

CENTRAL NERVOUS SYTEM TUMORS(1)



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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**



EPIDEMIOLOGY:

- **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.**



Characteristic features of CNS tumors:

- **No Premalignant stage: no** 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.

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 tumor type or grade due to local effects

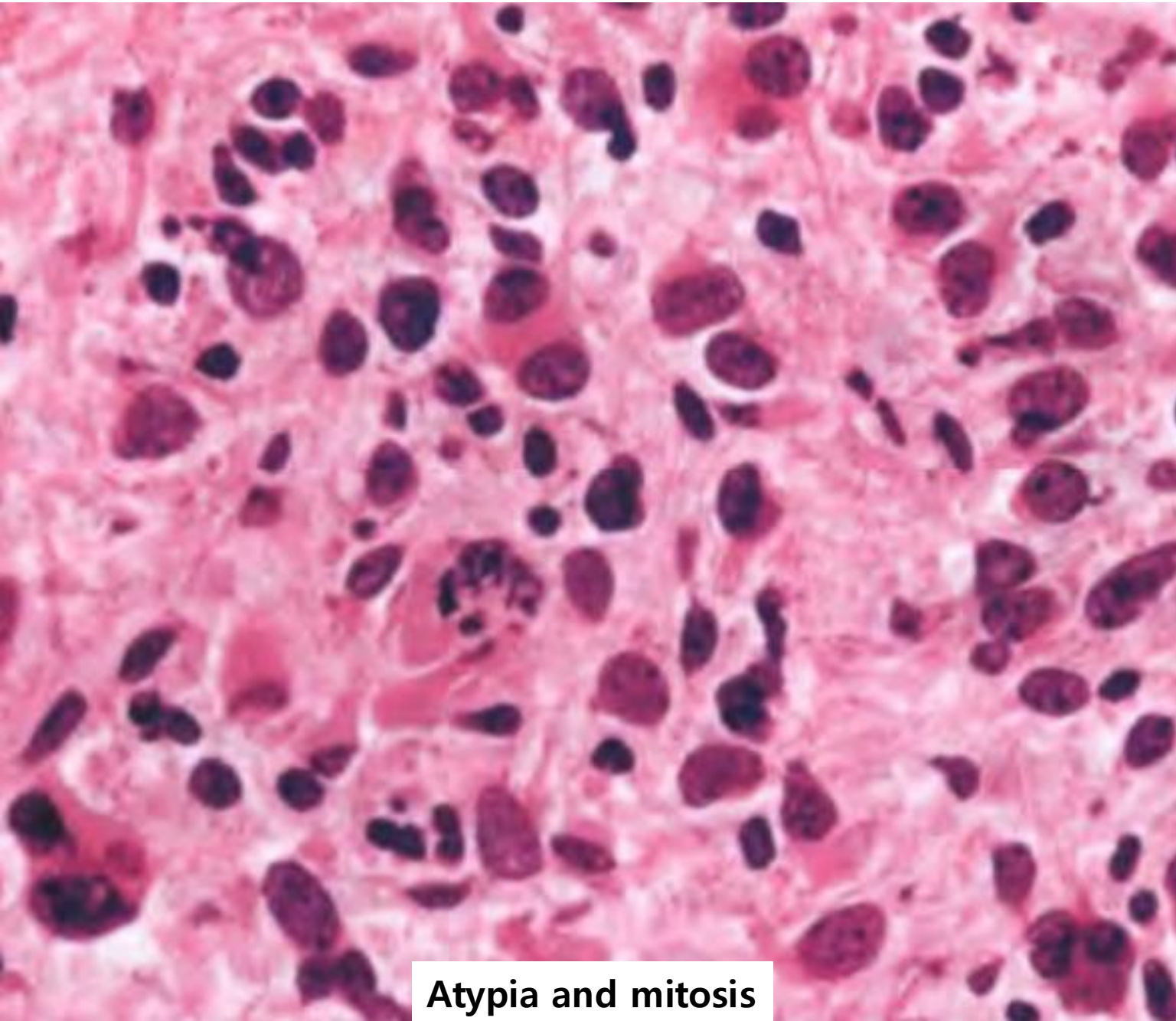
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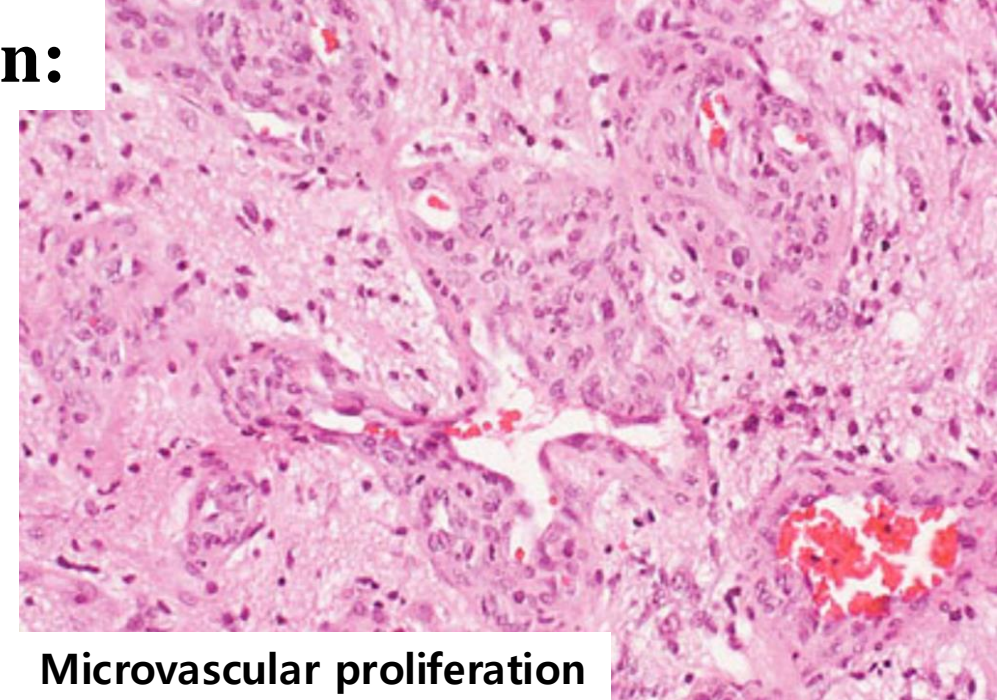
Histologic grading of CNS tumors



