Pathology of tumors of the central nervous system

Preetha Nair

Asst Pathologist

ACTREC & Tata memorial hospital

Plan of Discussion…

- *WHO classification -*
- *Diagnostic tools -*
- *Glioma - grading*
  - *Astrocytoma*
  - *Oligodendroglioma*
  - *Ependymoma*
- *Embryonal-*
  - *Medulloblastoma*
- *Meningioma*

General Considerations…

Primary *– children*
50% infiltrative

Metastatic *– Adults*
well-demarcated

- *Prognosis-*
  - *Tumor factors*
    - *Histologic type & grade*
    - *IHC- proliferation markers & molecular parameters*
  - *Patient factors*
    - *Age/ status*
    - *Tumor site- Limited space, Vital structures*
- *Rare: extra neural metastasis*

Types of Brain Tumors

- *Meninges: meningioma, hemangiopericytoma*
- *Glia: astrocytoma, oligodendroglioma, ependymoma, choroid plexus tumors*
- *Primitive cells: neuroblastoma, germinoma, medulloblastoma, pineoblastoma, retinoblastoma*
- *Neuronal: ganglioglioma, gangliocytoma*
- *Pituitary: adenoma, craniopharyngioma*
- *Nerves: schwannoma, neurofibroma, MPNST*

WHO classification [2000]

I] NEUROEPITHELIAL

- *Astrocytic*
  - **Diffuse-** *Fibrillary/ Protoplasmic/ Gemistocytic [II]*
  - *Anaplastic Astrocytoma [III]*
  - *GBM [IV]*
  - *PA [I]/ SEGA [I]/ PXA [II]*
- *Oligodendroglial: Oligodendroglioma [II]/ anapl. [III]*
- *Mixed glioma- OA [II]/ anaplastic OA [III]*

WHO classification [2000]

I] NEUROEPITHELIAL contd/-

- *Ependymal*
  - *Ependymoma & variants [II]/ anaplastic [III]*
  - *Myxopapillary E [II]/ Subependymoma [I]*
- *Glial tumors of uncertain origin- A' blastoma, Gl. cerebri, chordoid glioma of III ventricle*
- *Neuronal & mixed glial neuronal*
  - *Ganglioglioma/ G. cytoma/ DIGG/ DIA/ DNET/ CN*

WHO classification [2000]

I] NEUROEPITHELIAL *contd/-*

- Neuroblastic- Olf Nb/ N.epithelioma
- Pineal parenchymal tumors
  - P.cytoma/ P.blastoma/ PPTI
- Embryonal tumors
  - Medulloepithelioma/ Ependymoblastoma
  - Medulloblastoma/ ST- PNET/ ATRT

WHO classification [2000]

II] TUMORS OF MENINGES

- Meningothelial- Meningiomas
- Non – meningothelial - Mesenchymal

III] LYMPHOMA/ HEMOPOEITIC TUMORS

- Lymphoma/ Plasmacytoma/ Granulocytic sarcoma / HD

IV] GERM CELL TUMORS- germinoma/ EC/ YST

WHO classification [2000]

V] TUMORS OF SELLAR REGION-

- *Craniopharyngioma/ Granular cell tumor*

VI] TUMORS OF PERIPHERAL NERVES

- ***Schwannoma/ NF/ Perineurioma/ MPNST***

VII] METASTATIC

Diagnostic Tools: Histologic typing

Tumor	Microscopic
Astrocytoma	Fibrillary background; different cell types
Glioblastoma	Pseudopalisaded necrosis; microvascular proliferation (MVP)
Oligodendroglioma	Mosaic/ poached-egg appearance
Ependymoma	Perivascular pseudorosettes
Medulloblastoma	undifferentiated round cells; rosettes (Homer-Wright)
Meningioma	Whorls and psammoma bodies

Diagnostic Tools- Immunohistochemistry

- Glial: GFAP
  - Astrocytic / oligodendroglial / ependymal
- Neuronal: Synaptophysin / chromogranin / NSE
- Vascular: CD34, CD 31
- Epithelial markers- EMA, CK
- Proliferation marker- Mib-1 (Ki-67) labeling index

Special stains - Reticulin / PTAH / PAS

Molecular markers - 1p 19q del- FISH

EM: Ependymoma/ meningioma

GLIOMA

BIOLOGICALLY -

- ***Diffuse***
  - *Young adults, cerebral hemisphere and brainstem*
  - *Astrocytoma II - IV Oligodendroglioma*
- ***Circumscribed***
  - *Children, characteristic location/ morphology)*
  - *PA/ PXA/ SEGA/ Ependymoma*
- *No vascular changes*
  - *BBB intact*
  - *no edema / enhancement*

GRADING

- *Nuclear atypia,*
- *Mitotic activity*
- *Necrosis (sign of uncontrolled growth)*
- *Vascular changes (tumor neovascularity; microvascular poliferation- MVP)*

- *4tiered system-*
- *GRADE I* - "Low-Grade" - *Surgery curative*
- *GRADE II* - nuclear pleomorphism
  - *Surgery mainstay of treatment*
  - *RT for incomplete resection*

GRADING...

- *GRADE III* - *ANAPLASTIC*, + mitoses
  - *Surgery for HPR & debulking + RT +/- CT*

- *GRADE IV* - *MALIGNANT*, + 'vascularity'/ MVP +/- necrosis: Glioblastoma multiforme
  - *Surgery for debulking + RT + CT (PCV/ Temozolamide)*

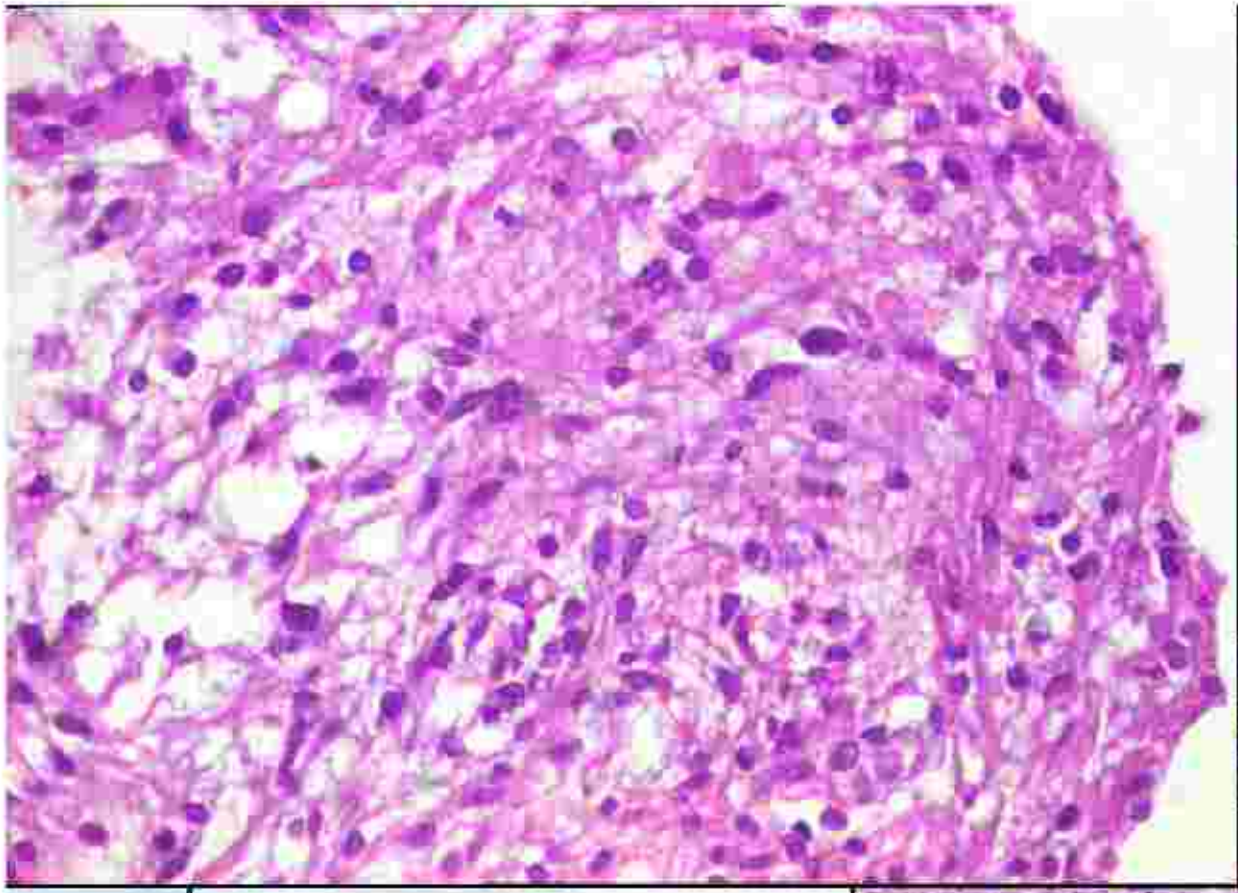
PILOCYTIC ASTROCYTOMA [WHO I]

