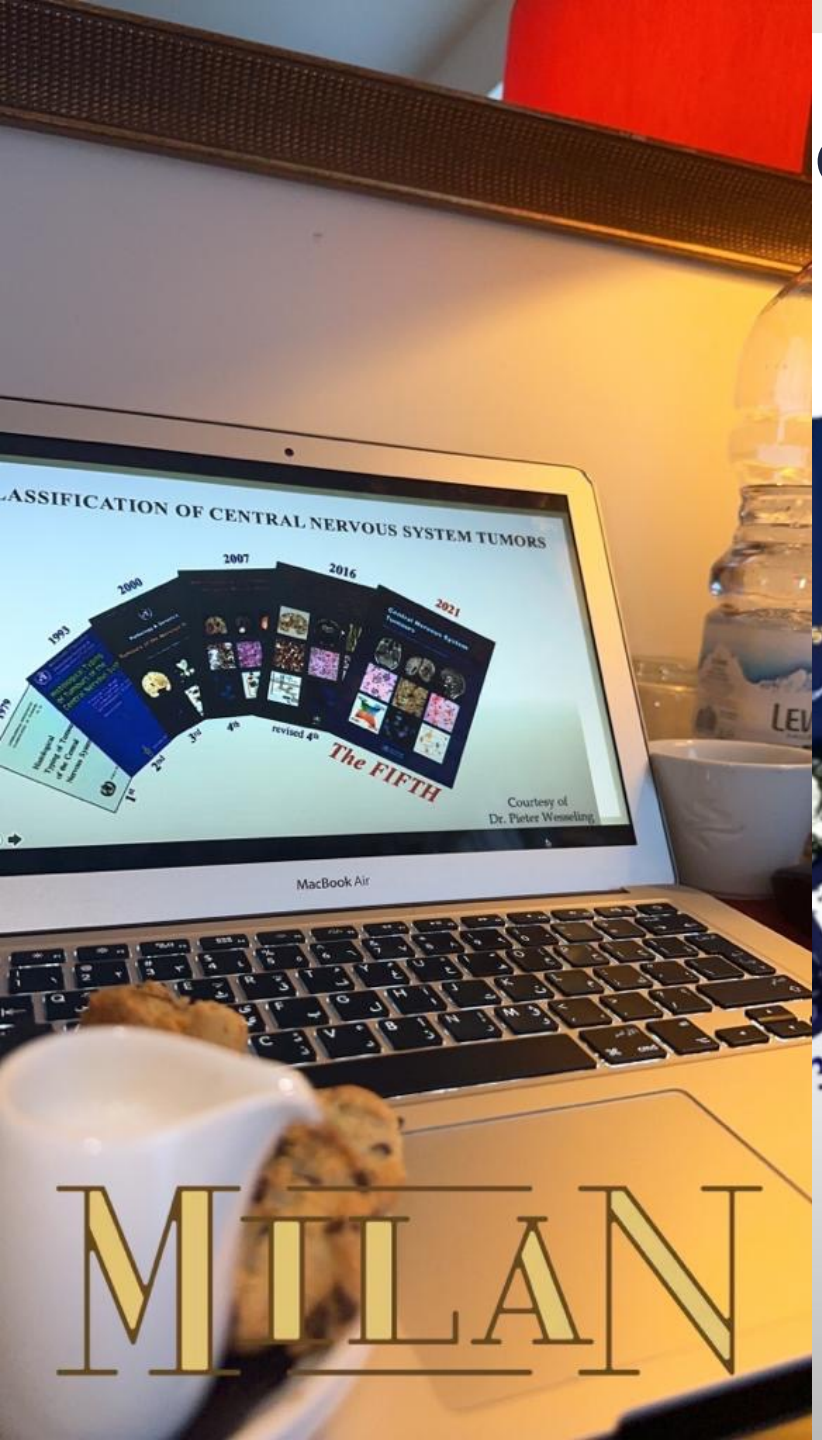
Tumours of the sellar region

Craniopharyngioma	I
Granular cell tumour	I
Pituicytoma	I
Spindle cell oncocytoma	I

UPDATE

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)
    - 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).



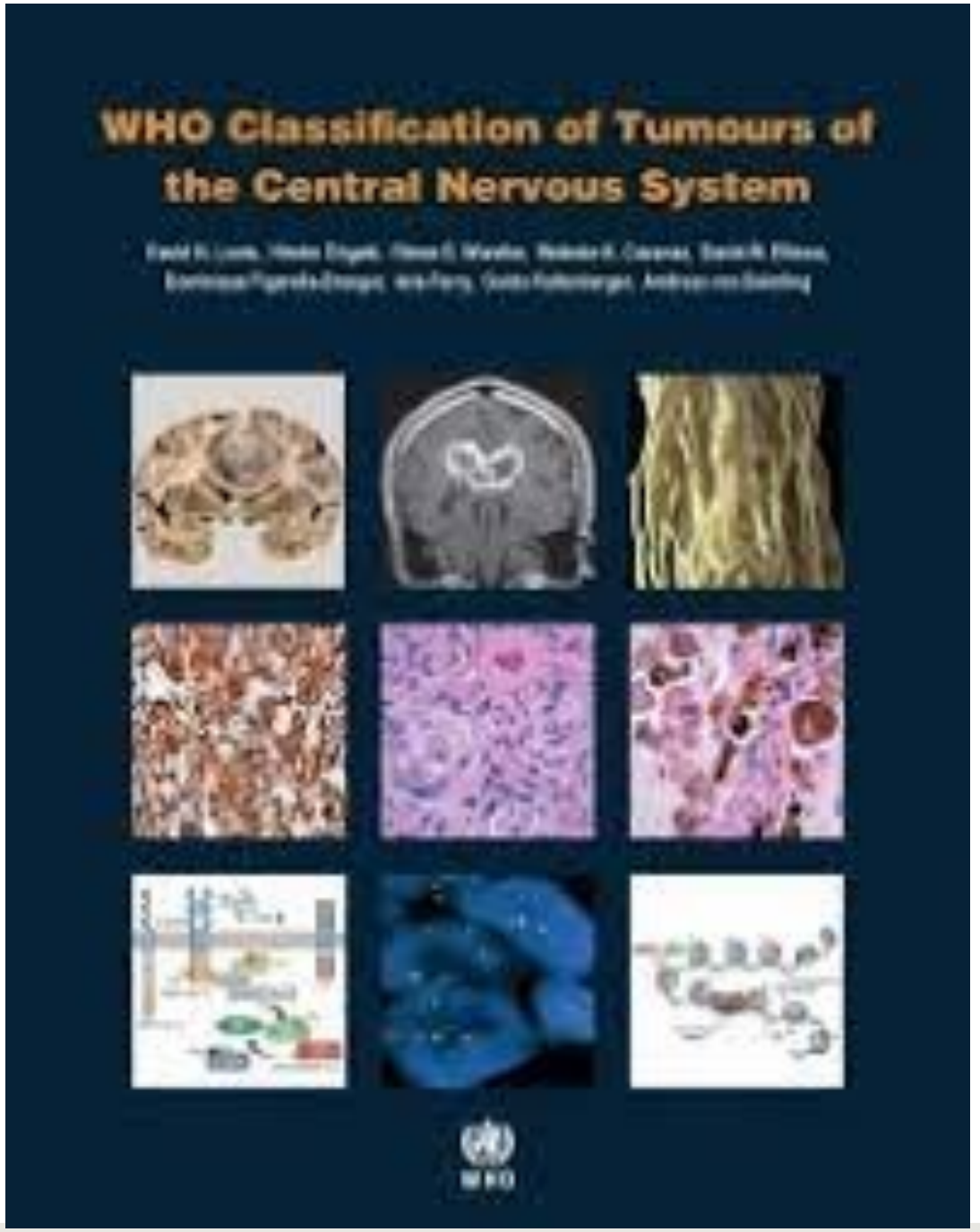
OF CENTRAL NERVOUS SYSTEM TUMORS

Courtesy of
Dr. Pieter Wesseling

- 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 2000 and 2007 WHO classifications were based on the described classification and unfortunately your pathology textbook is outdated.


What's new?


WHO Classification of Tumours of the Central Nervous System

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

WHO classification of tumours of the central nervous system

2016

Diffuse astrocytic and oligodendroglial tumours	
Diffuse astrocytoma, IDH-mutant	9400/3
Gemistocytic astrocytoma, IDH-mutant	9411/3
Diffuse astrocytoma, IDH-wildtype	*9400/3*
Diffuse astrocytoma, NOS	9400/3
Anaplastic astrocytoma, IDH-mutant	9401/3
Anaplastic astrocytoma, IDH-wildtype	*9401/3*
Anaplastic astrocytoma, NOS	9401/3
Glioblastoma, IDH-wildtype	9440/3
Giant cell glioblastoma	9441/3
Gliosarcoma	9442/3
Epithelioid glioblastoma	*9440/3*
Glioblastoma, IDH-mutant	9445/3*
Glioblastoma, NOS	9440/3
Diffuse midline glioma, H3 K27M-mutant	9385/3*
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9450/3
Oligodendroglioma, NOS	9450/3
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9451/3
Anaplastic oligodendroglioma, NOS	*9451/3*
Oligoastrocytoma, NOS	*9382/3*
Anaplastic oligoastrocytoma, NOS	*9382/3*
Other astrocytic tumours	
Pilocytic astrocytoma	9421/1
Pilomyxoid astrocytoma	9425/3
Subependymal giant cell astrocytoma	9384/1
Pleomorphic xanthoastrocytoma	9424/3
Anaplastic pleomorphic xanthoastrocytoma	9424/3
Ependymal tumours	
Subependymoma	9383/1
Myxopapillary ependymoma	9394/1
Ependymoma	9391/3
Papillary ependymoma	9393/3
Clear cell ependymoma	9391/3
Tanycytic ependymoma	9391/3
Ependymoma, *RELA* fusion-positive	9396/3*
Anaplastic ependymoma	9392/3
Other gliomas	
Chordoid glioma of the third ventricle	9444/1
Angiocentric glioma	9431/1
Astroblastoma	9430/3
Choroid plexus tumours	
Choroid plexus papilloma	9390/0
Atypical choroid plexus papilloma	9390/1
Choroid plexus carcinoma	9390/3
Neuronal and mixed neuronal-glial tumours	
Dysembryoplastic neuroepithelial tumour	9413/0
Gangliocytoma	9492/0
Ganglioglioma	9505/1
Anaplastic ganglioglioma	9505/3
Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease)	9493/0
Desmoplastic infantile astrocytoma and ganglioglioma	9412/1
Papillary glioneuronal tumour	9509/1
Rosette-forming glioneuronal tumour	9509/1
Diffuse leptomeningeal glioneuronal tumour	
Central neurocytoma	9506/1
Extraventricular neurocytoma	9506/1
Cerebellar liponeurocytoma	9506/1
Paraganglioma	8693/1
Tumours of the pineal region	
Pineocytoma	9361/1
Pineal parenchymal tumour of intermediate differentiation	9362/3
Pineoblastoma	9362/3
Papillary tumour of the pineal region	9395/3
Embryonal tumours	
Medulloblastomas, genetically defined	
Medulloblastoma, WNT-activated	9475/3*
Medulloblastoma, SHH-activated and *TP53*-mutant	9476/3*
Medulloblastoma, SHH-activated and *TP53*-wildtype	9471/3
Medulloblastoma, non-WNT/non-SHH	9477/3*
Medulloblastoma, group 3	
Medulloblastoma, group 4	
Medulloblastomas, histologically defined	
Medulloblastoma, classic	9470/3
Medulloblastoma, desmoplastic/nodular	9471/3
Medulloblastoma with extensive nodularity	9471/3
Medulloblastoma, large cell / anaplastic	9474/3
Medulloblastoma, NOS	9470/3
Embryonal tumour with multilayered rosettes, C19MC-altered	9478/3*
Embryonal tumour with multilayered rosettes, NOS	*9478/3*
Medulloepithelioma	9501/3
CNS neuroblastoma	9500/3
CNS ganglioneuroblastoma	9490/3
CNS embryonal tumour, NOS	9473/3
Atypical teratoid/rhabdoid tumour	9508/3
CNS embryonal tumour with rhabdoid features	*9508/3*
Tumours of the cranial and paraspinal nerves	
Schwannoma	9560/0
Cellular schwannoma	9560/0
Plexiform schwannoma	9560/0
Melanotic schwannoma	9560/1
Neurofibroma	9540/0
Atypical neurofibroma	9540/0
Plexiform neurofibroma	9550/0
Perineurioma	9571/0
Hybrid nerve sheath tumours	9540/3
Malignant peripheral nerve sheath tumour	
Epithelioid MPNST	9540/3
MPNST with perineurial differentiation	9540/3
Meningiomas	9530/0
Meningioma	
Meningothelial meningioma	9531/0
Fibrous meningioma	9532/0
Transitional meningioma	9537/0
Psammomatous meningioma	9533/0
Angiomatous meningioma	9534/0
Microcystic meningioma	9530/0
Secretory meningioma	9530/0
Lymphoplasmacyte-rich meningioma	9530/0
Metaplastic meningioma	9530/0
Chordoid meningioma	9538/1
Clear cell meningioma	9538/1
Atypical meningioma	9539/1
Papillary meningioma	9538/3
Rhabdoid meningioma	9538/3
Anaplastic (malignant) meningioma	9530/3
Mesenchymal, non-meningothelial tumours	8815/0
Solitary fibrous tumour / haemangiopericytoma**	
Grade 1	
Grade 2	8815/1
Grade 3	8815/3
Haemangioblastoma	9161/1
Haemangioma	9120/0
Epithelioid haemangioendothelioma	9133/3
Angiosarcoma	9120/3
Kaposi sarcoma	9140/3
Ewing sarcoma / PNET	9364/3
Lipoma	8850/0
Angiolipoma	8861/0
Hibernoma	8880/0
Liposarcoma	8850/3
Desmoid-type fibromatosis	8821/1
Myofibroblastoma	8825/0
Inflammatory myofibroblastic tumour	8825/1
Benign fibrous histiocytoma	8830/0
Fibrosarcoma	8810/3
Undifferentiated pleomorphic sarcoma / malignant fibrous histiocytoma	8802/3
Leiomyoma	8890/0
Leiomyosarcoma	8890/3
Rhabdomyoma	8900/0
Rhabdomyosarcoma	8900/3
Chondroma	9220/0
Chondrosarcoma	9220/3
Osteoma	9180/0
Osteochondroma	9210/0
Osteosarcoma	9180/3
Melanocytic tumours	
Meningeal melanocytosis	8728/0
Meningeal melanocytoma	8728/1
Meningeal melanoma	8720/3
Meningeal melanomatosis	8728/3
Lymphomas	
Diffuse large B-cell lymphoma of the CNS	9680/3
Immunodeficiency-associated CNS lymphomas	
AIDS-related diffuse large B-cell lymphoma	
EBV-positive diffuse large B-cell lymphoma, NOS	
Lymphomatoid granulomatosis	9766/1
Intravascular large B-cell lymphoma	9712/3
Low-grade B-cell lymphomas of the CNS T-cell and NK/T-cell lymphomas of the CNS Anaplastic large cell lymphoma, ALK-positive	9714/3
Anaplastic large cell lymphoma, ALK-negative	9702/3
MALT lymphoma of the dura	9699/3
Histiocytic tumours	
Langerhans cell histiocytosis	9751/3
Erdheim-Chester disease	9750/1
Rosai-Dorfman disease	9755/3
Juvenile xanthogranuloma	
Histiocytic sarcoma	
Germ cell tumours	
Germinoma	9064/3
Embryonal carcinoma	9070/3
Yolk sac tumour	9071/3
Choriocarcinoma	9100/3
Teratoma	9080/1
Mature teratoma	9080/0
Immature teratoma	9080/3
Teratoma with malignant transformation	9084/3
Mixed germ cell tumour	9085/3
Tumours of the sellar region	
Craniopharyngioma	9350/1
Adamantinomatous craniopharyngioma	9351/1
Papillary craniopharyngioma	9352/1
Granular cell tumour of the sellar region	9582/0
Pituicytoma	9432/1
Spindle cell oncocytoma	8290/0
Metastatic tumours	