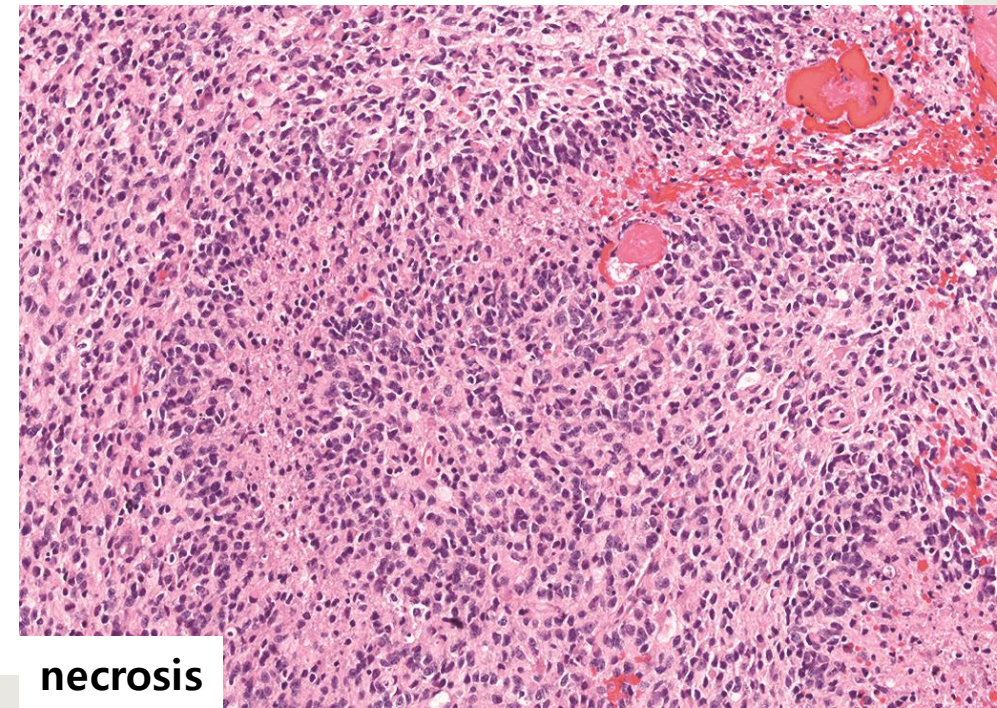
The histologic grading of CNS tumors depends on:



Atypia and mitosis



Microvascular proliferation



necrosis

- **Grade 1 lesions:**

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

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.

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

- **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, IDH-wildtype, medulloblastoma, pineoblastoma, and most embryonal neoplasms

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

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)
 - **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



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 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.

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
- IDH2 mutation: R172K is the most frequent IDH2 mutation

- ✓ 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 co-deleted 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.

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-codeleted

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

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 Diffuse midline 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

CNS tumors

GLIOMA, NEURONAL AND GLIONEURONAL TUMORS

adult type
diffuse
glioma

pediatric type
diffuse low grade
glioma

Pediatric type
high grade
glioma

Circumscribed
astrocytic
gliomas

Glioneuronal
and neuronal
tumors

Ependymoma

EMBRYONAL (primitive) TUMORS

MEDULLOBLASTOMA

OTHER PARENCHYMAL TUMORS

PRIMARY CNS
LYMPHOMA

MENINGIOMA

METASTATIC TUMORS

lung, breast, skin
(melanoma), kidney,
and colon

GLIOMA



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graph TD; A[GLIOMA] --> B[Adult type diffuse glioma]; A --> C[Pediatric type glioma]; B --> D[Astrocytoma, IDH- mutant (grade 2,3,4)]; B --> E[glioblastoma, IDH-wild- type, grade 4]; B --> F[Oligodendroglioma, IDH- mutant and 1p/19q- codeleted, grade 2 or 3]; C --> G[circumscribed]; C --> H[Diffuse]; H --> I[low grade]; H --> J[high grade]
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The diagram is a hierarchical flowchart classifying gliomas. At the top is the root node 'GLIOMA'. It branches into two main categories: 'Adult type diffuse glioma' and 'Pediatric type glioma'. 'Adult type diffuse glioma' further branches into three subtypes: 'Astrocytoma, IDH- mutant (grade 2,3,4)', 'glioblastoma, IDH-wild- type, grade 4', and 'Oligodendroglioma, IDH- mutant and 1p/19q- codeleted, grade 2 or 3'. 'Pediatric type glioma' branches into 'circumscribed' and 'Diffuse'. 'Diffuse' further branches into 'low grade' and 'high grade'. All nodes are contained within light blue rounded rectangular boxes with dark blue borders, connected by thin black lines. The background is a blurred image of a person's hand holding a wooden block.

Adult type diffuse glioma

Astrocytoma,
IDH- mutant
(grade 2,3,4)

glioblastoma,
IDH-wild- type,
grade 4

Oligodendroglioma, IDH-
mutant and 1p/19q-
codeleted, grade 2 or 3

Pediatric type glioma

circumscribed

Diffuse

low
grade

high
grade

The image is a composite of four histological micrographs. The top-left panel shows a high-magnification view of tumor cells with large, dark, hyperchromatic nuclei and some prominent nucleoli. The top-right panel shows a lower magnification view of the tumor tissue, featuring a dense population of cells and a prominent area of hemorrhage (red) within a cystic or necrotic space. The bottom-left panel shows a high-magnification view of cells with smaller, more uniform nuclei. The bottom-right panel shows a high-magnification view of cells with large, pale, foamy or vacuolated cytoplasm, characteristic of xanthoma cells or foamy macrophages. A yellow banner with black text is overlaid across the center of the image.