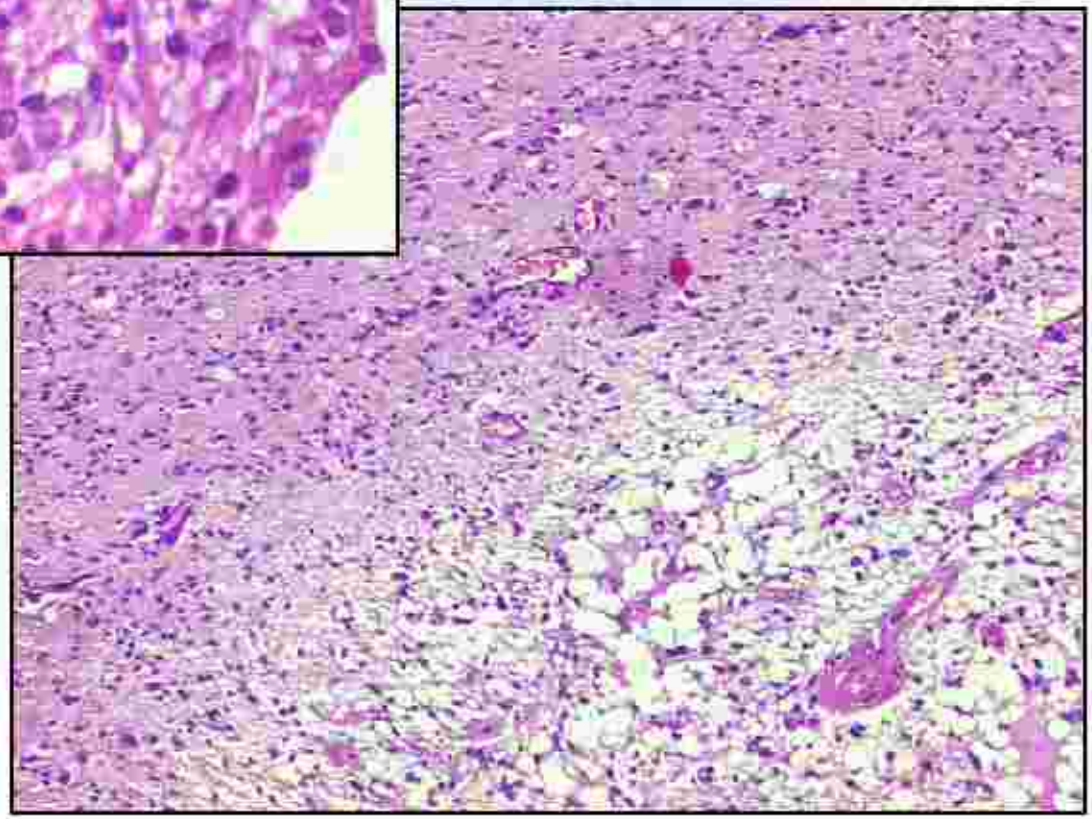
- *Cell of Origin: Astrocyte (bi-polar, hairlike)*
- *Associations: in ON (optic nerve) w/ NF-1*
- *Location: Cerebellum (85%), Cerebral hemisphere (10%), Chiasm/ Hypothal, Optic Nerve, Cx spinal cord*
- *Circumscribed – Enhancing;*
- *Cyst with a mural nodule*
- *Treatment: Surgery, patience (radiation and chemotherapy uncommon)*

Pathology

- *Biphasic pattern-*
  - ***dense pilocytic glia***
    - *Rosenthal fibers: Dense, eosinophilic fibers (intermediate filaments)within cytoplasmic processes of astrocytes*
  - ***loose microcystic areas with EGB***
- ***Abnormal capillaries- pericystic MVP***
- ***+/- necrosis, occasional mitosis***
- ***Degenerative nuclear changes***
- **Low grade**
- ***Mib1 LI > 2%- ↑risk of recurrence***

PILOCYTIC ASTROCYTOMA





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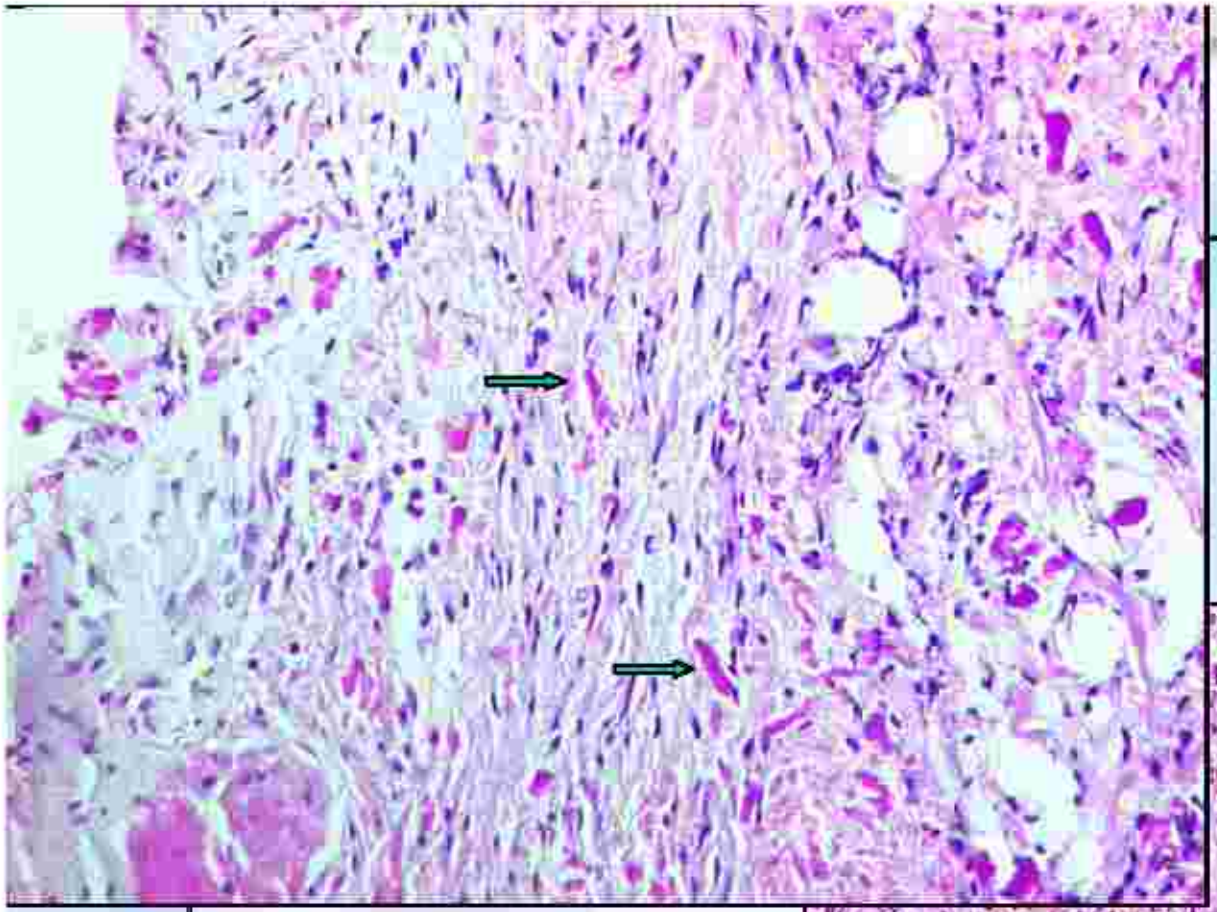
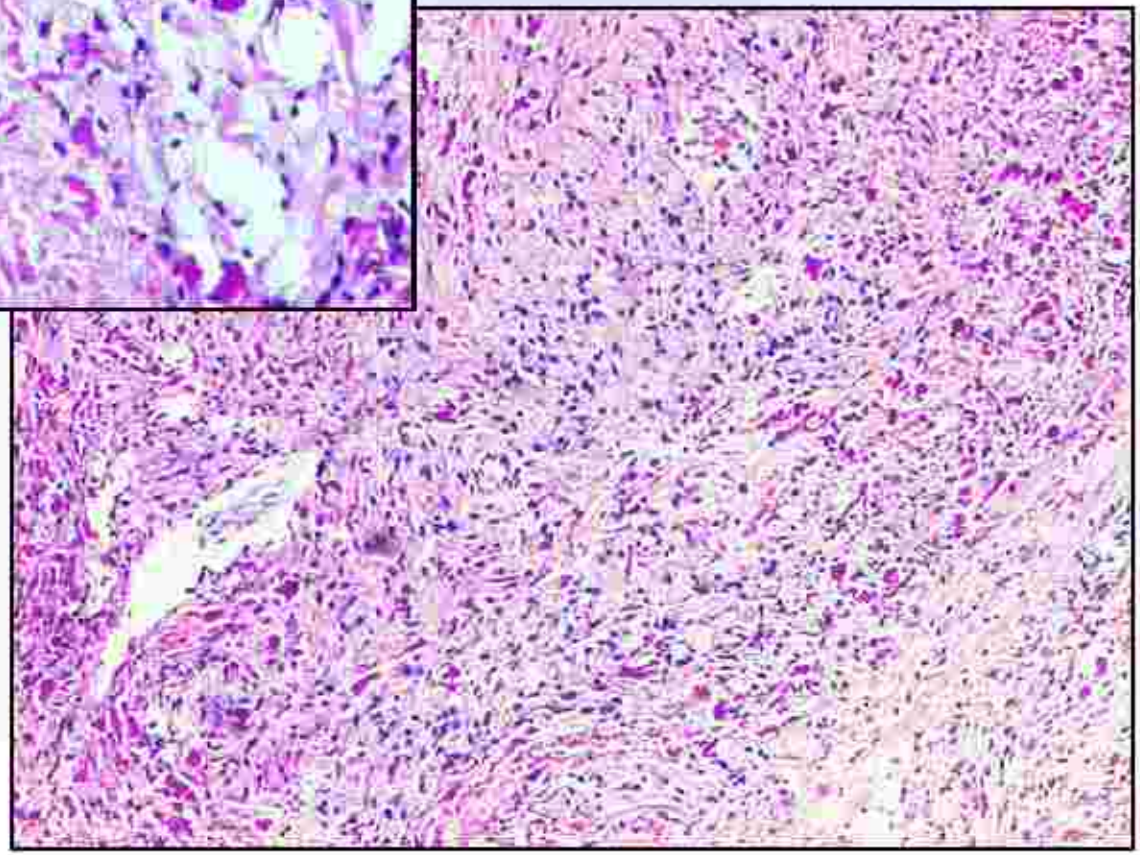