The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) (742A). Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours. The classification is modified from the previous WHO classification, taking into account changes in our understanding of these lesions.
*These new codes were approved by the IARC/WHO Committee for ICD-O. Provisional tumour entities. **Grading according to the 2013 *WHO Classification of Tumours of Soft Tissue and Bone*.

UPDATE

genetic alterations in gliomas:

1- **Mutations in isocitrate dehydrogenase (IDH) genes:**

- observed as an early event in gliomagenesis
- Seen in astrocytomas and 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
- Other rare mutations: R132C, R132G, R132S, & R132L
- IDH2 mutation: R172K is the most frequent IDH2 mutation

genetic alterations in gliomas:

Can be detected by immunohistochemical stains and molecular studies:

- IDH1-R132H immune stain
- IDH sequencing for IDH1 codon 132 and IDH2 codon 172

- 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

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

- Diagnostic of oligodendrogliomas in the presence of IDH mutation.

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

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

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

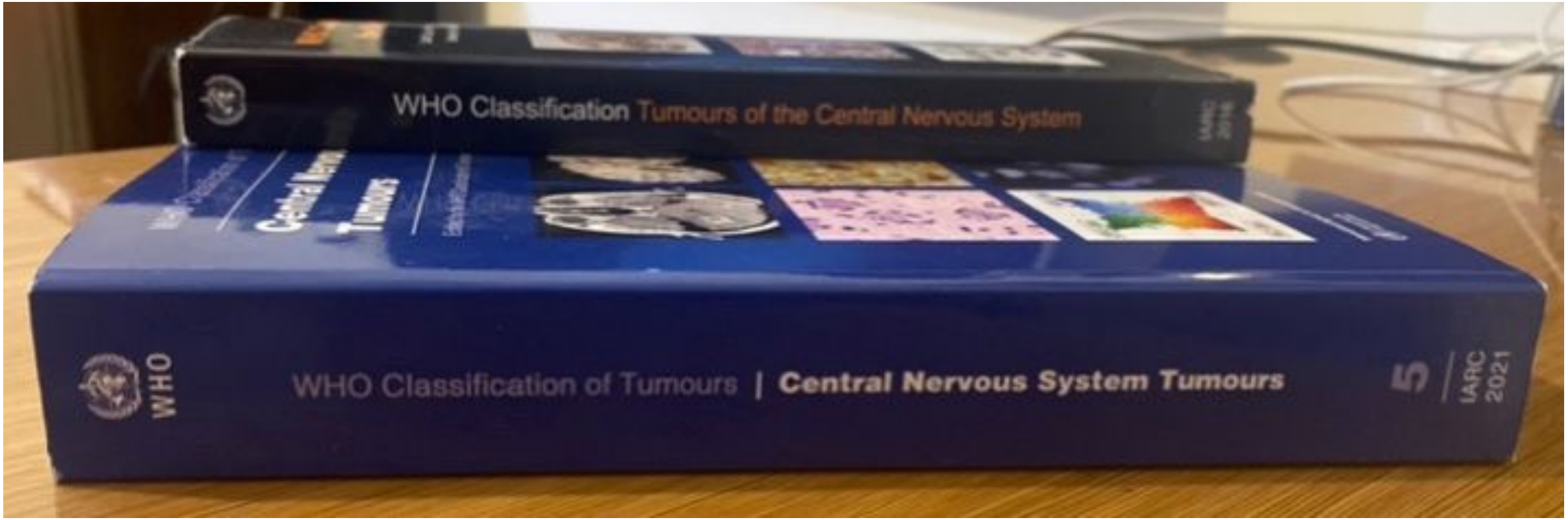
- Both occur in IDH mutant astrocytomas
- **ATRX mutation:** induces abnormal telomeres maintenance mechanism known as **"alternative lengthening of telomeres"**
- **ATRX mutation is Mutual exclusive with the activating promoter mutation of the TERT gene (1p/19q codeletion)**
- **P53 mutation:** enable tumor cell survival
  - ATRX → associated with genomic instability → induces P53 dependent cell death→mutation in P53 helps these cells to survive.

4- **Other genetic alterations:**

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


2021


Great event.
Now what?


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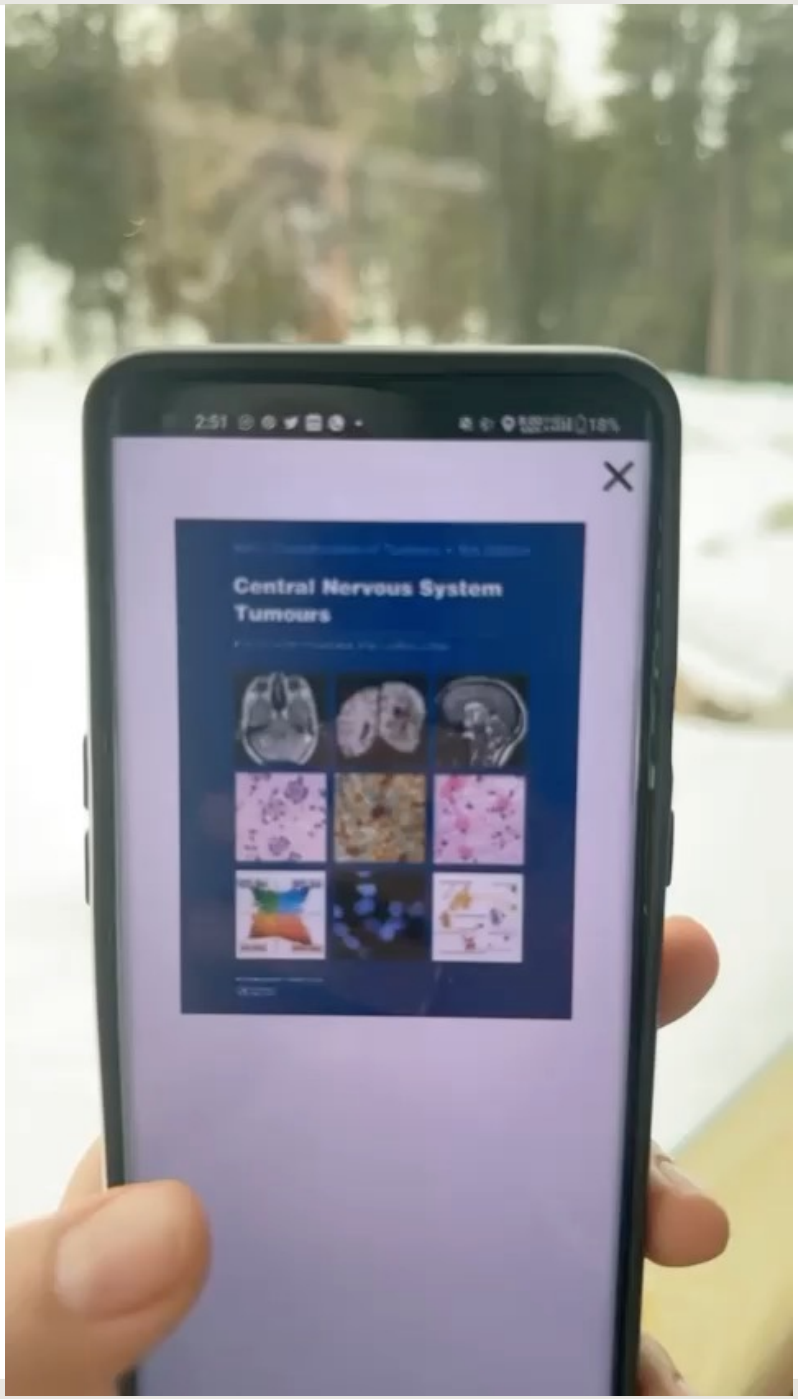
IARC
2021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Central Nervous System Tumours

22 New Entities

- Diffuse astrocytoma, *MYB* or *MYBL1*-altered
- Polymorphous low-grade neuroepithelial tumor of the young
- Diffuse low-grade glioma, MAPK pathway-altered
- Diffuse hemispheric glioma, H3.3 G34-mutant
- Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype
- Infant-type hemispheric glioma
- High-grade astrocytoma with piloid features **(Methylation only dx)**

7 Gliomas

- Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters (provisional entity)
- Myxoid glioneuronal tumor
- Multinodular and vacuolating neuronal tumor

3 Glioneuronal

- Supratentorial ependymoma, *YAP1* fusion-positive
- Posterior fossa ependymoma, PFA
- Posterior fossa ependymoma, PFB
- Spinal ependymoma, *MYCN*-amplified

4 Ependymomas

- Cribriform neuroepithelial tumor (provisional entity)
- CNS neuroblastoma, *FOXR2*-activated
- CNS tumor with *BCOR* internal tandem duplication
- Desmoplastic myxoid tumor, *SMARCB1*-mutant

4 Embryonal

- Angiomatoid fibrous histiocytoma / Intracranial myxoid mesenchymal tumor
- CIC-rearranged sarcoma
- Primary intracranial sarcoma, *DICER1*-mutant

3 Sarcomas

- Pituitary blastoma

1 Pituitary

UPDATE

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

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

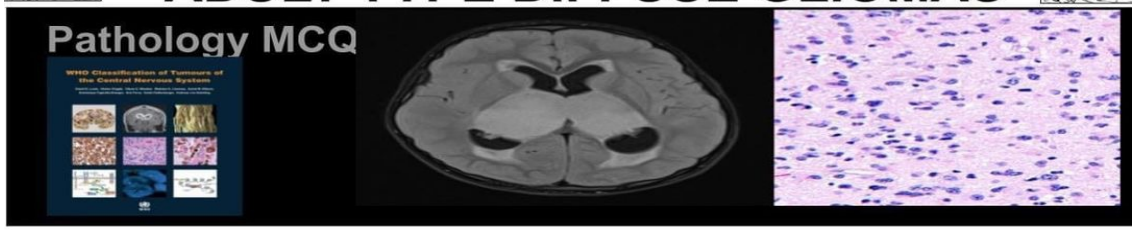
WHO 2021

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

2.1: Gliomas, Glioneuronal and Neuronal Tumours

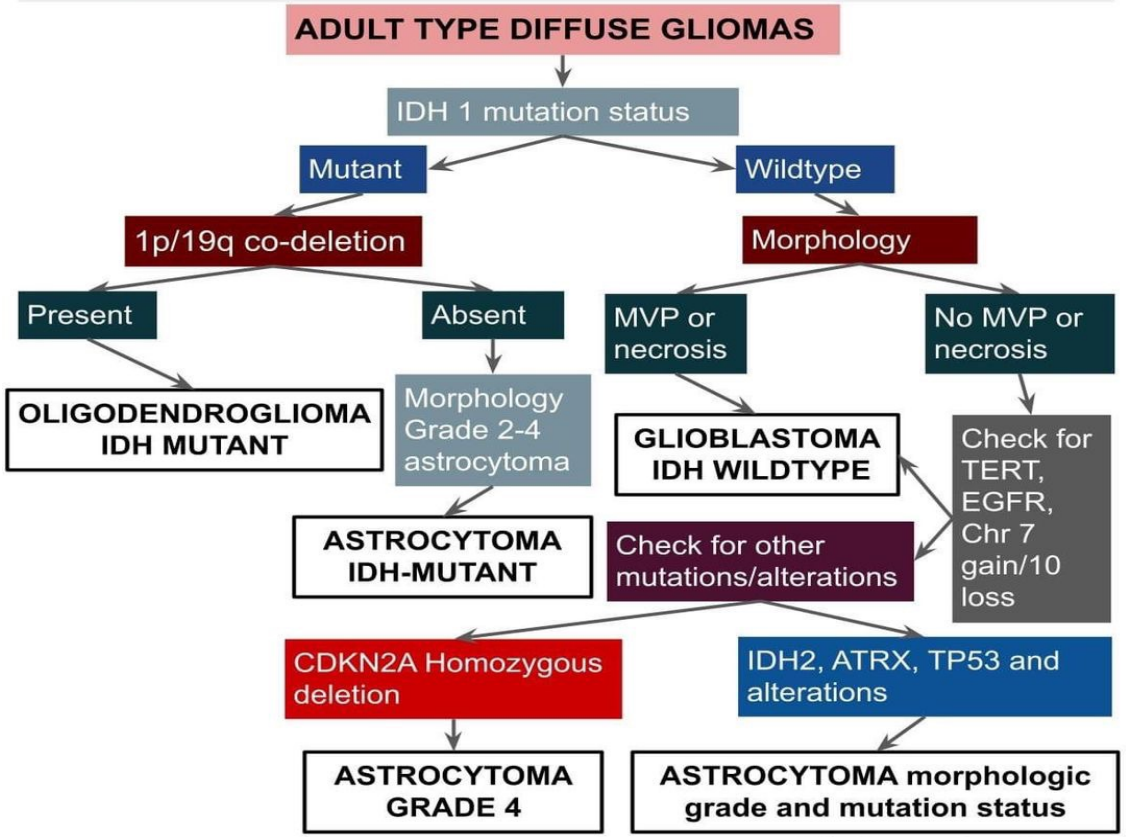
- Adult-type diffuse gliomas
  - 2.1.1.1: Astrocytoma, IDH-mutant
  - 2.1.1.2: Oligodendroglioma, IDH-mutant and 1p/19q-codeleted
  - 2.1.1.3: Glioblastoma, IDH-wildtype
- Paediatric-type diffuse low-grade gliomas
  - 2.1.4.1: Diffuse astrocytoma, MYB or MYBL1-altered
  - 2.1.4.2: Angiocentric glioma
  - 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 Bithalamic glioma, 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