Astrocytoma, IDH- mutant

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

- **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

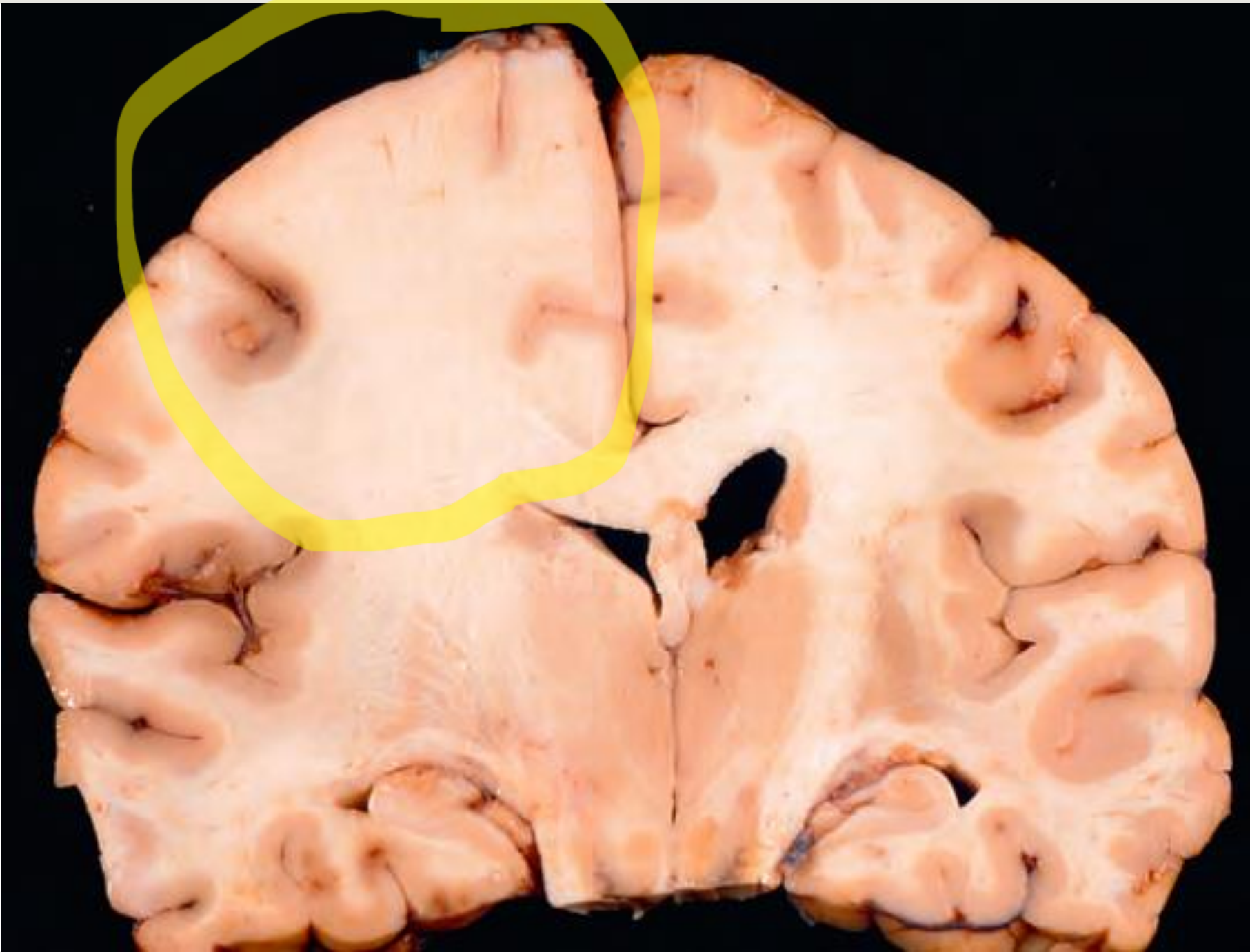
Morphology, macroscopic:

Grade 2 &3:

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

Grade 4:

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



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

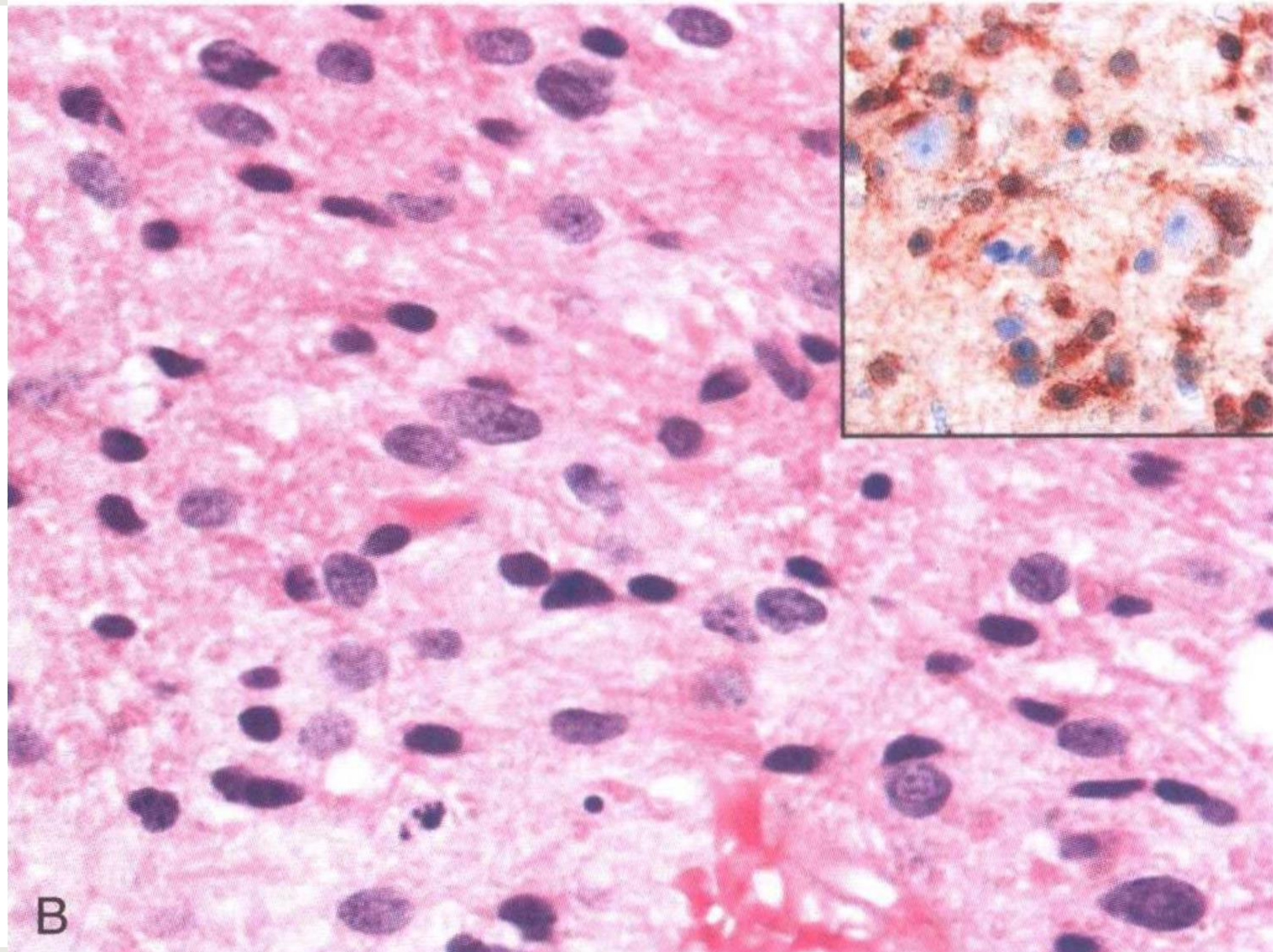
- The transition between neoplastic and normal tissue is indistinct
- tumor cells infiltrate normal tissue many centimeters from the main lesion.
- **Hypercellular** (compared to normal white matter): mild to moderate increase in the number of glial cell nuclei.
- **Cytologic atypia:**
 - mild
 - enlarged, elongated or irregular hyperchromatic nuclei
 - No prominent atypia