ROSENTHAL FIBRES



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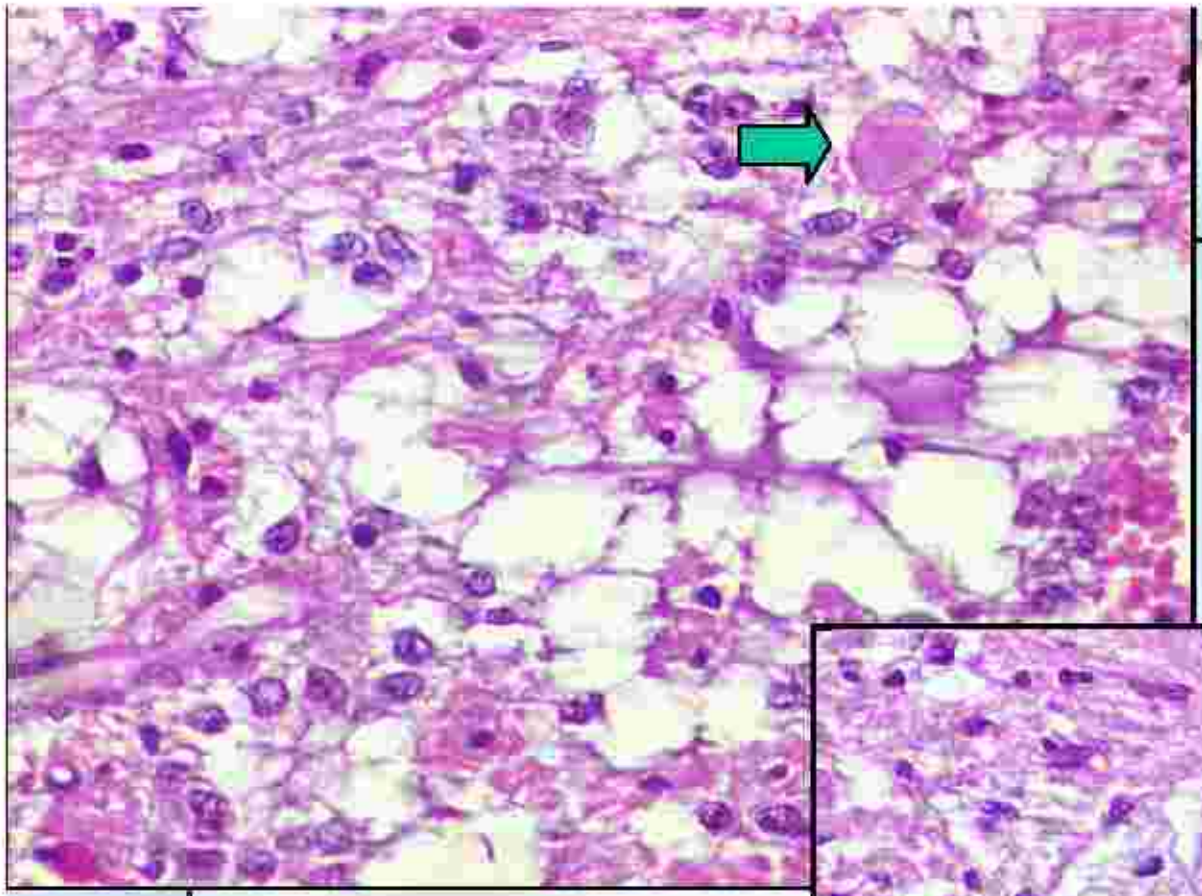
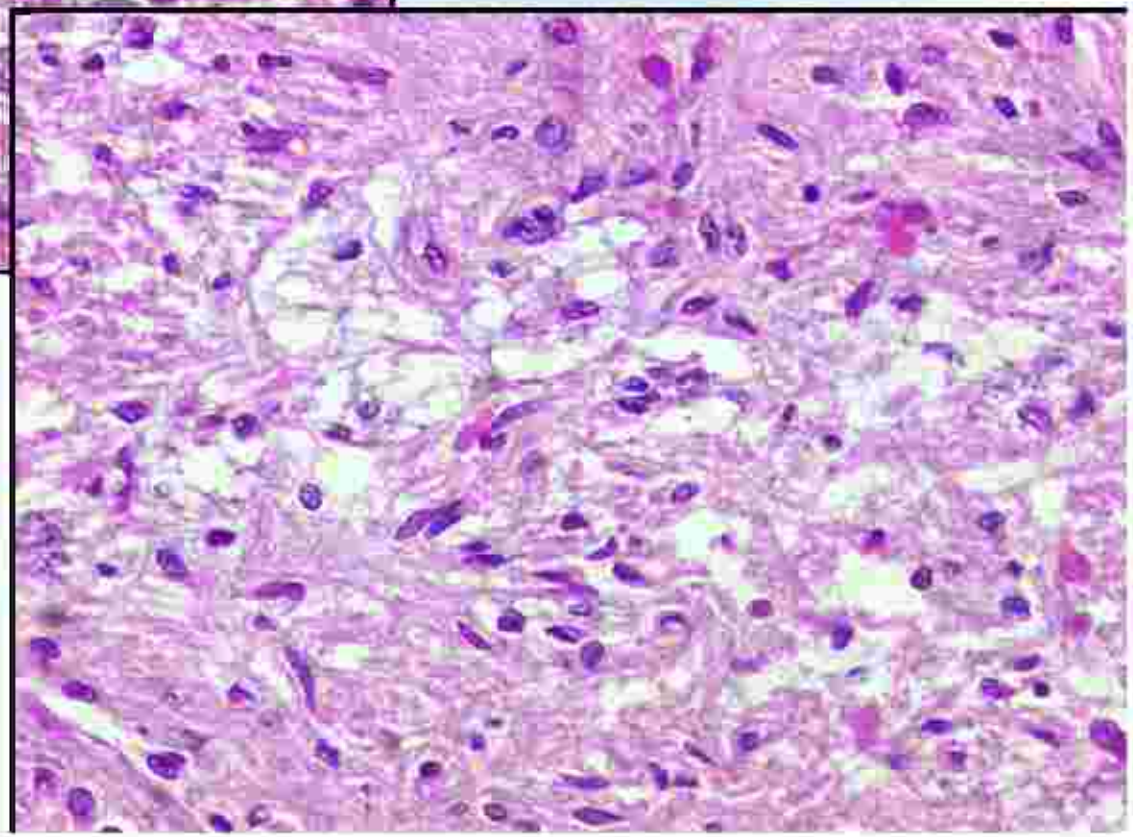


EGB



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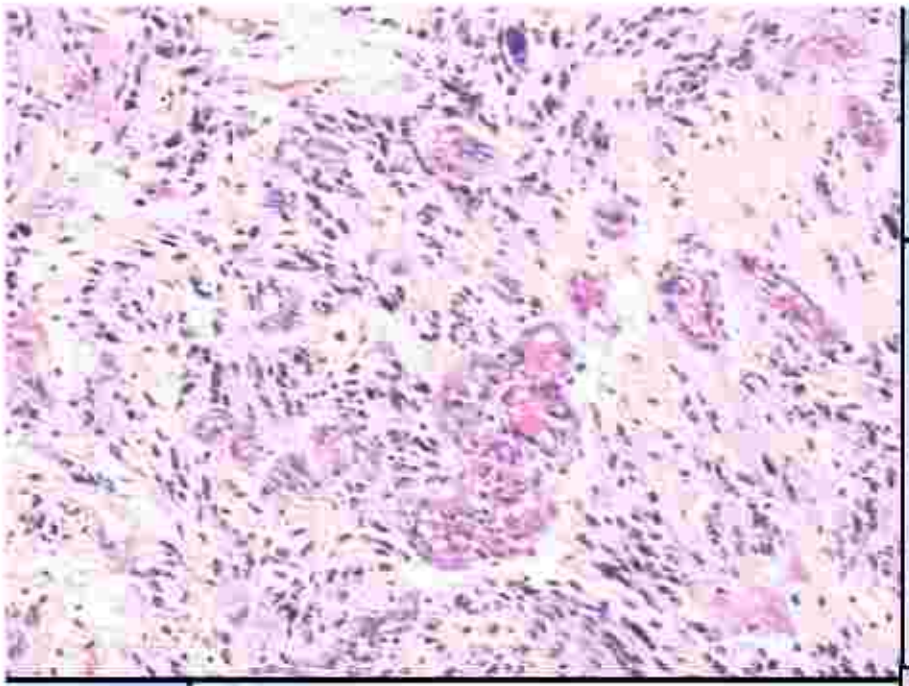
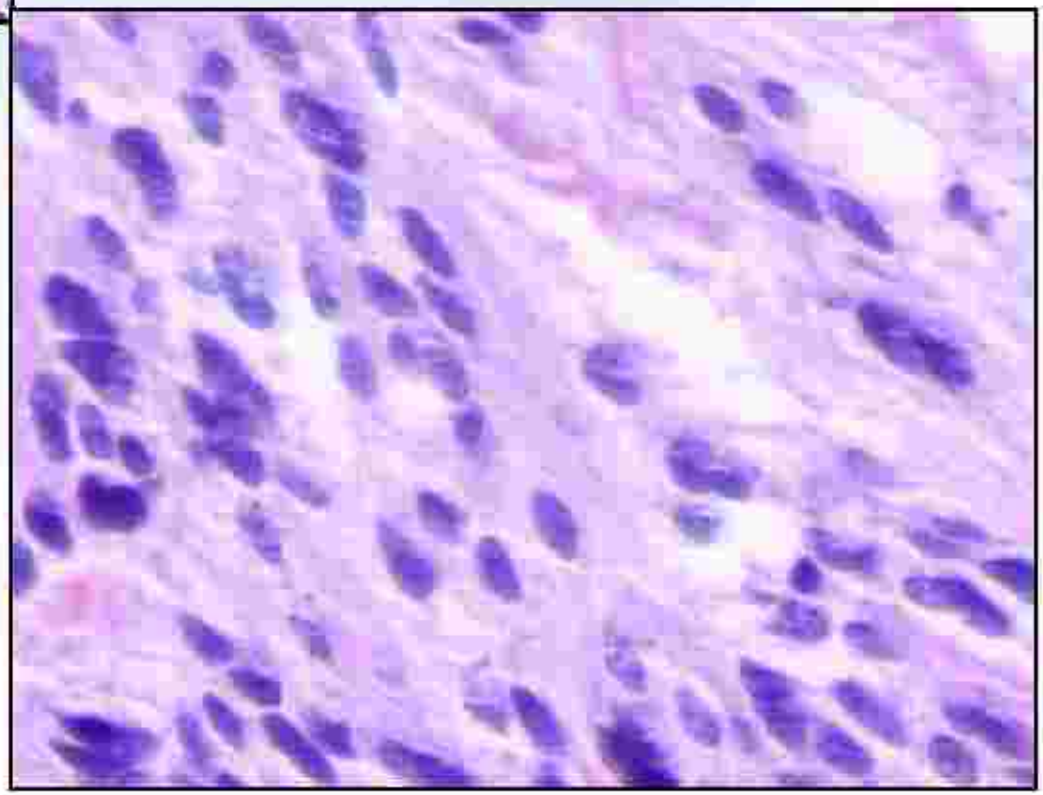