ADULT TYPE DIFFUSE GLIOMAS



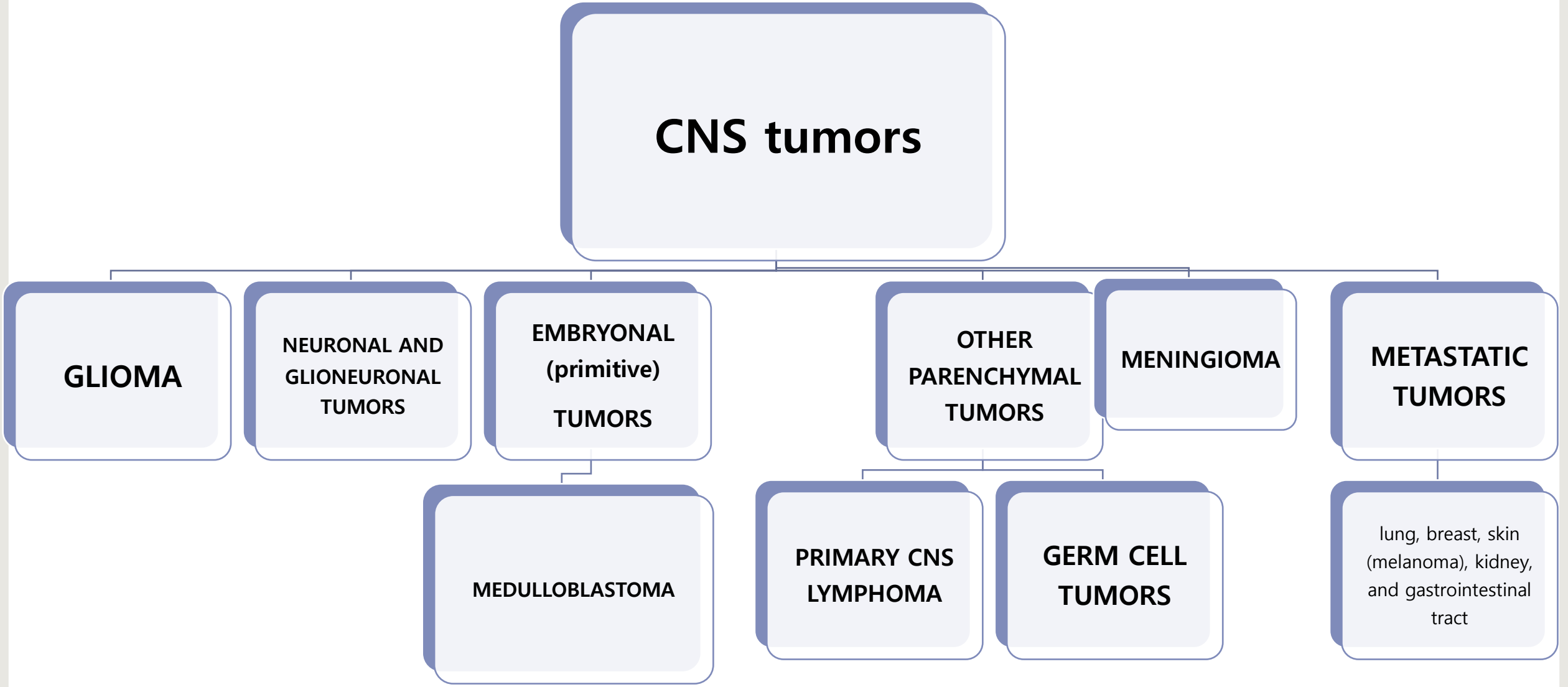
MAJOR CHANGES- WHO CNS 2021

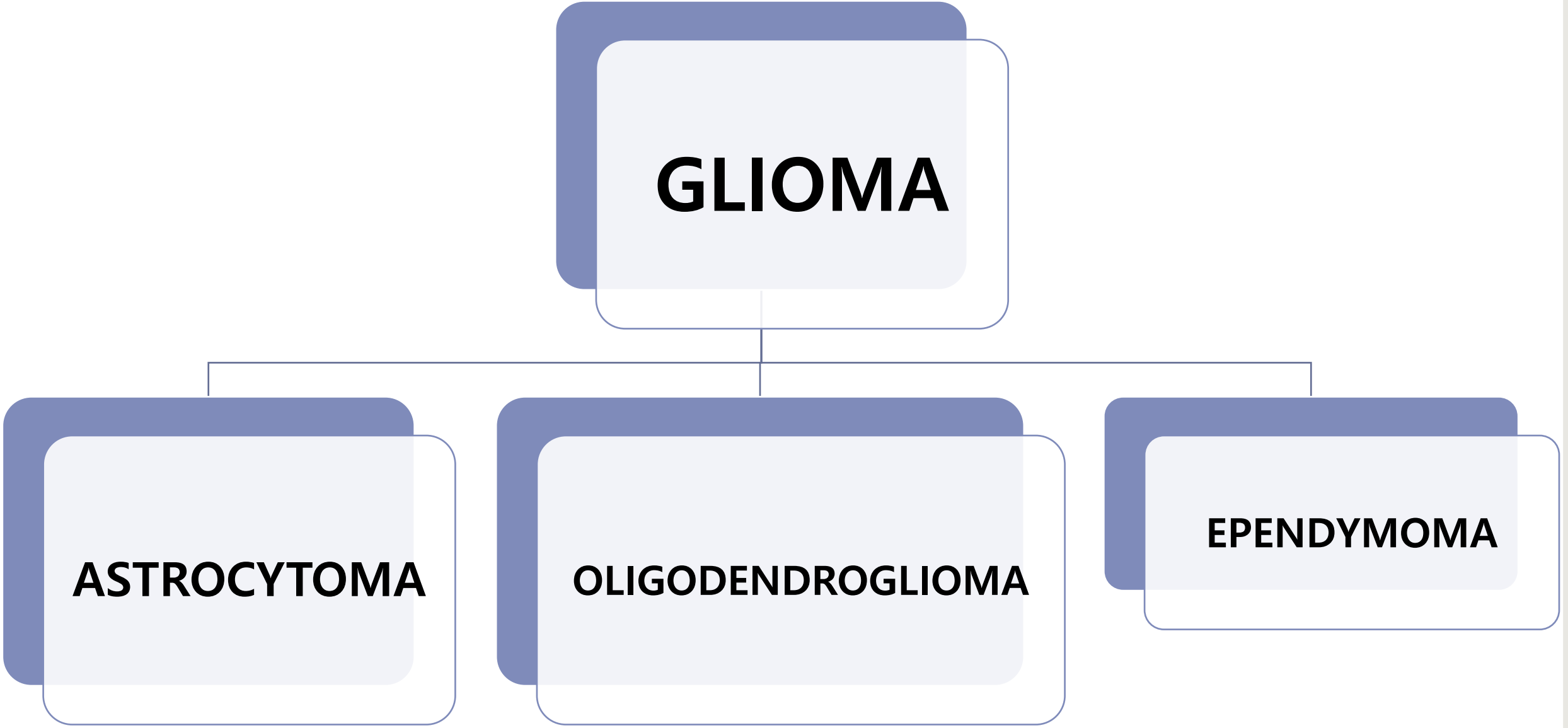
1. All glioblastomas are IDH- wild type (No IDH mutant glioblastoma)!!!!
2. Presence of TERT promoter mutation, EGFR amplification, chromosome 7 gain and 10 loss is classified as glioblastoma irrespective of histology
3. Presence if CDKN2A/B homozygous deletion in astrocytoma is classified as Grade 4 irrespective of morphology

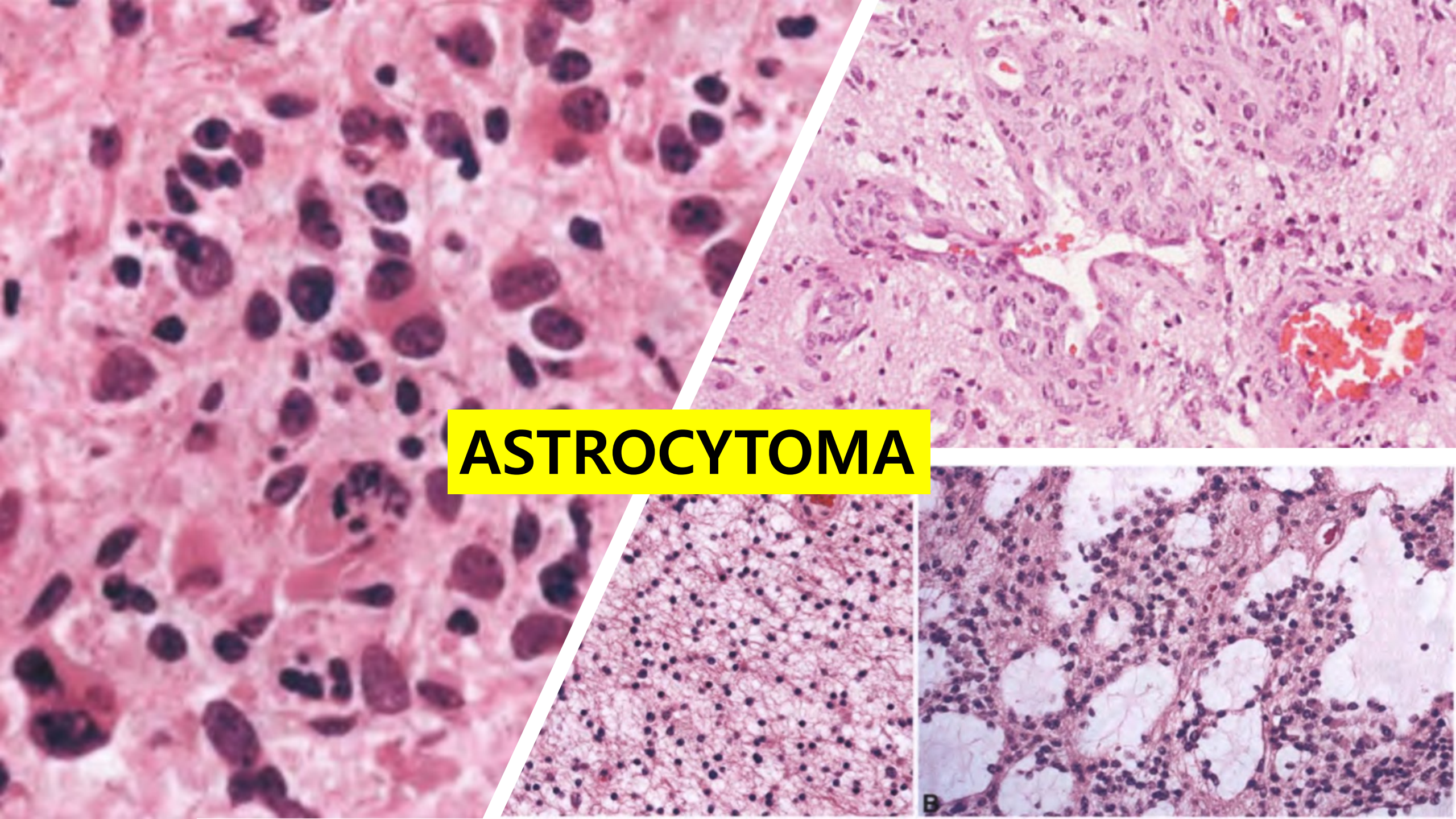


UPDATE

Let’s return to your textbook
“ Robbin basic pathology”, 10th edition


CNS tumors
GLIOMA
NEURONAL AND GLIONEURONAL TUMORS
EMBRYONAL (primitive) TUMORS
MEDULLOBLASTOMA
OTHER PARENCHYMAL TUMORS
PRIMARY CNS LYMPHOMA
GERM CELL TUMORS
MENINGIOMA
METASTATIC TUMORS
lung, breast, skin (melanoma), kidney, and gastrointestinal tract


GLIOMA
ASTROCYTOMA
OLIGODENDROGLIOMA
EPENDYMOMA


ASTROCYTOMA
B

Astrocytomas:

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

1- **diffuse (infiltrating) astrocytoma (WHO grade 2-4)**

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

Diffuse (infiltrating) Astrocytoma:

- **80%** of primary brain tumors in adults.
- **Age at diagnosis:** 40–60 year old.