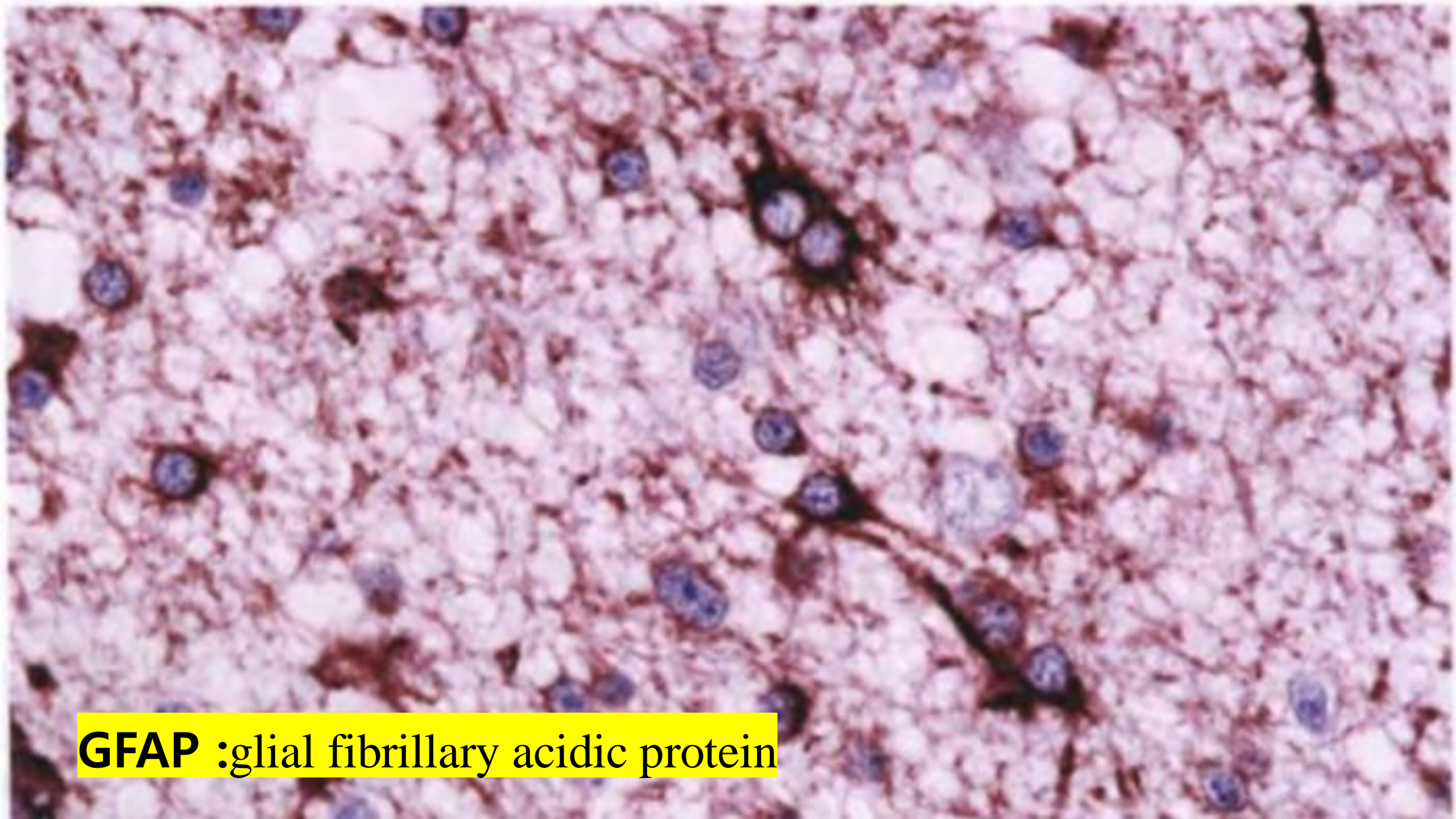
+ **fibrillary background** made of a network of fine astrocytic cell processes