MVP

Degenerative nuclear atypia

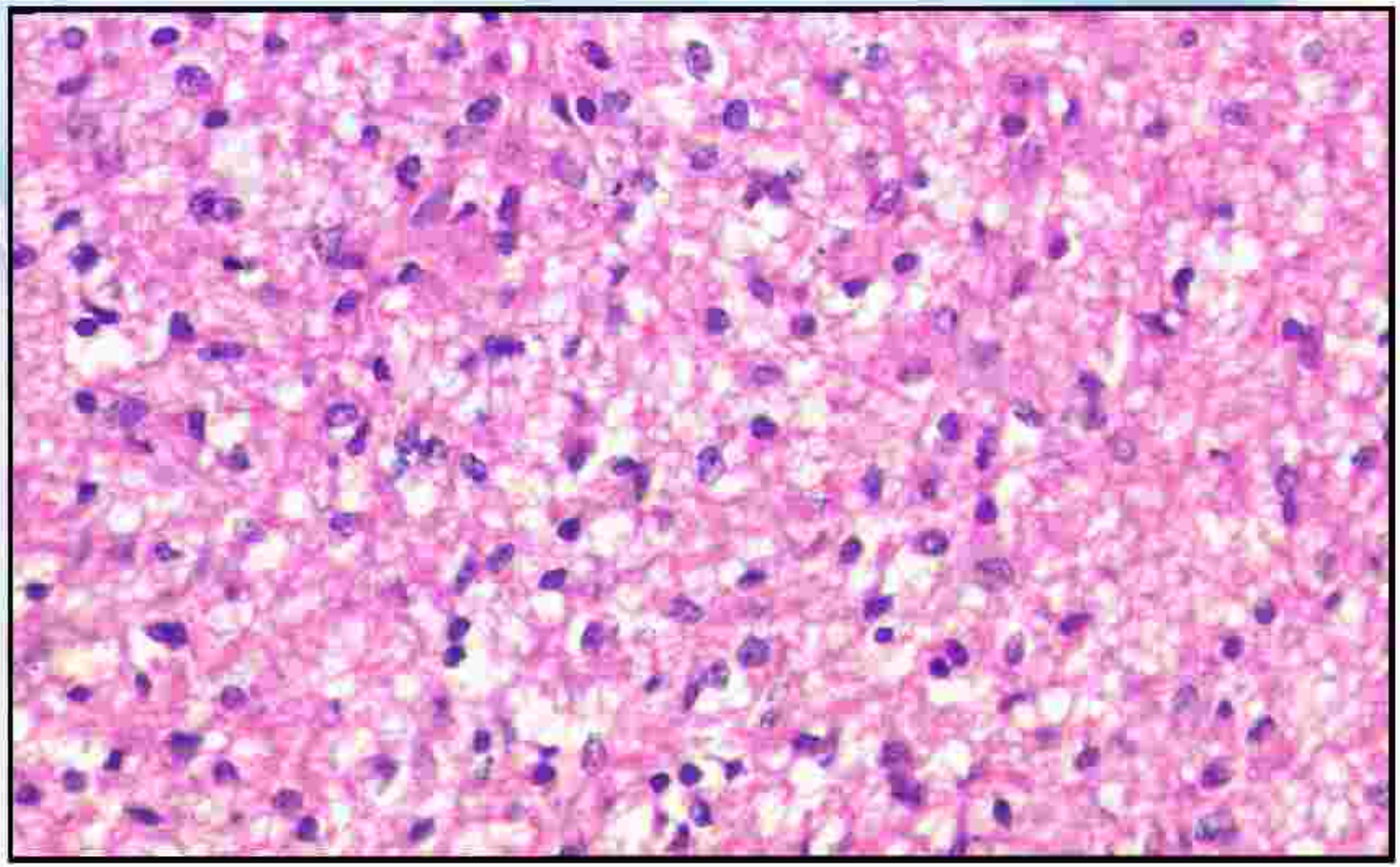


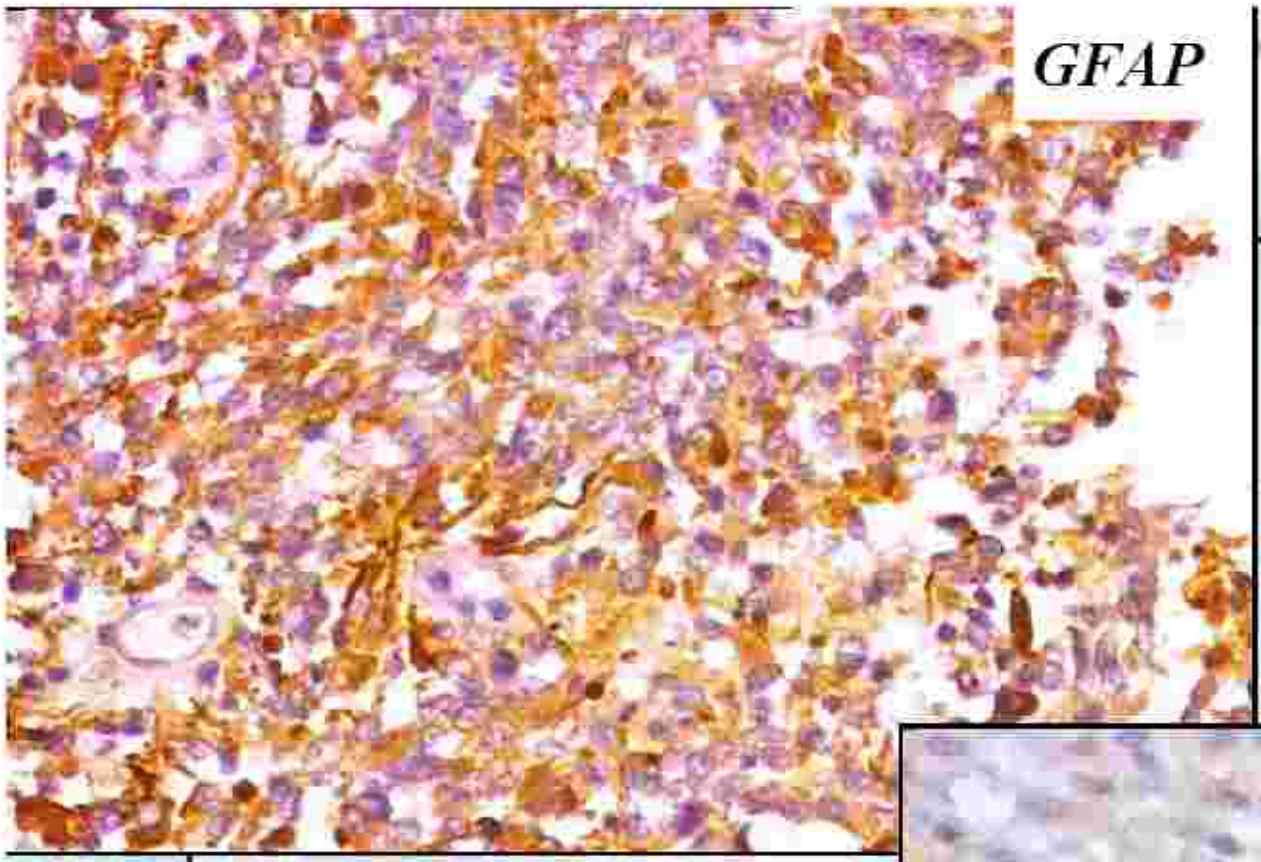
DIFFUSE ASTROCYTOMA WHO II

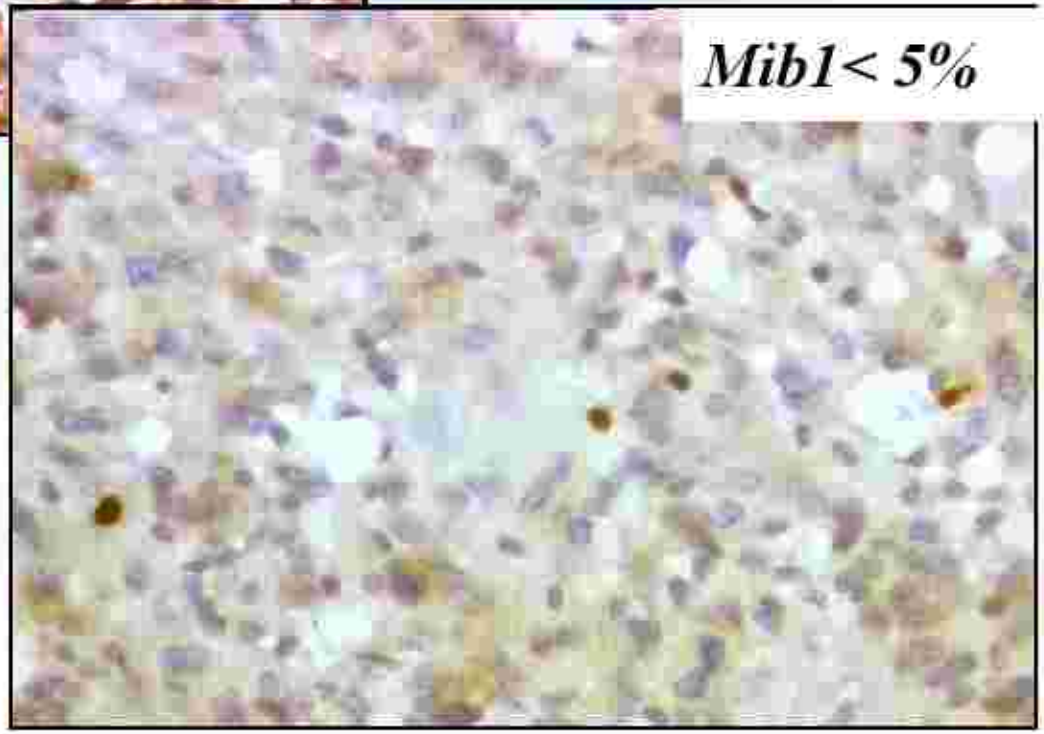
- *(Fibrillary, Protoplasmic, Gemistocytic)*
- *"Adult type" or "Hemispheric" Astrocytoma*
  Diffusely infiltrate brain irrespective of grade
- *continuum from low - grade to high - grade; progress over time*
  Grade 2 ☞ 3 ☞ 4 (GBM)
- *Imaging correlates with histology*

Fibrillary Astrocytoma

- *WHO grade II; Nuclear atypia +:* enlarged, irregular, hyperchromatic
- *No mitotic activity / necrosis/ MVP*