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

-

- **Presentation:**
  - seizures, headaches, and focal neurologic deficits related to the anatomic site of involvement.
  - static for years

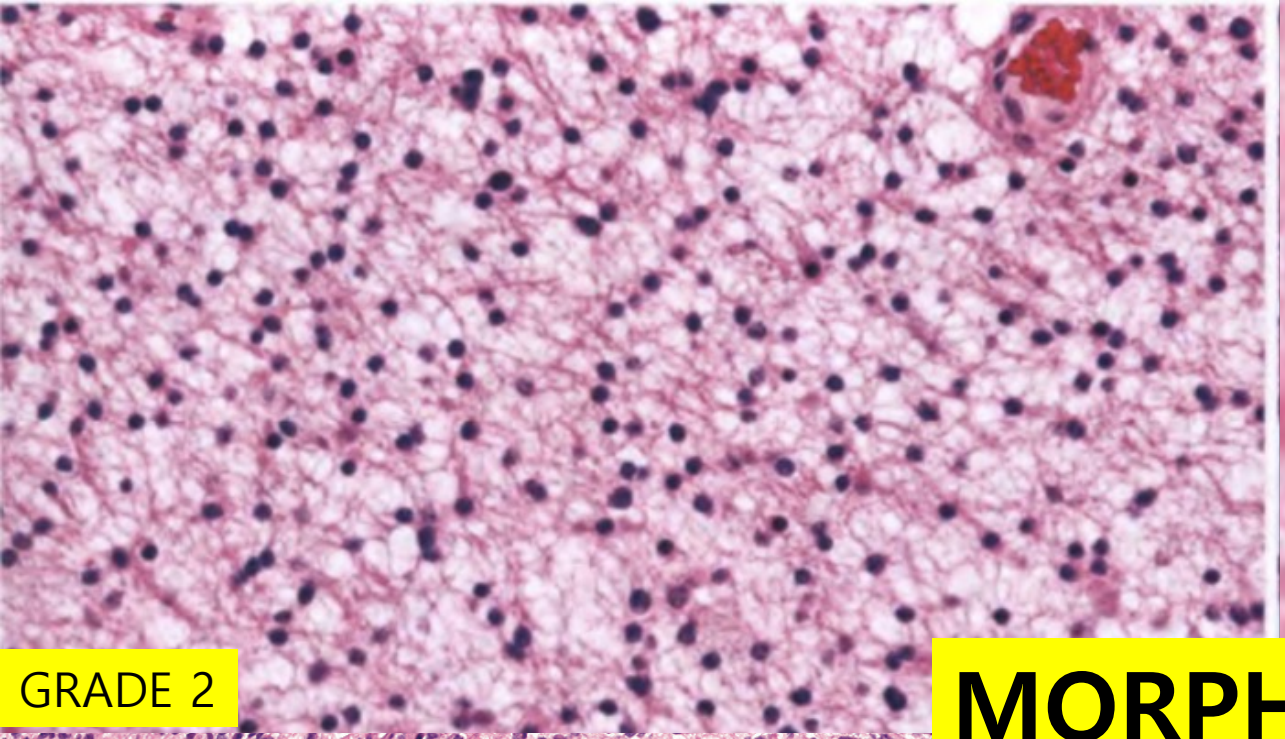
  or

  - Progressive : such as rapid clinical deterioration, due to the appearance of higher-grade component and more rapid tumor growth.

- **On the basis of histologic features astrocytomas are stratified into three groups**
  - diffuse astrocytoma (grade 2), mean survival is > 5 years.
  - anaplastic astrocytoma (grade 3), mean survival is 2-3 years
  - Glioblastoma (grade 4), mean survival is 15 months.

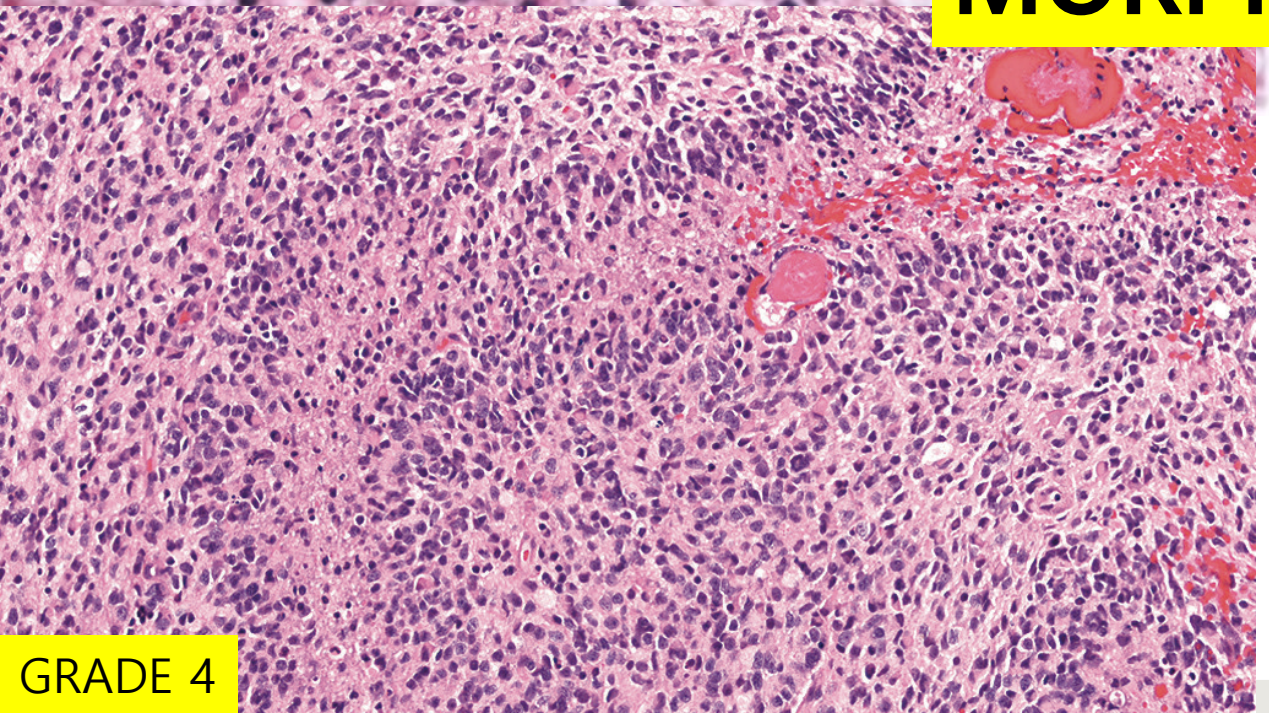
The prognosis gets poorer as the grade increases

NO grade 1 diffuse astrocytoma

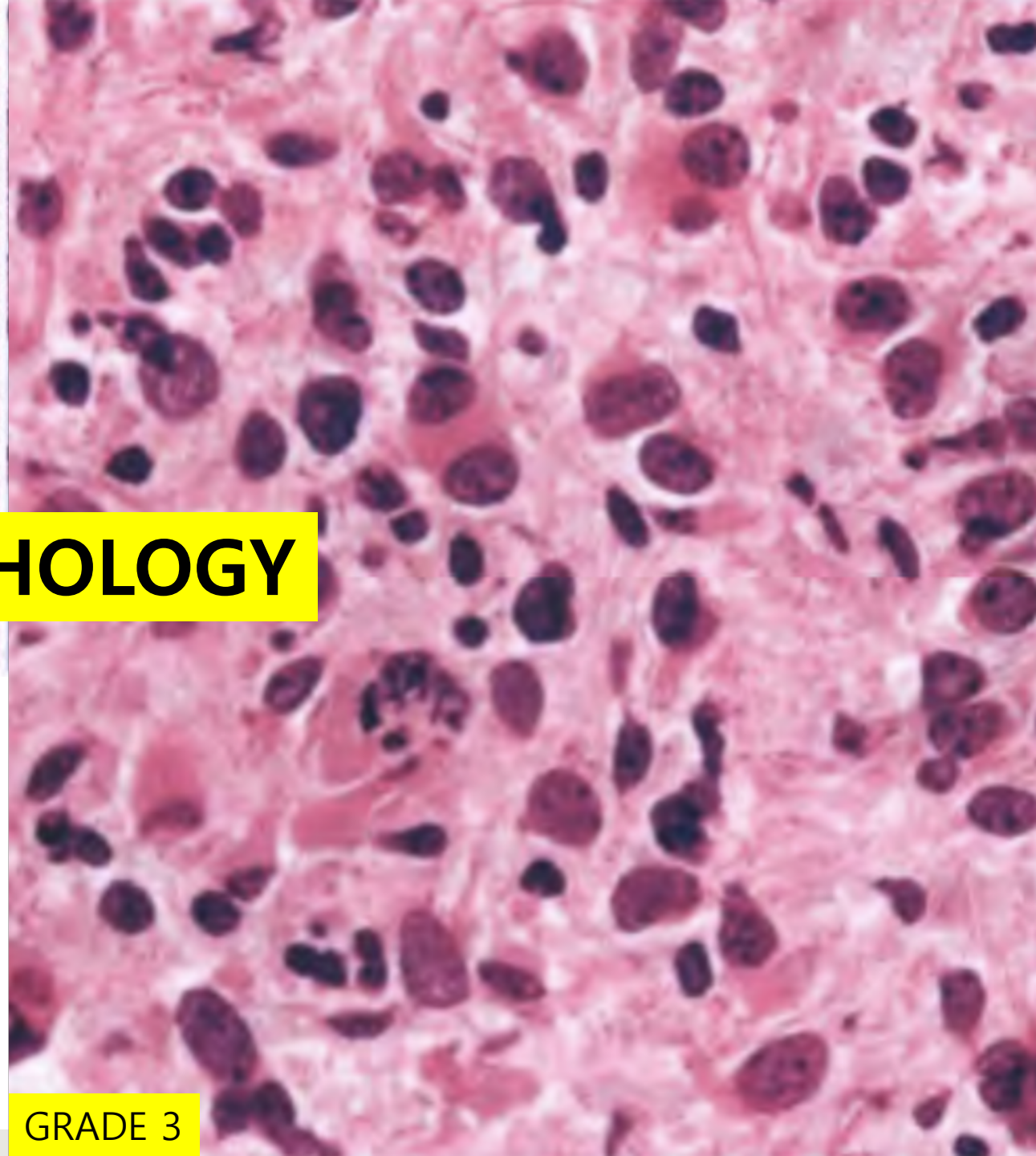


GRADE 2

MORPHOLOGY



GRADE 4

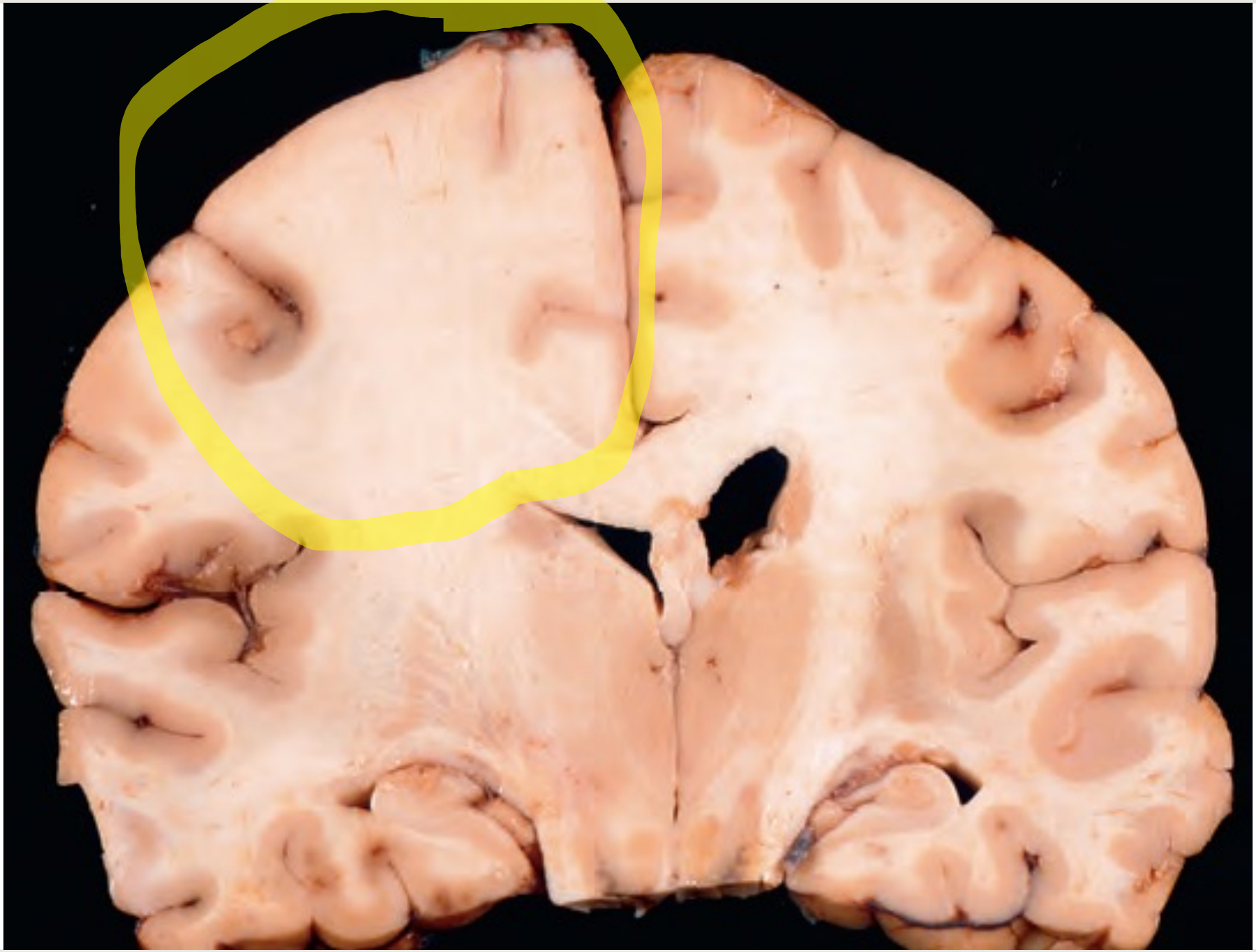


GRADE 3

Diffuse astrocytoma, WHO grade 2 & 3, Morphology:

Macroscopic:

- poorly defined, infiltrative tumors
- expand and distort the invaded brain without forming a discrete mass
- Infiltration beyond the grossly evident margins.
- +/- cystic degeneration



Diffuse astrocytoma, 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 cells.
- **Cytologic atypia**:
  - mild
  - enlarged, elongated or irregular hyperchromatic nuclei
  - No prominent atypia