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

Enlarged irregular
nuclei embedded
within fibrillar matrix
of the brain

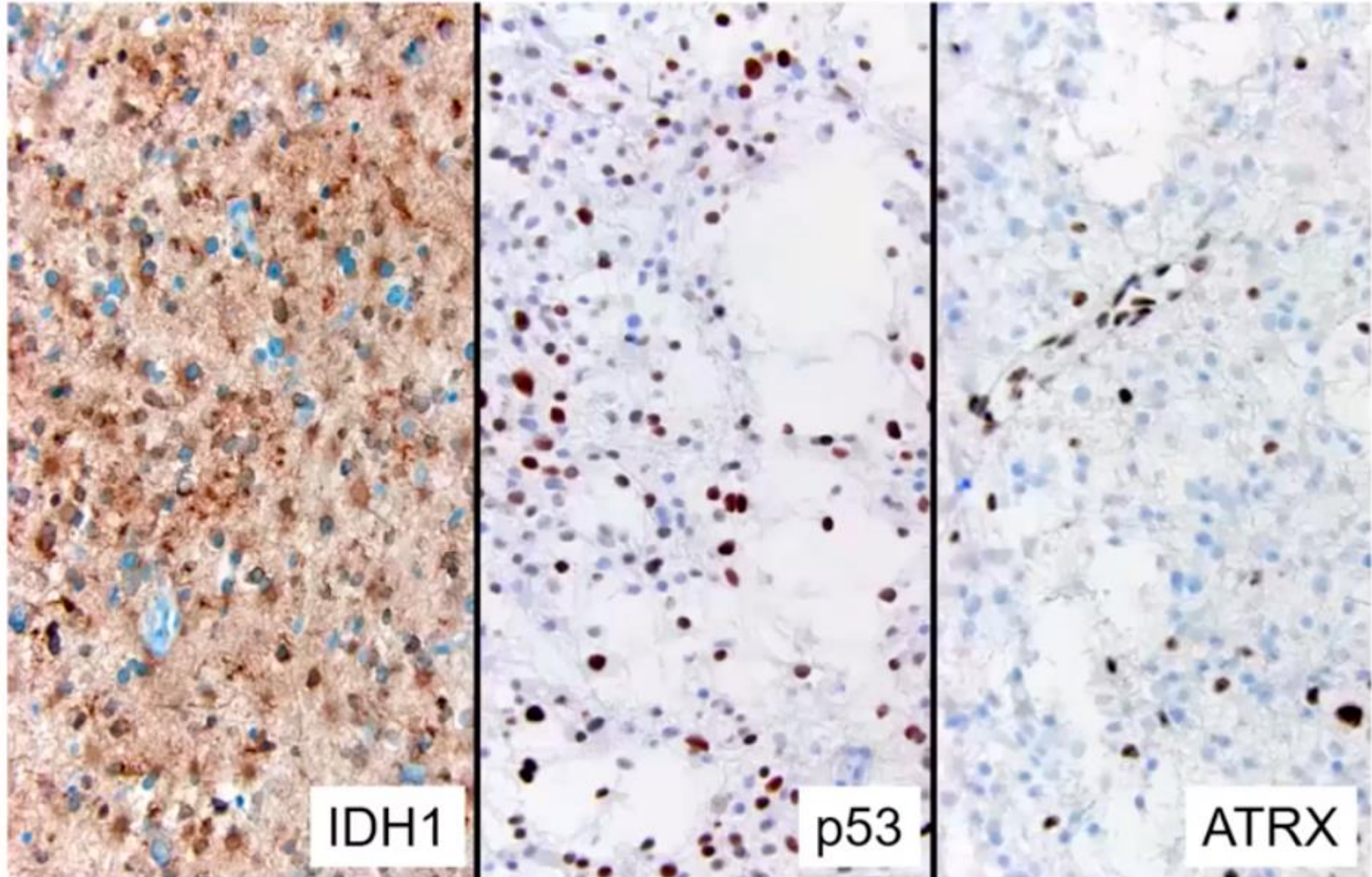
Inset: IDH1 immune
stain is positive in
tumor cells