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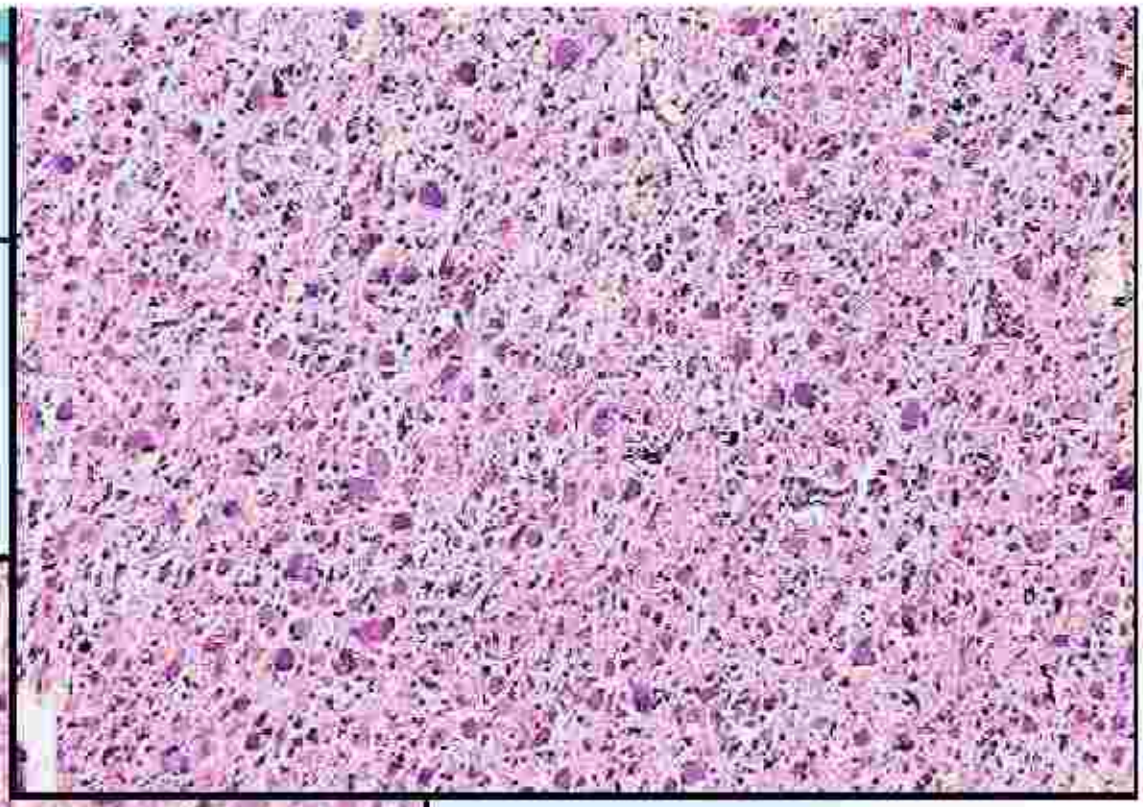
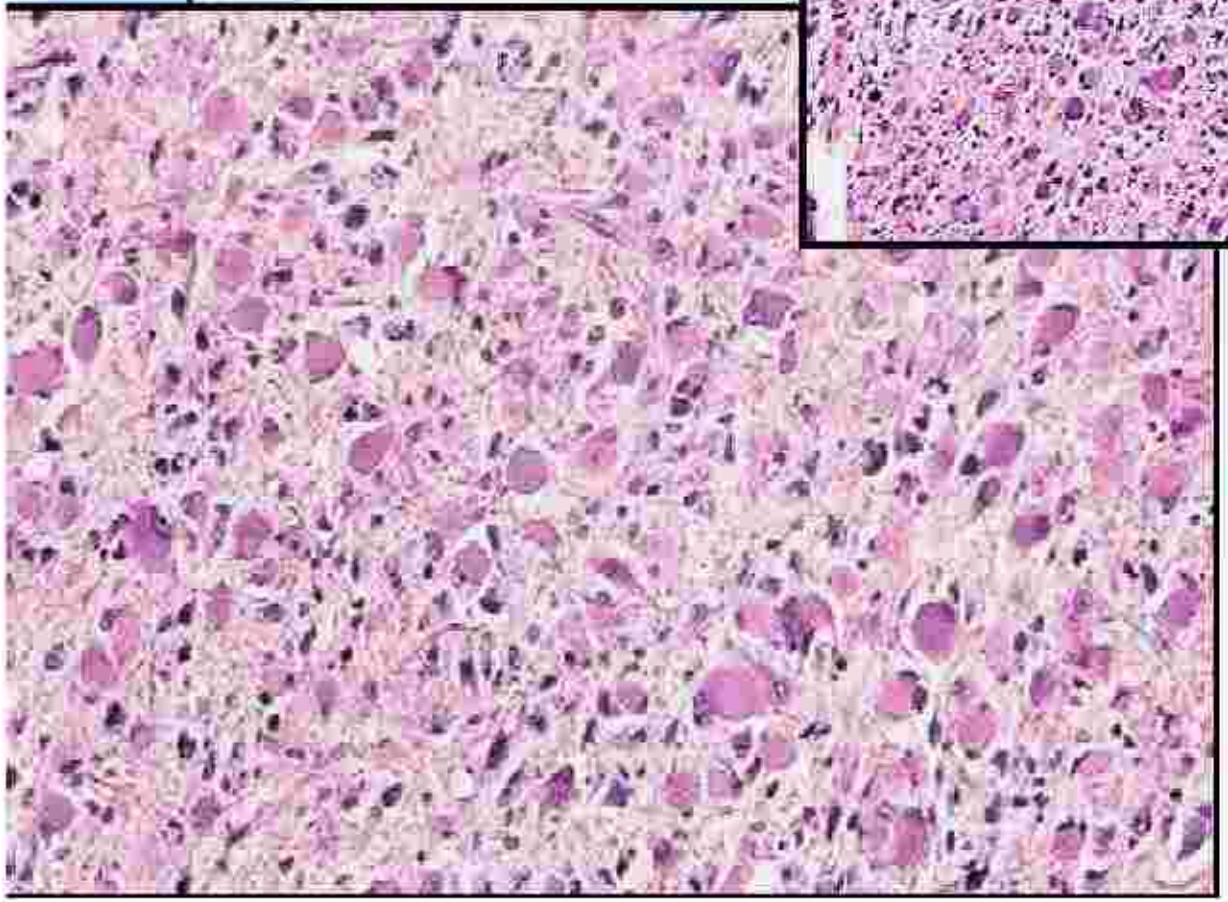
Gemistocytic Astrocytoma [II]





PROGRESSION

Astrocytoma II

Mib1> 6 %

p53 +

L- 9p, 19q, 11p; CDK4 amplifiicn
(4- 5 years)

Anaplastic Astrocytoma III

PTEN mutn, MDM2 amplificn,
EGFR amplification*

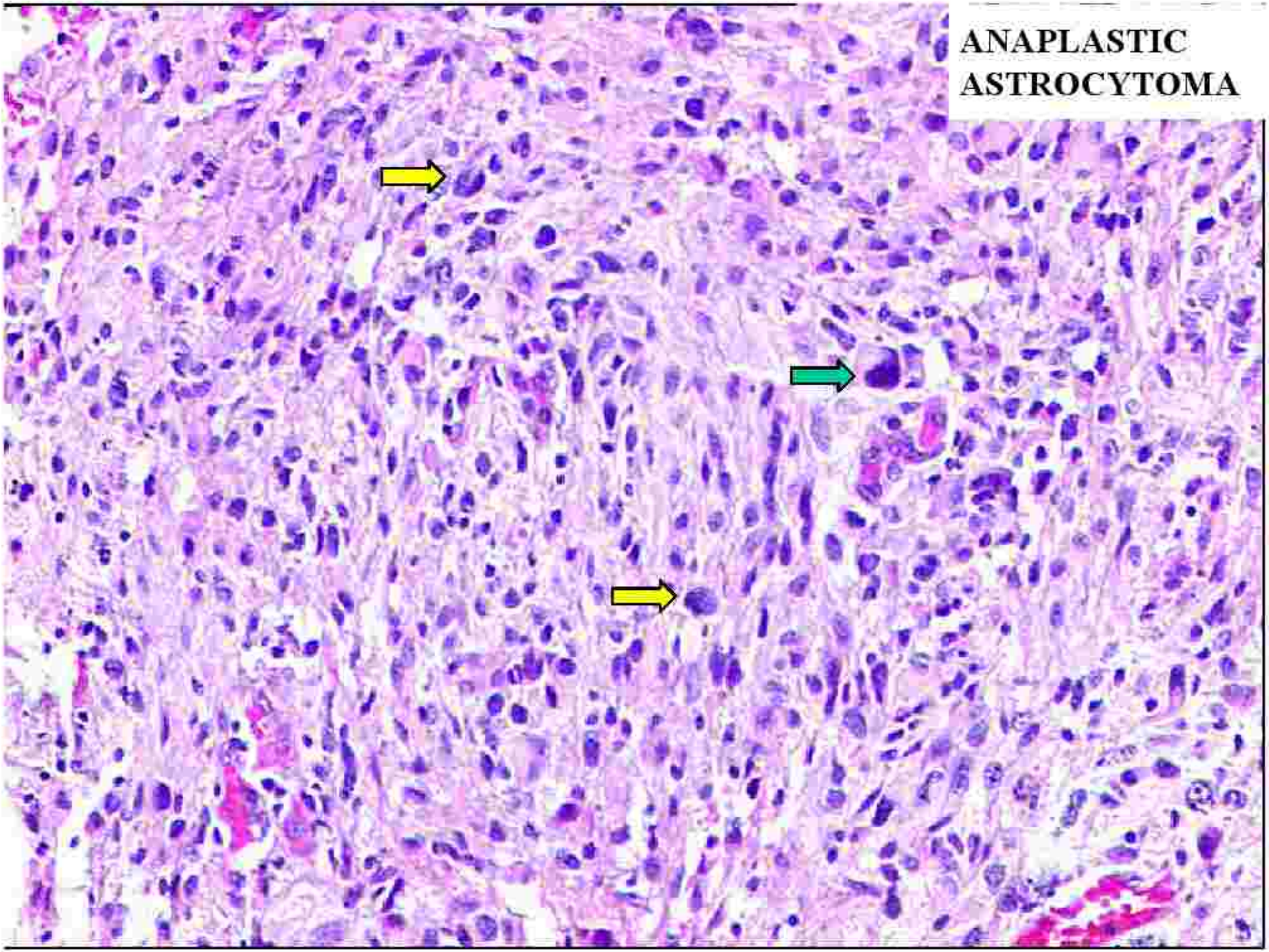
(< 2 years)