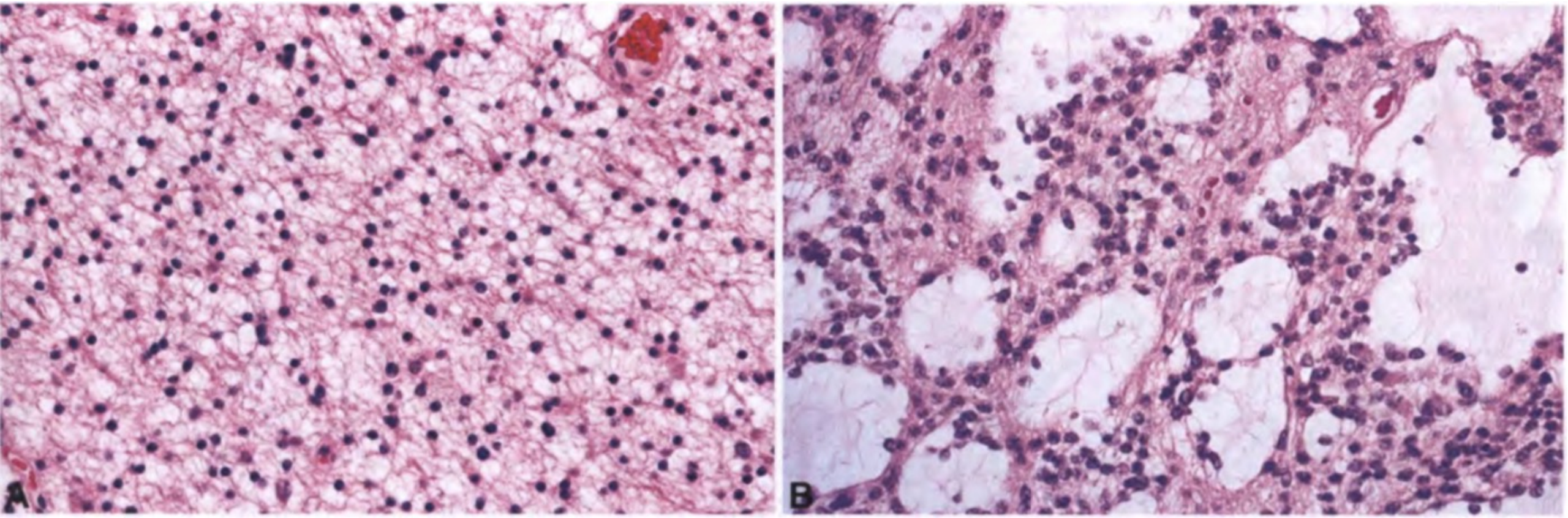
+ **fibrillary background** made of fine astrocytic cell processes

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

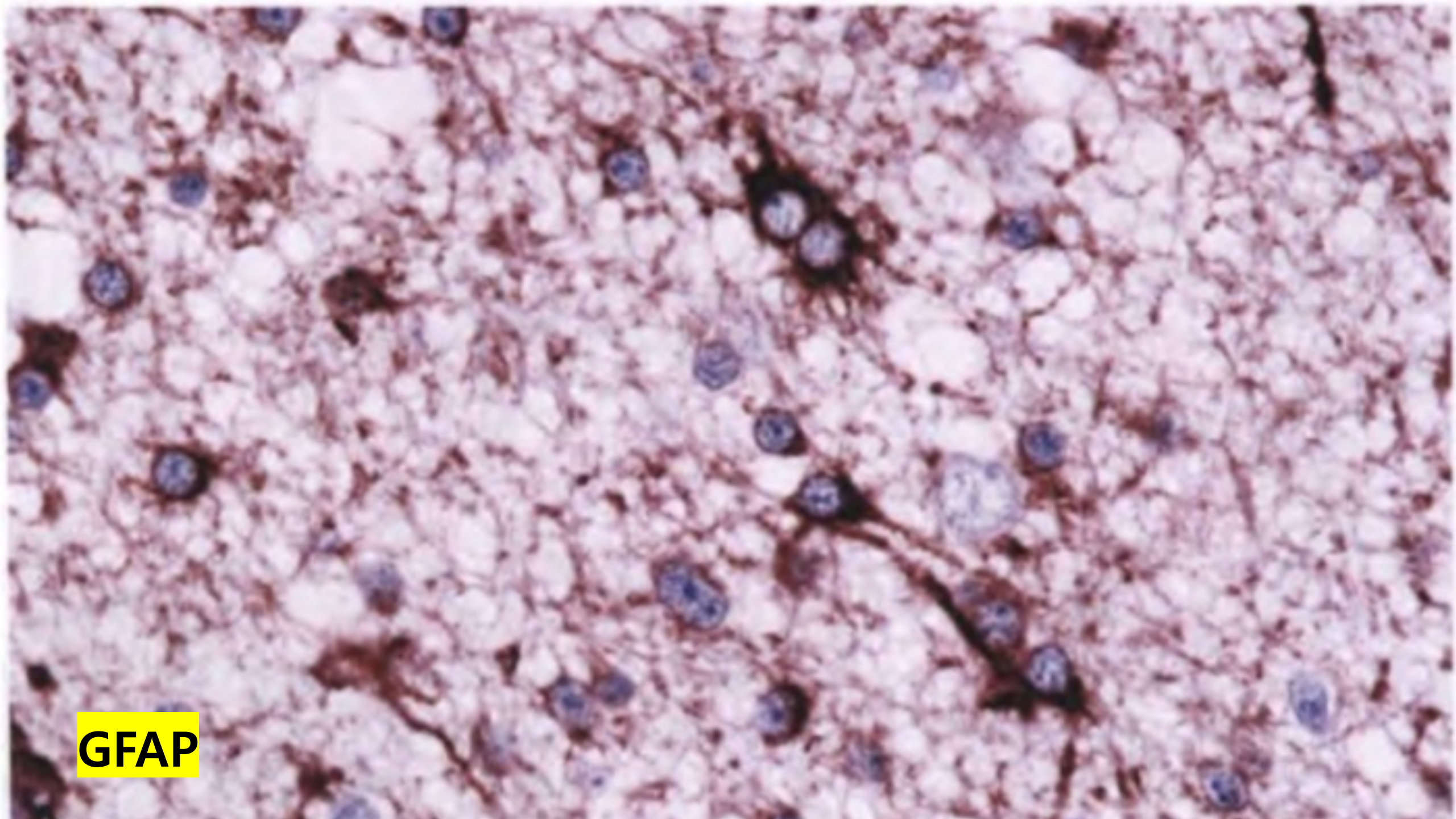
Diffuse astrocytoma, WHO grade 2, Microscopic:

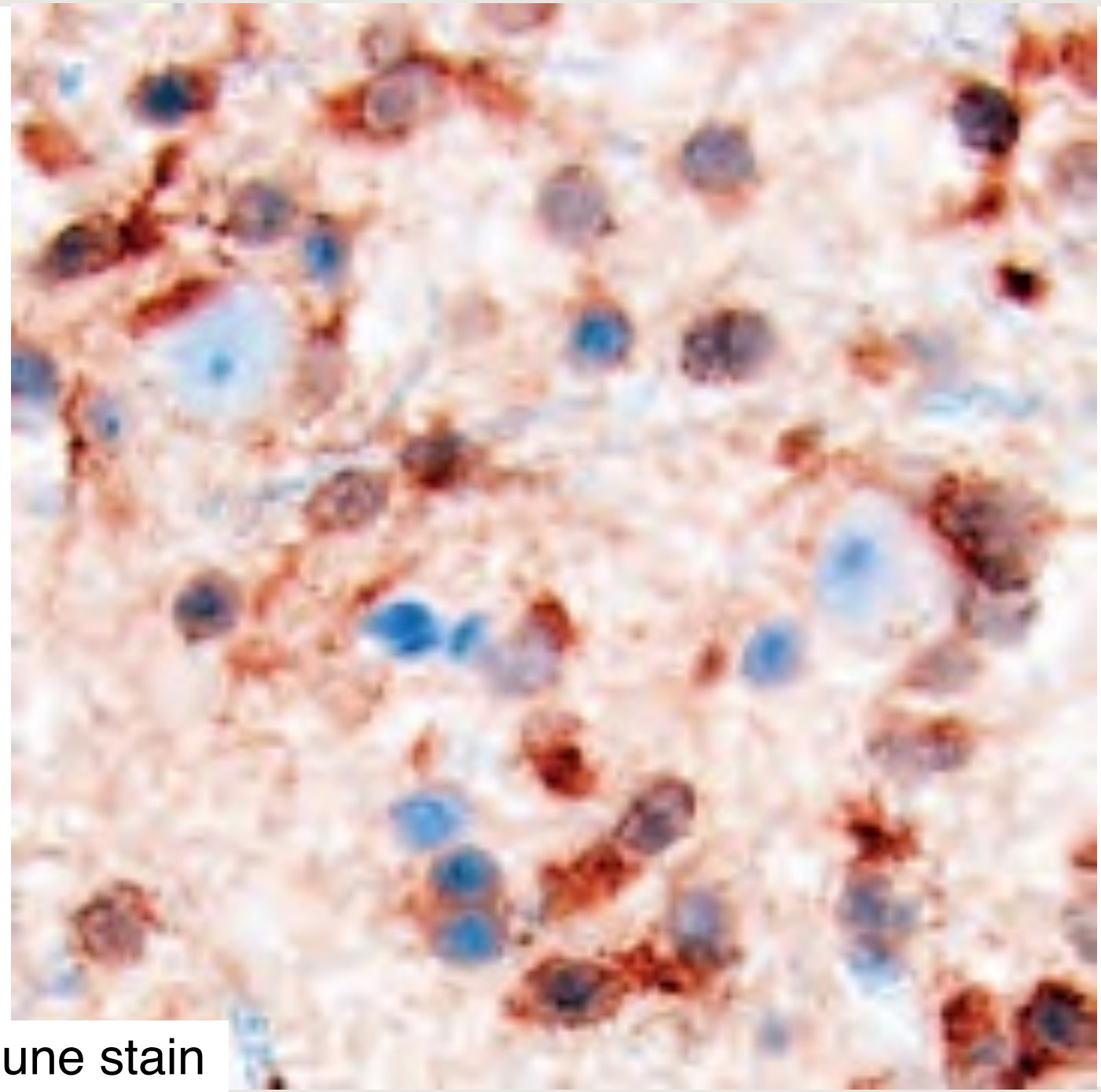
Positive for:

- Glial fibrillary acidic protein (GFAP) immune stain
- IDH1 R132H immune stain (83-91%) of IDH mutant cases.
- If IDH1 immune stain is negative→ IDH1 and IDH2 sequencing

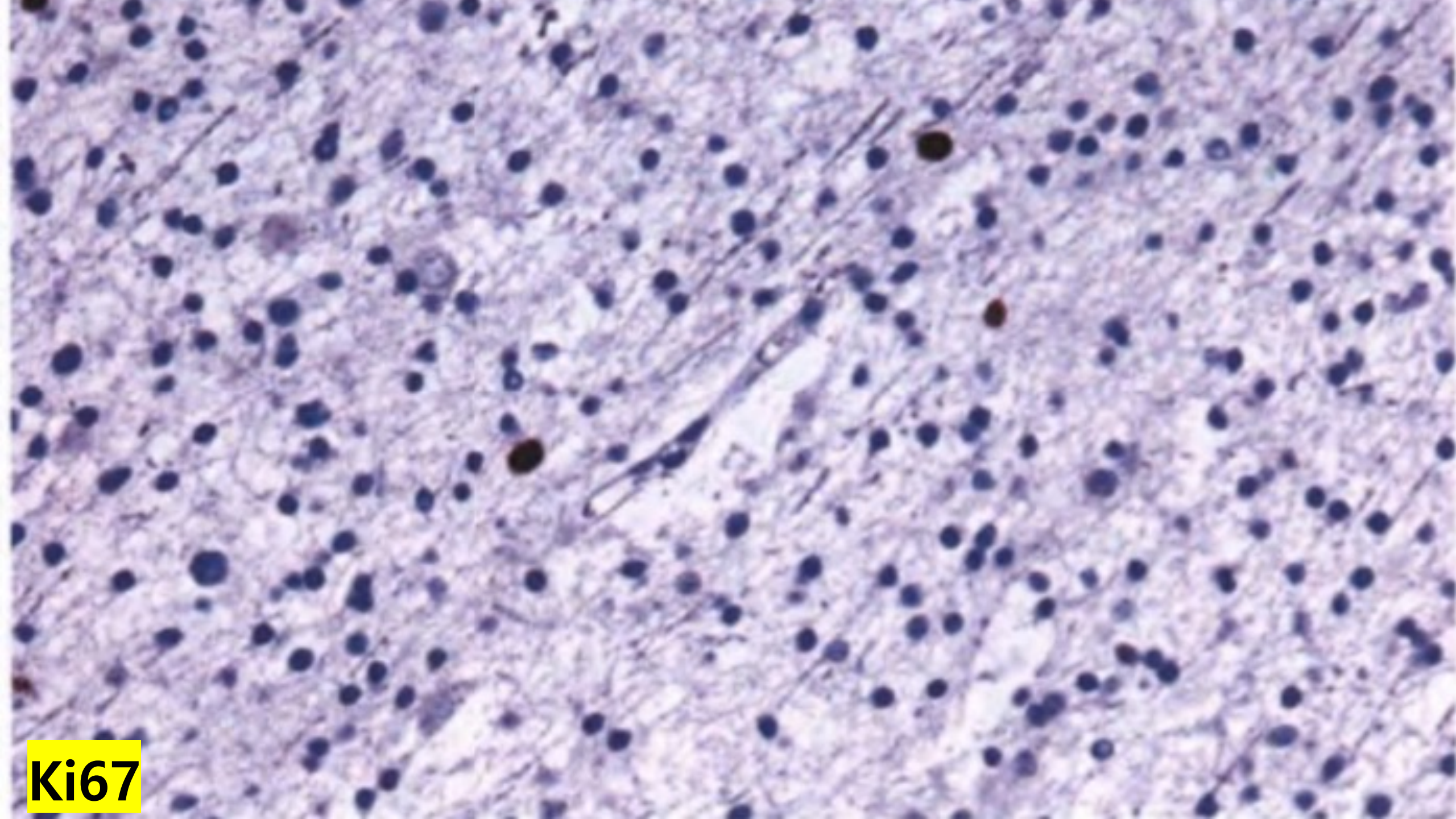


WHO classification of tumors of the central nervous system revised 4th edition,2016,