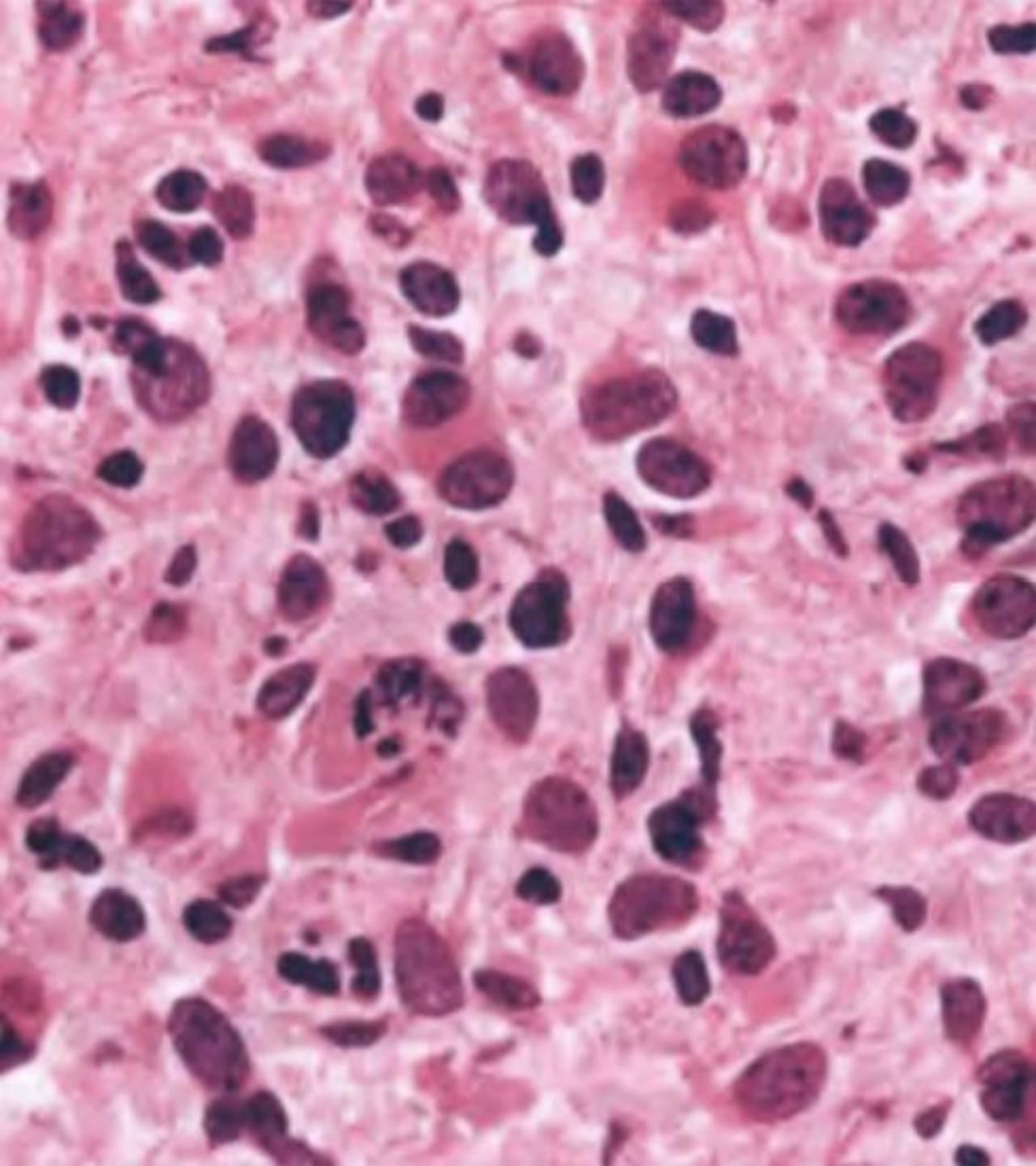




GFAP :glial fibrillary acidic protein

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





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)**.