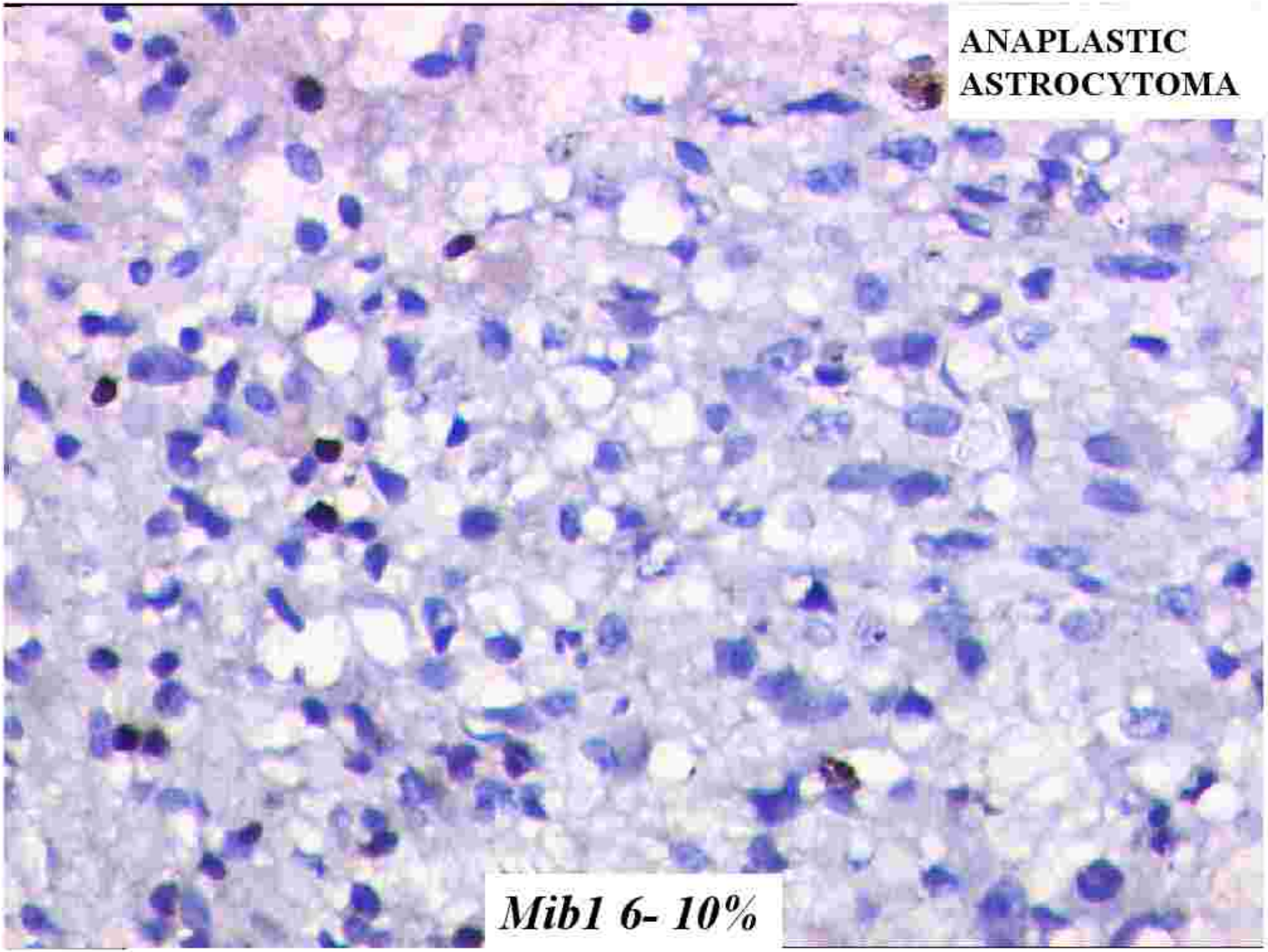
GBM (secondary); **young adults, BS in children**

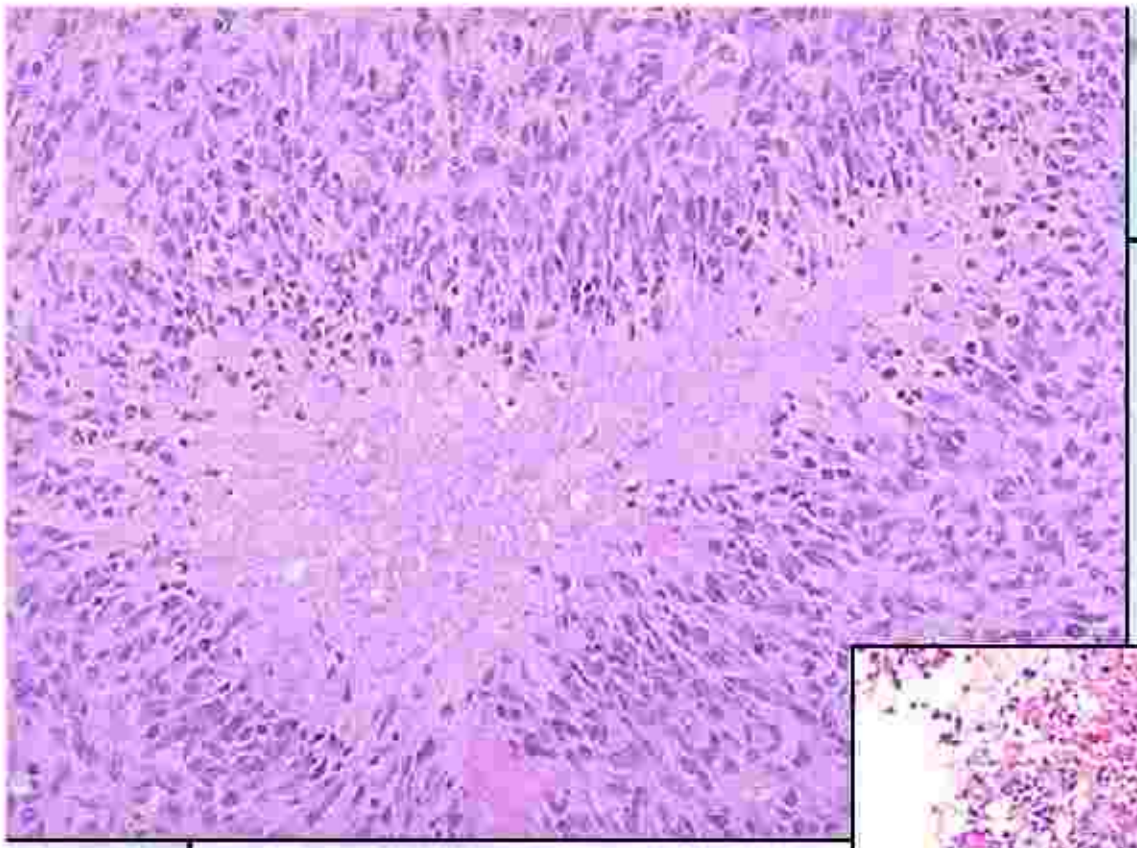
*** in Primary (de novo) GBM; older adults, rapid progression**

Prognostic factors

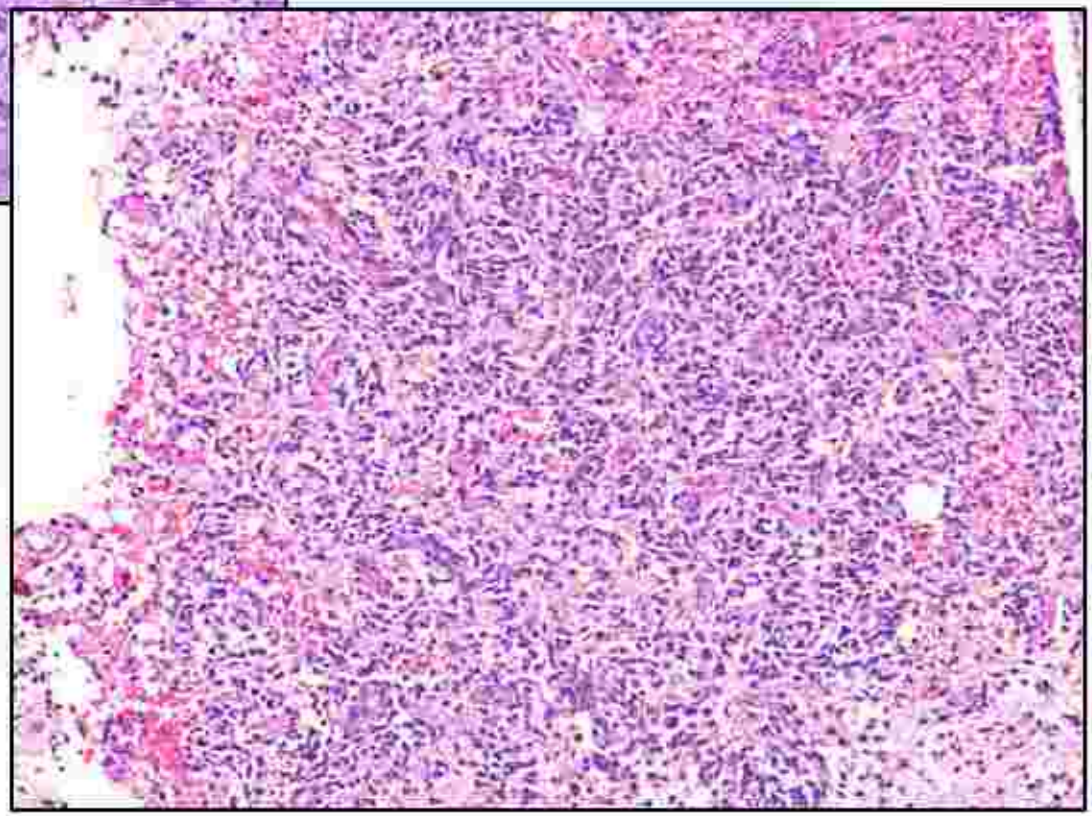
Good	Poor
Young	TP53 mutation
Gross total resection	Mib-1 > 5%
M/S	M/S
Microcysts	Gemistocytes ++
Perivascular lymphocytes	