GFAP



IDH1 R132H immune stain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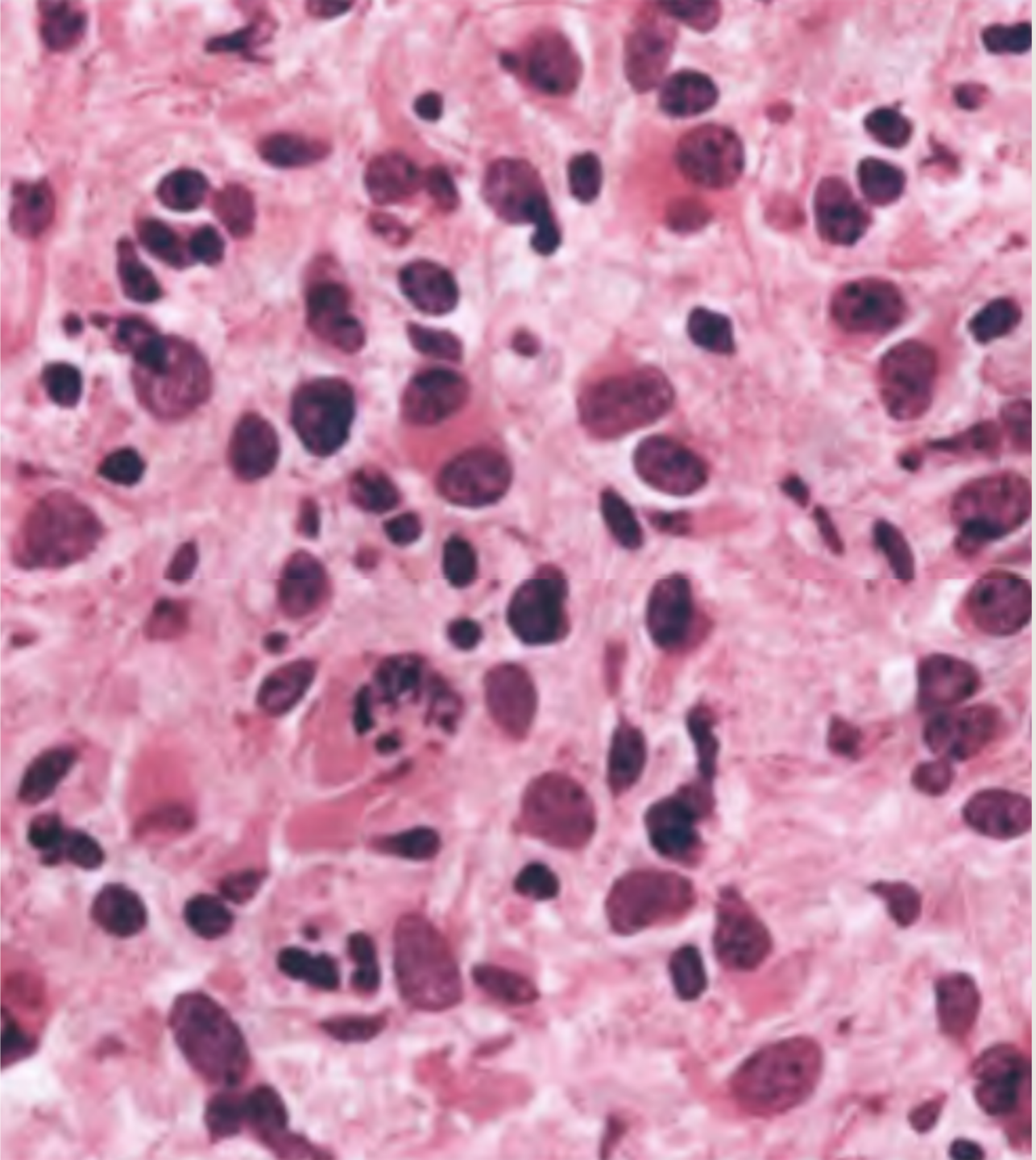


Anaplastic astrocytoma, grade 3:

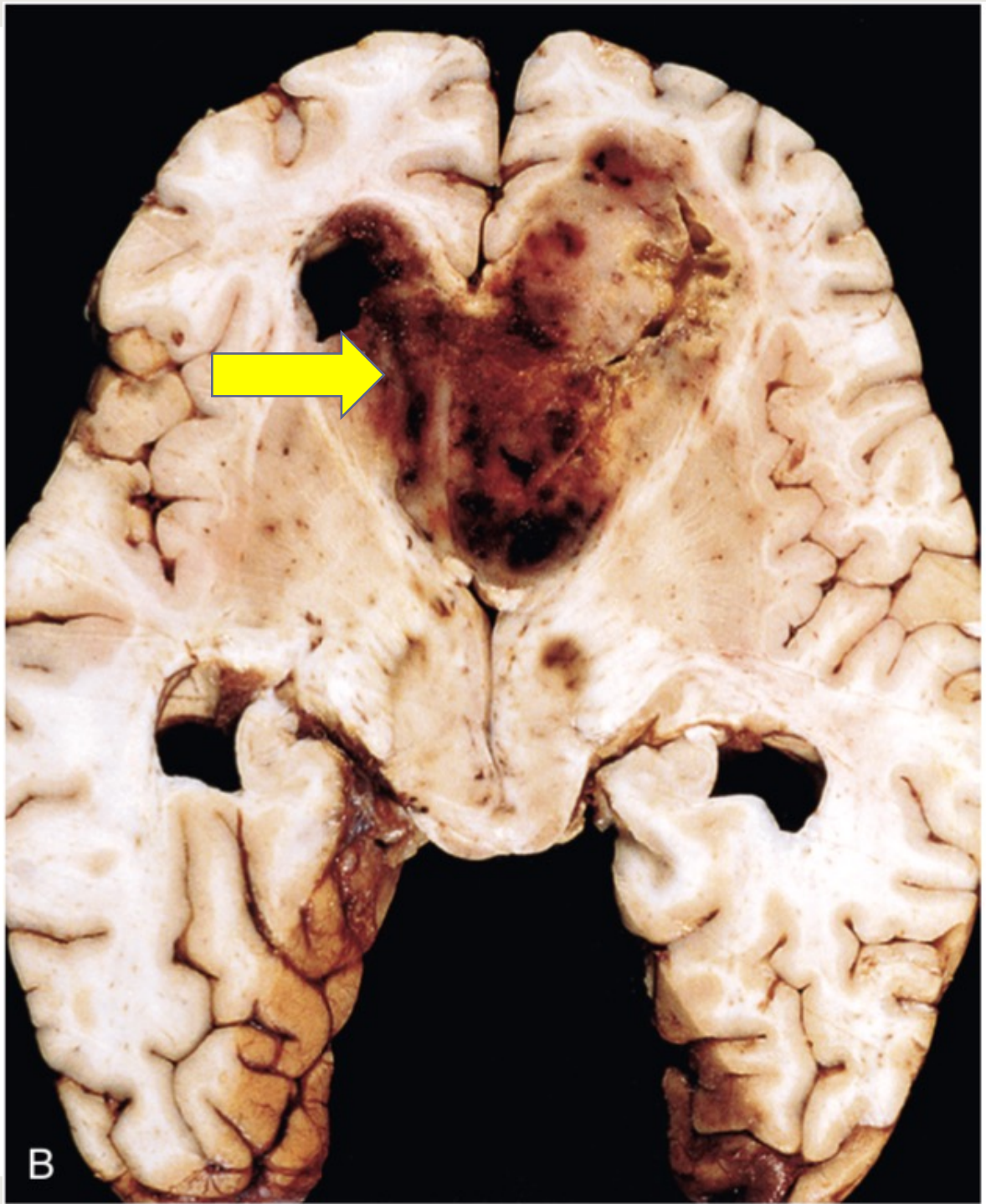
- cellular
- nuclear pleomorphism
- mitotic figures are **present**
- **NO** necrosis
- **NO** microvascular proliferation

Glioblastomas, grade 4:

- Lesions can start as Glioblastoma from the beginning or progress from a previous grade 2 or 3 tumors to grade 4
- 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), others show regions of cystic degeneration and hemorrhage.



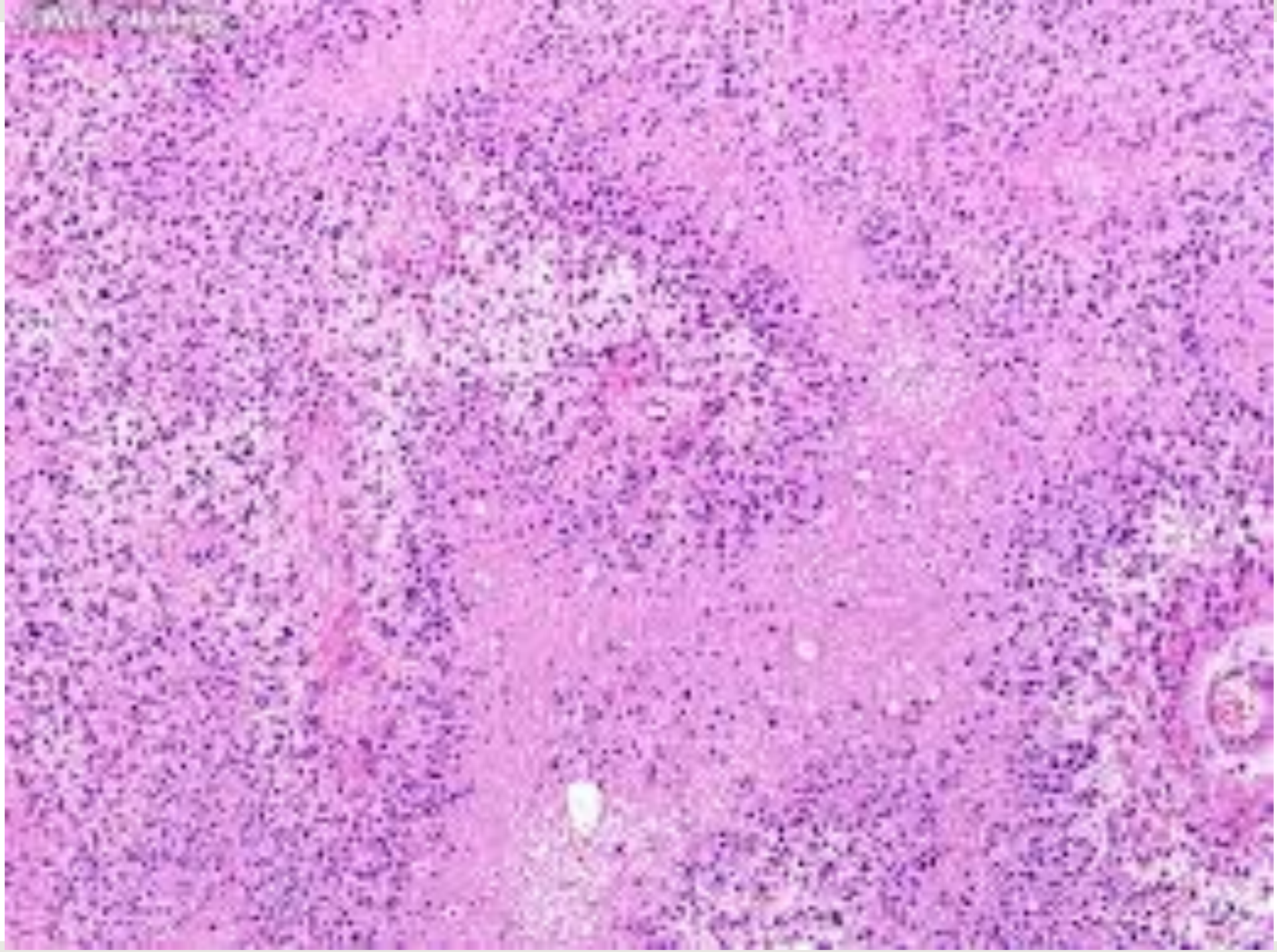
- **Microscopic:**
  - anaplastic astrocytoma features + either:

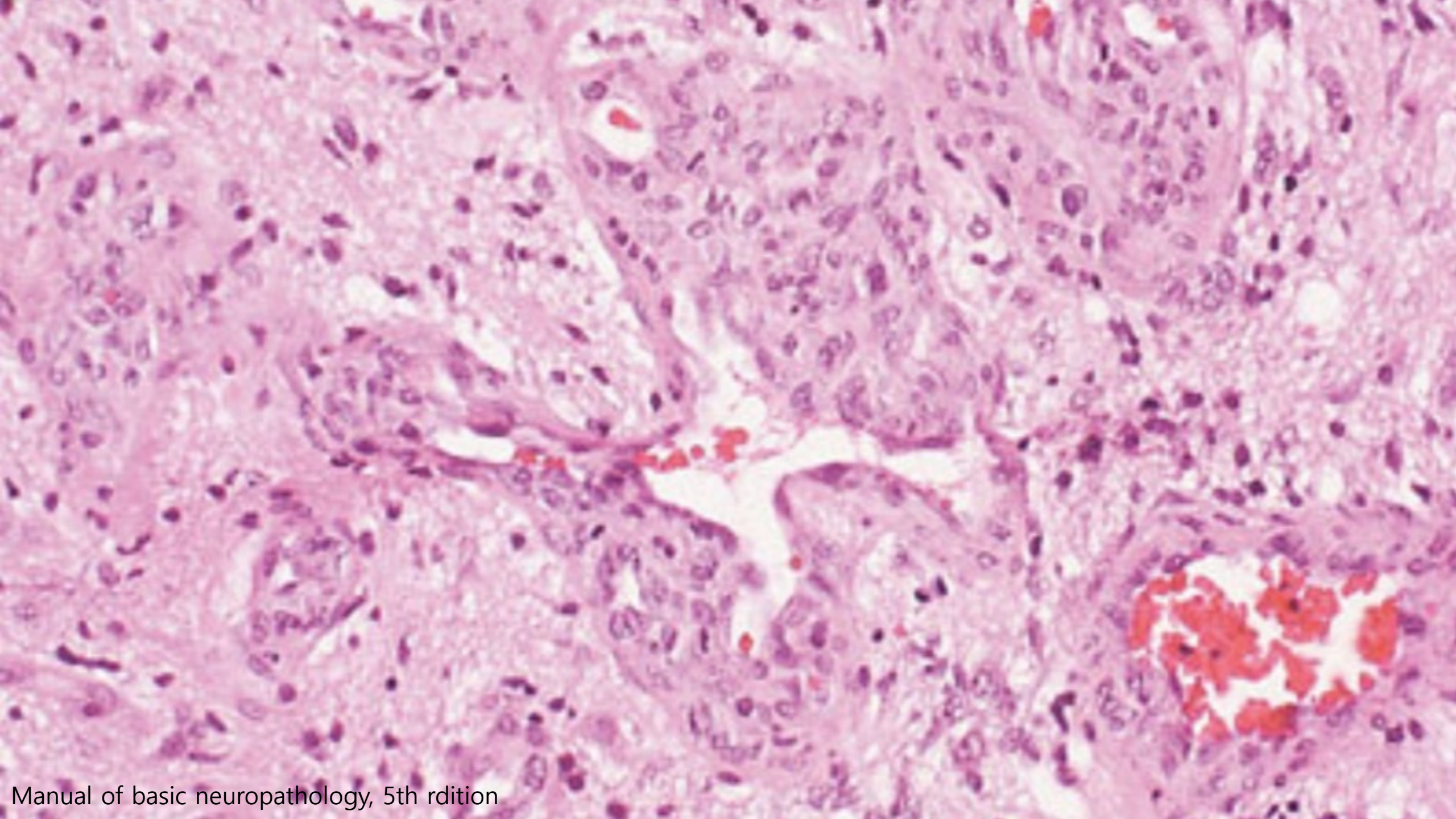
Necrosis: irregular zones of necrosis surrounded by dense accumulations of tumor cells (**palisading necrosis)**

or

microvascular proliferation:

the presence of abnormal vessels with walls composed **2** ≥ layers of vascular wall cells.





Manual of basic neuropathology, 5th rdition


2021

cIMPACT:Update 6

Suggested Definitions and grading of Astrocytomas, IDH mutant

- Astrocytoma, IDH mutant, WHO grade 2
  - No-low mitotic activity
  - No microvascular proliferation, necrosis or *CDKN2A/B* homozygous deletions
- Astrocytoma, IDH mutant, WHO grade 3
  - Significant mitotic activity
  - No microvascular proliferation, necrosis or *CDKN2A/B* homozygous deletions
- Astrocytoma, IDH mutant, WHO grade 4
  - microvascular proliferation, necrosis or *CDKN2A/B* homozygous deletions

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

Essential:

A diffusely infiltrating glioma

AND

Mutation in *IDH1* or *IDH2*

AND

Loss of nuclear ATRX expression or *ATRX* mutation

OR

Exclusion of 1p/19q codeletion

Desirable:

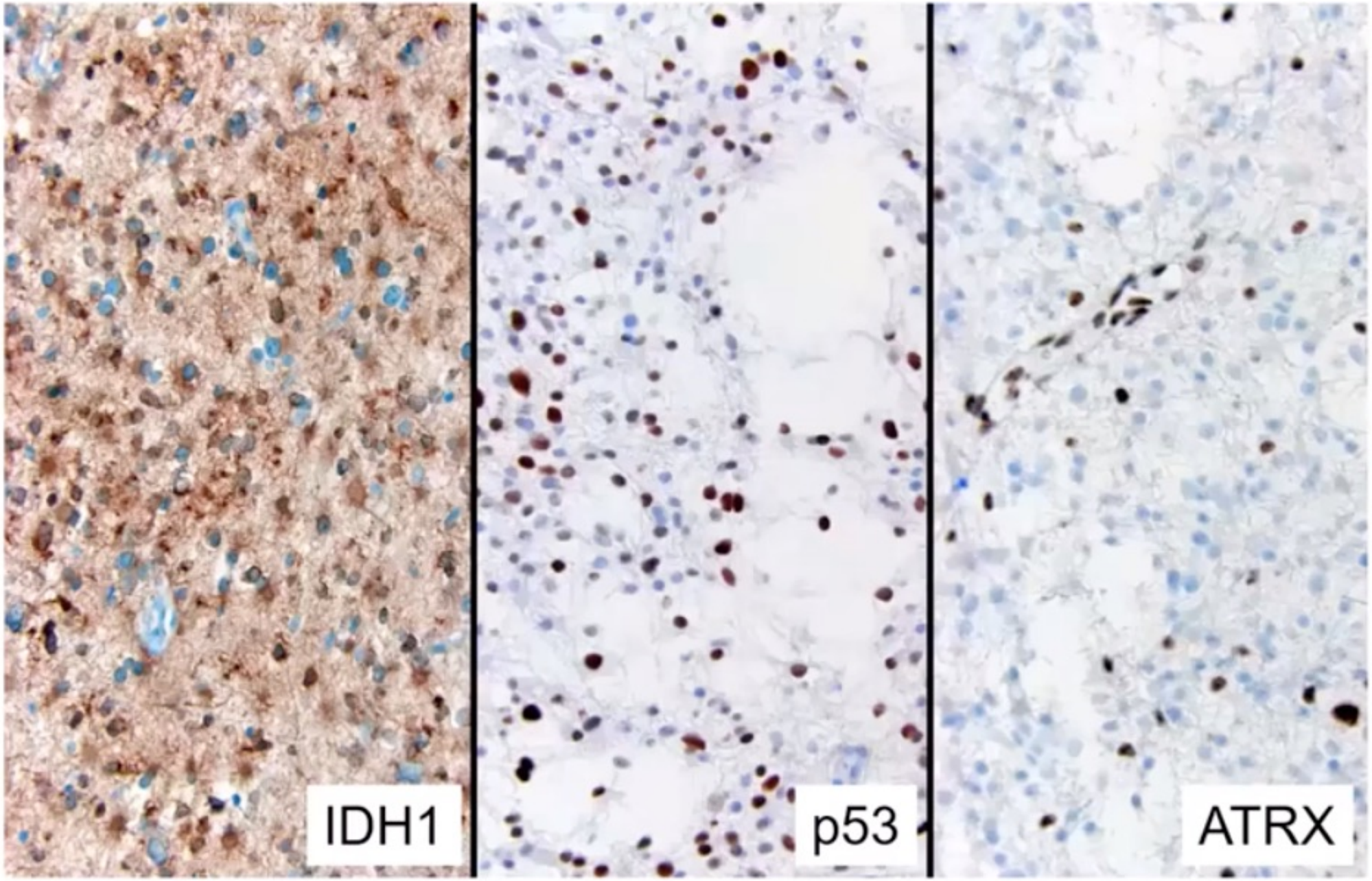
TP53 mutation or strong nuclear expression of p53 in > 10% of tumour cells

Methylation profile of astrocytoma, IDH-mutant

Astrocytic differentiation by morphology

UPDATE

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



Title: Grading criteria Astrocytoma, IDH-mutant

Source:

Astrocytoma, IDH-mutant	
WHO CNS grade 2	A diffusely infiltrative astrocytic glioma with an *IDH1* or *IDH2* mutation that is well differentiated and lacks histologic features of anaplasia. Mitotic activity is not detected or very low. Microvascular proliferation, necrosis and *CDKN2A/B*homozygous deletions are absent.
WHO CNS grade 3	A diffusely infiltrative astrocytic glioma with an *IDH1* or *IDH2* mutation that exhibits focal or dispersed anaplasia and displays significant mitotic activity. Microvascular proliferation, necrosis and *CDKN2A/B* homozygous deletions are absent.
WHO CNS grade 4	A diffusely infiltrative astrocytic glioma with an *IDH1* or *IDH2* mutation that exhibits microvascular proliferation or necrosis or *CDKN2A/B* homozygous deletion, or any combination of these features.

UPDATE

Glioblastoma, IDH-wildtype, grade 4

Essential and desirable diagnostic criteria

Essential diagnostic criteria:
An IDH-wildtype, H3-wildtype, diffuse astrocytic glioma with one or more of the following:
1. Microvascular proliferation
2. Necrosis
3. *TERT* promoter mutation
4. *EGFR* gene amplification
5. +7/-10 chromosome copy number changes

Desirable diagnostic criteria:
An IDH-wildtype, H3-wildtype, diffuse astrocytic glioma with a DNA methylome/molecular profile pattern of glioblastoma, IDH-wildtype
In selected cases, methylation analysis may be helpful.

UPDATE

Circumscribed astrocytic gliomas

Pilocytic Astrocytoma

Pilocytic Astrocytoma, WHO grade 1:

- **Age at presentation:** children and young adults.
- **Location:**
  - cerebellum (especially in children)
  - Optic nerve
  - Midline locations: Brainstem, optic chiasm/ hypothalamus, basal ganglia
  - Spinal cord
  - Cerebral hmispheres:
    - Rare in children
    - Happen in adults with equal frequency as in cerebellum

Pilocytic Astrocytoma, WHO grade 1:

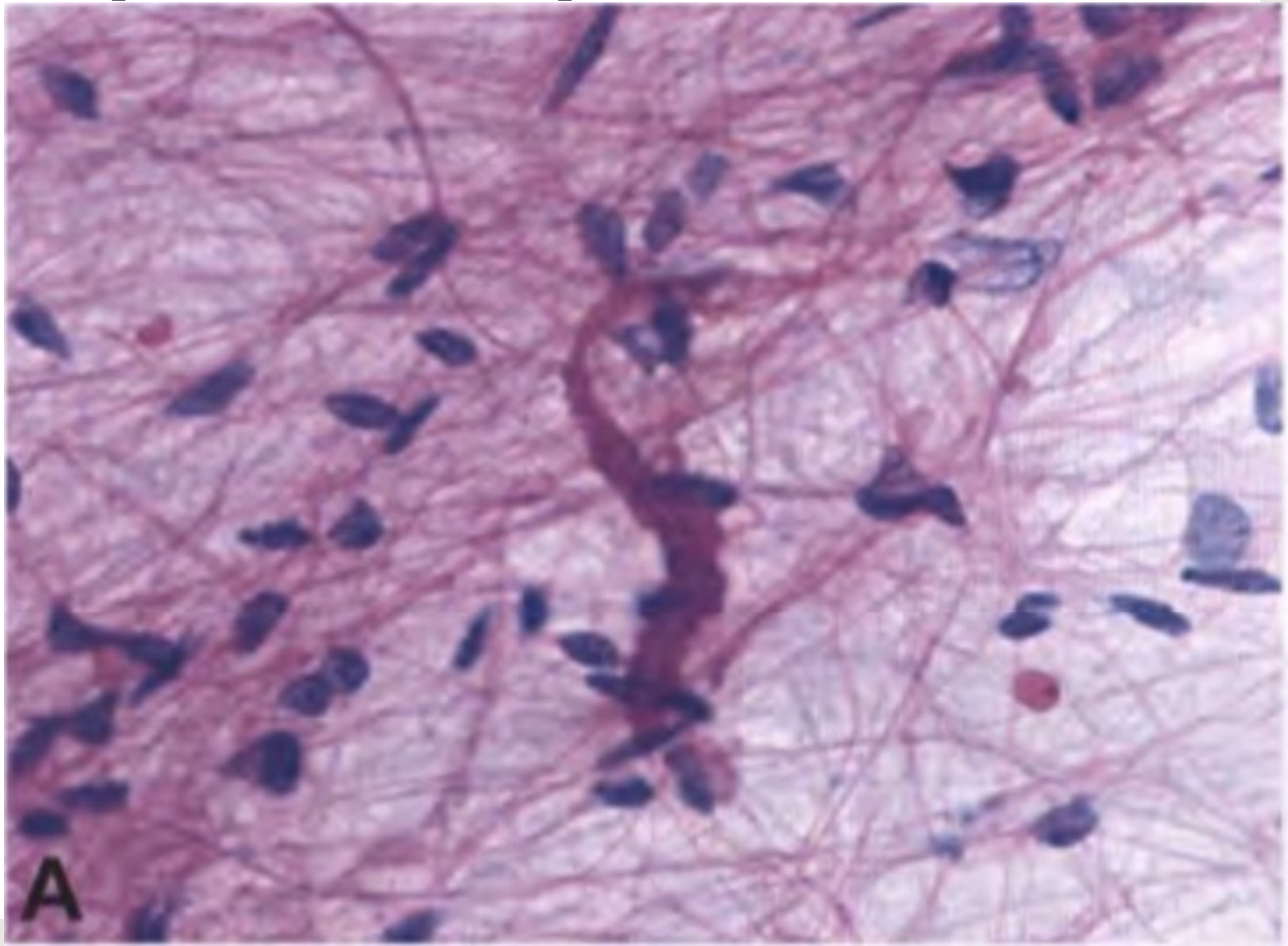
- **Molecular profile:**
  - activating mutations or translocations involving the gene encoding the BRAF→ resulting in activation of the MAPK signaling pathway.

- **do not have mutations in IDH1 and IDH2,** supporting their distinction from the low-grade diffuse gliomas.