ANAPLASTIC
ASTROCYTOMA

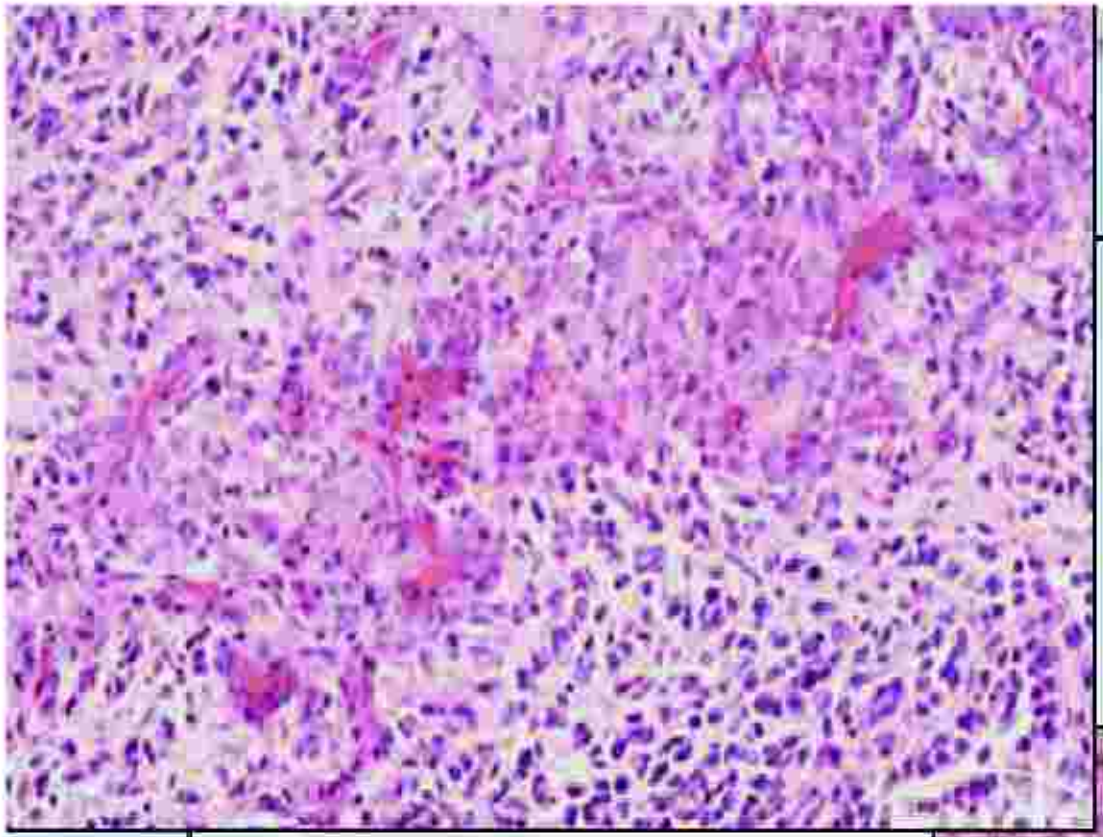

ANAPLASTIC
ASTROCYTOMA
Mib1 6- 10%



Pseudopalisaded necrosis

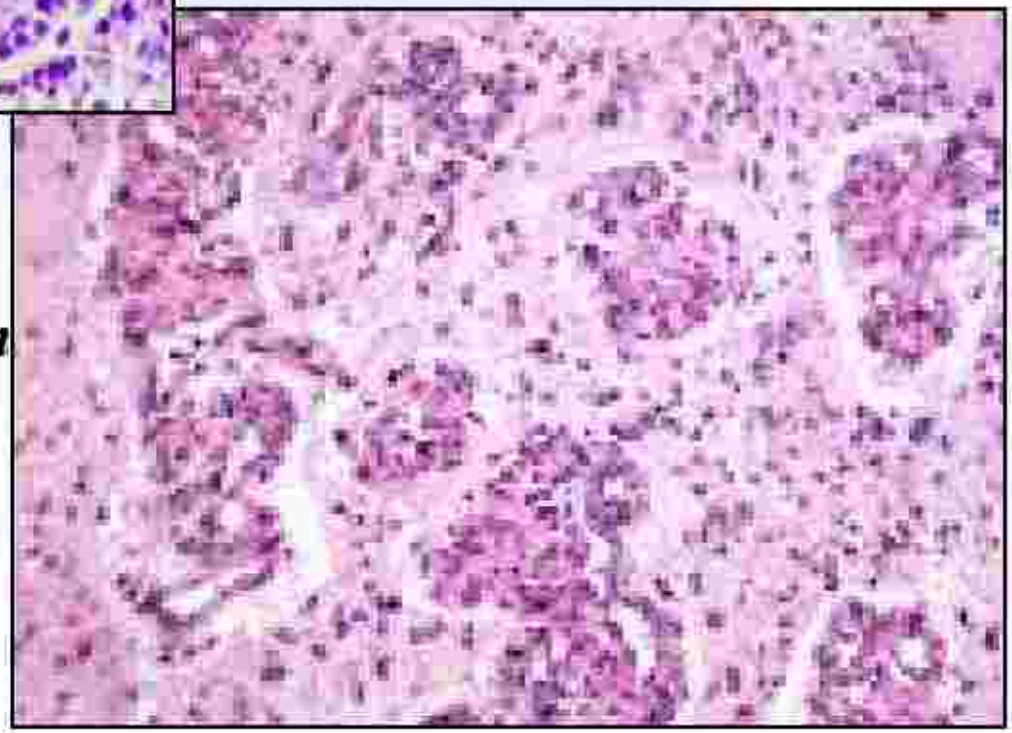


GLIOBLASTOMA MULTIFORME



GLIOBLASTOMA MULTIFORME

Microvascular proliferation



GLIOBLASTOMA MULTIFORME

Good

- < 50 years
- ↑ preop KPS
- Resection of enhancing tumor
- M/S:
  - Giant cell
  - Capillary MVP
  - Oligodendroglial component
- MGMT

Poor

- ↑↑ Mib1
- Glomeruloid MVP
- Molecular
  - *VEGF+
  - *EGFR+
  - *her2 amplificn
  - *PTEN/ Rb1 mutn

* *Stealth invasion' - hinders surgical disease control*

* *CT/ RT resistance*

- *MODES OF SPREAD*
  - *Natural passages*
  - *Along surfaces- leptomeningeal*
  - *Along tracts- corona radiata, peduncles, corpus callosum, anterior commissure, arcuate fibres*
  - *Across the meninges*