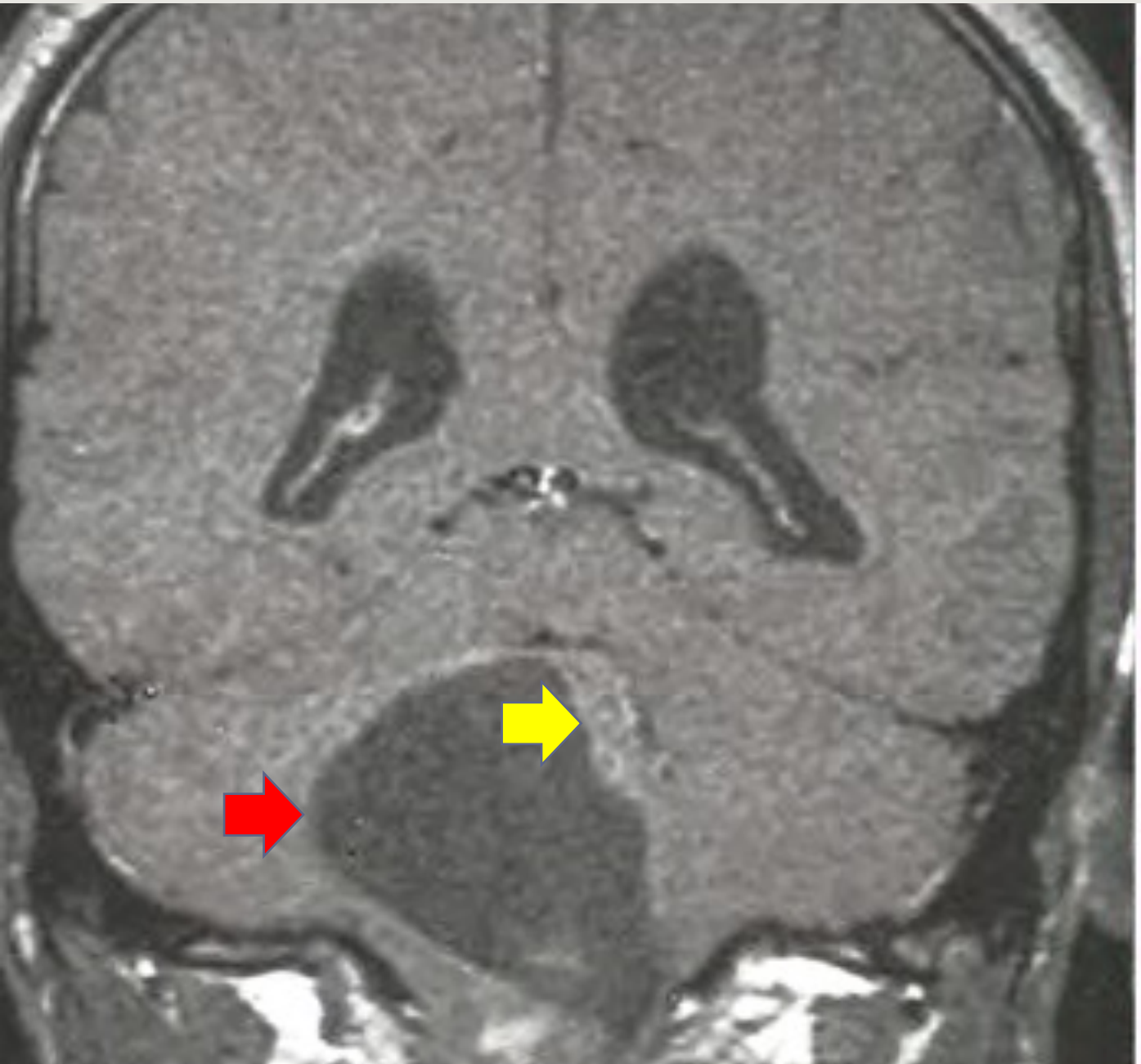
- **Macroscopic:**
  - well circumscribed and cystic

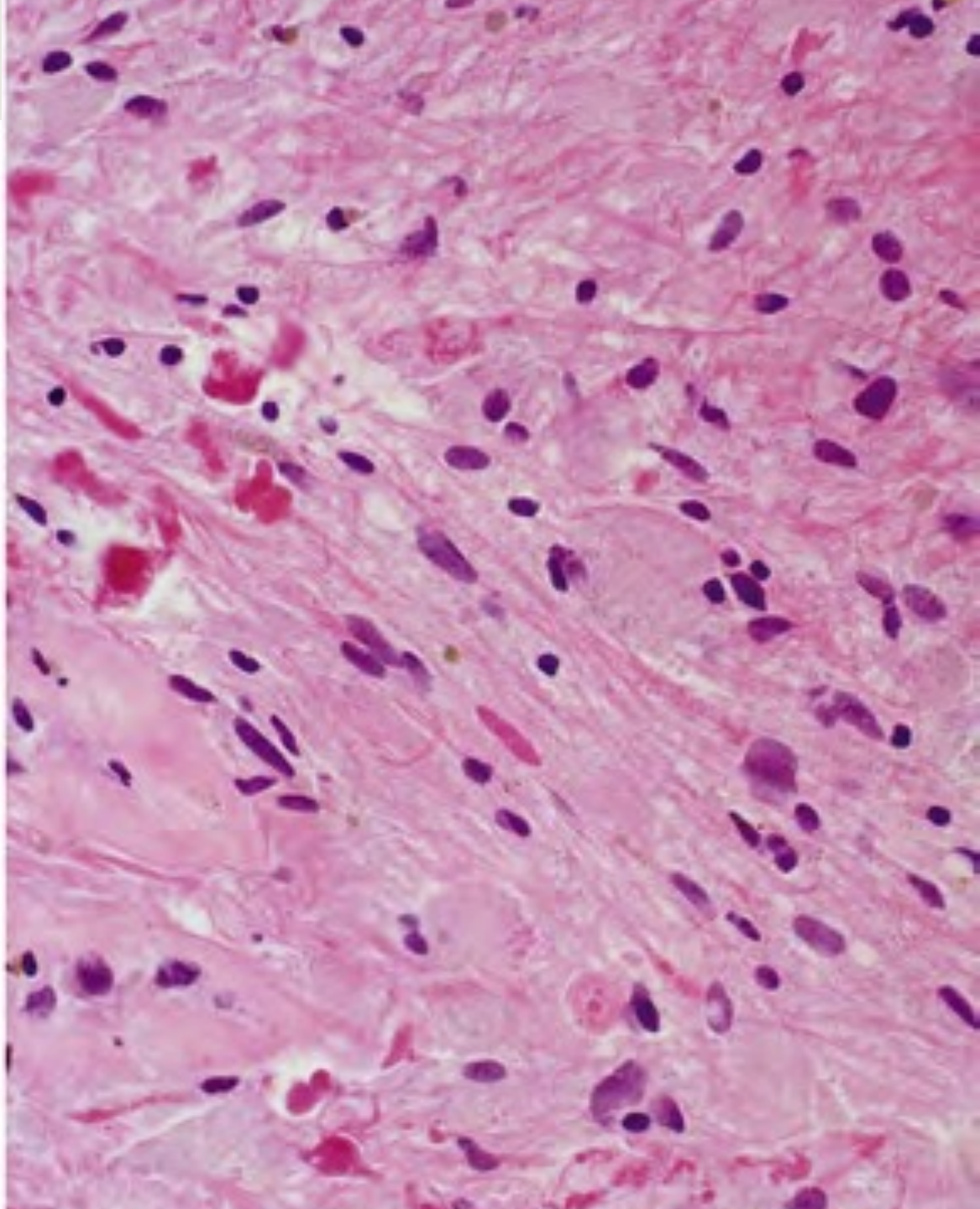
Morphology, microscopic:

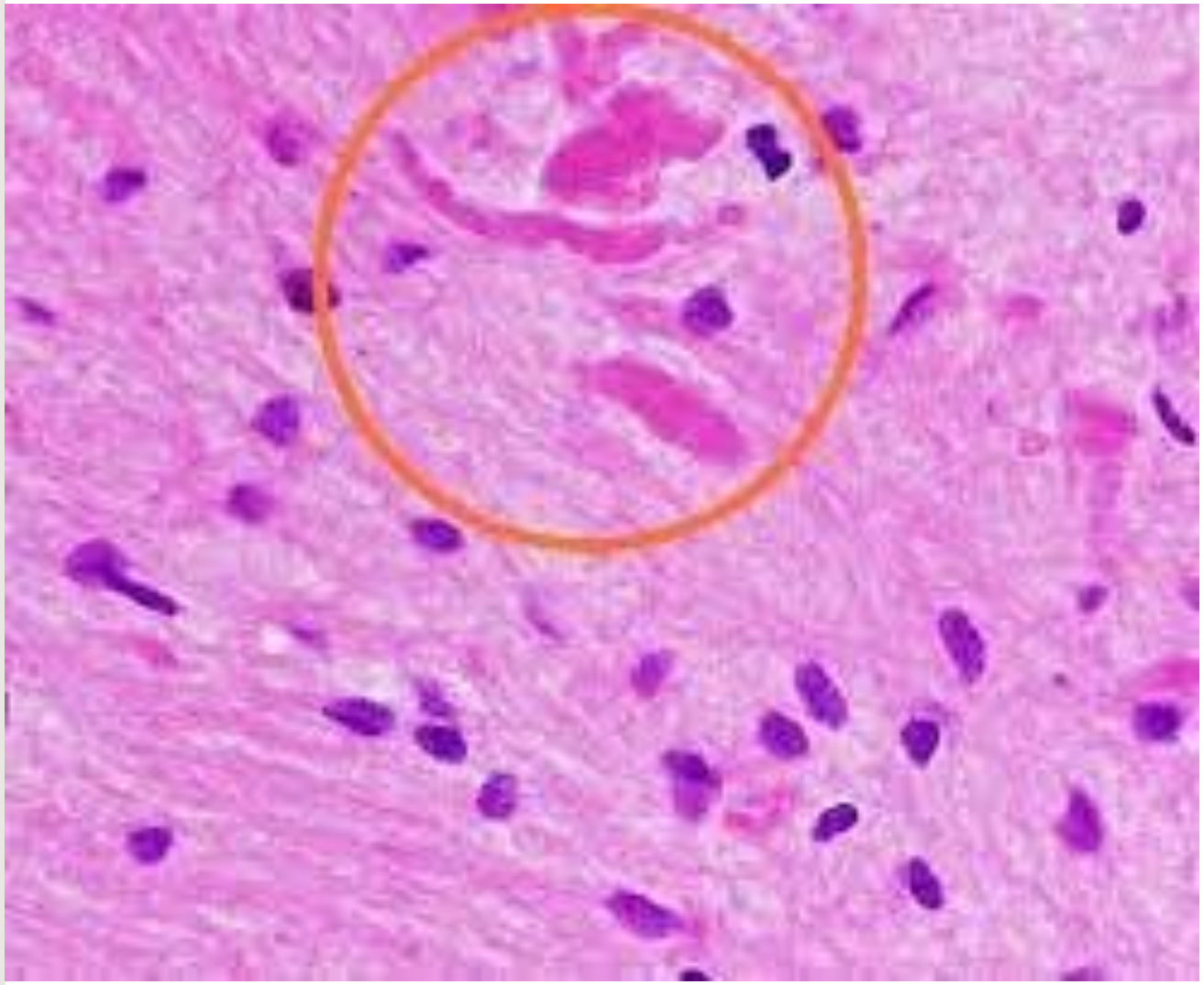
- bipolar cells with long, thin GFAP positive “hairlike” processes
- Rosenthal fibers
- eosinophilic granular bodies
- microcysts are often present
- necrosis and mitoses are rare.



well circumscribed, cystic with a mural nodule in the wall of the cyst or solid

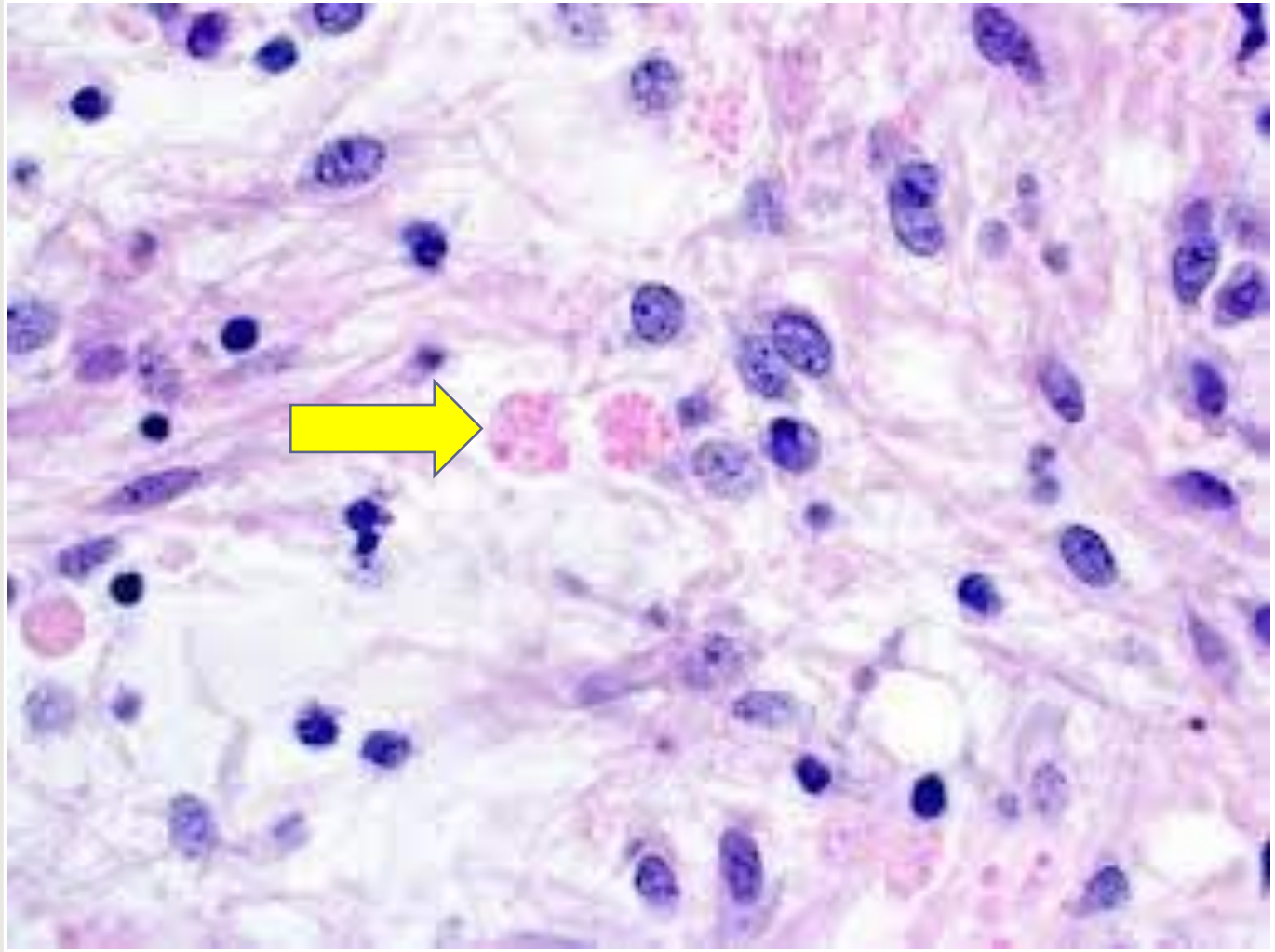






Rosenthal fibers

- are rounded or elongated, homogenous, and brightly eosinophilic structures within the astrocytic processes
- made of clumped intermediate filament proteins, primarily glial fibrillar protein
- Can be physiologic (gliosis) or pathologic (PA) and Alexander disease



Eosinophilic granular bodies:

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


thank you