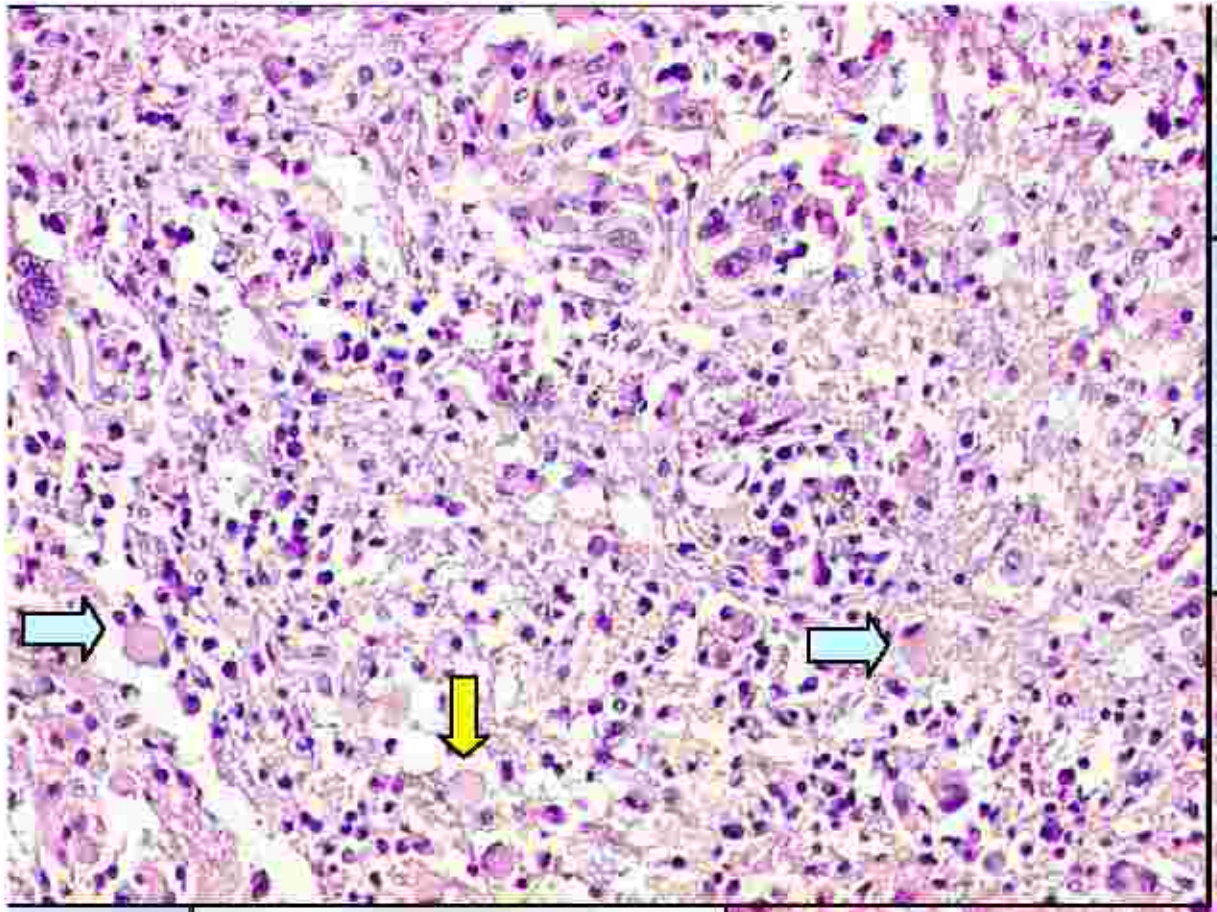
Pleomorphic Xanthoastrocytoma WHO II

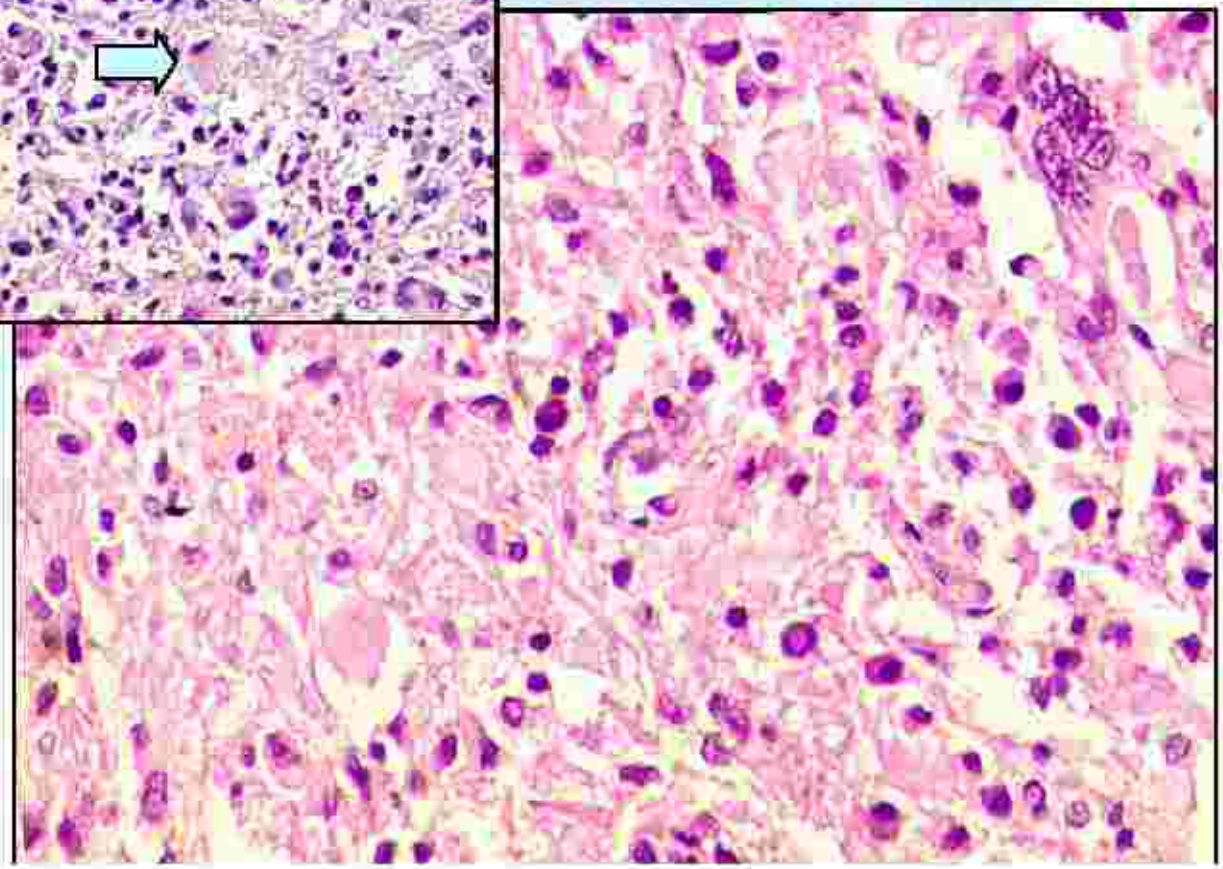
- *Meningocerebral*
- *Pleomorphic & foam cells*
- *EGB*
- *Pericellular reticulin*

Anaplastic PXA: III

- *Mitoses > 5 / 10 HPF*
- *+/- palisaded necrosis* ⇨ *D/D- GBM*

PXA [II]





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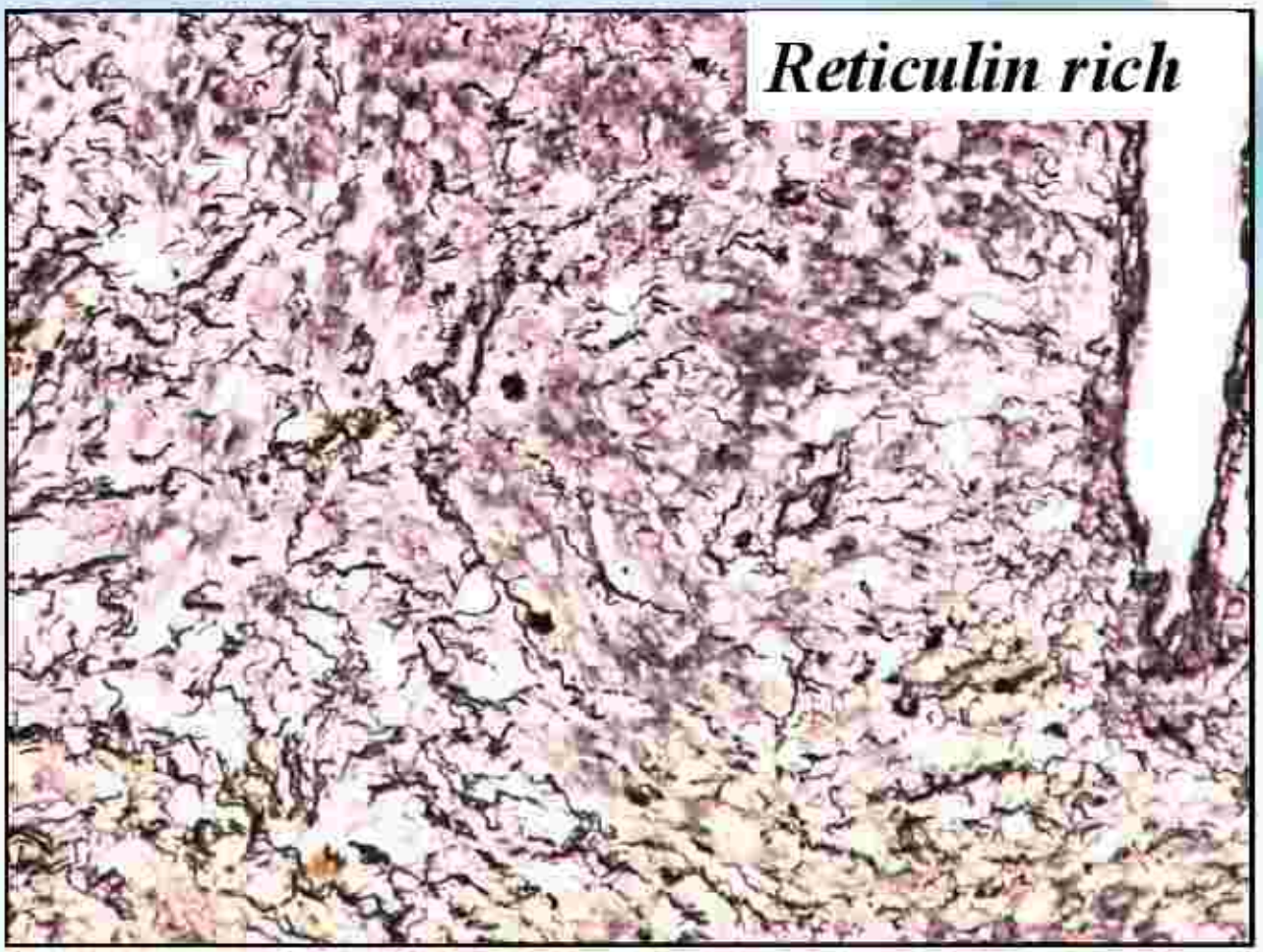
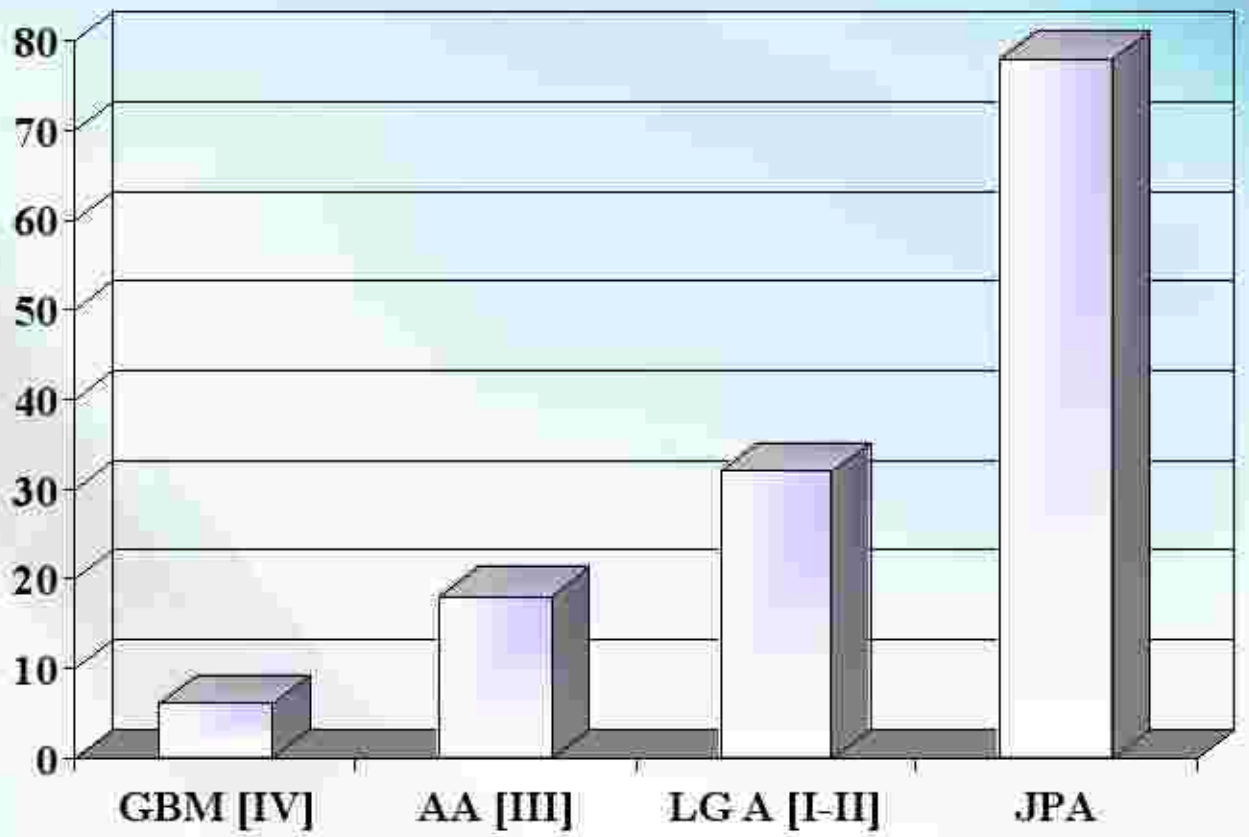
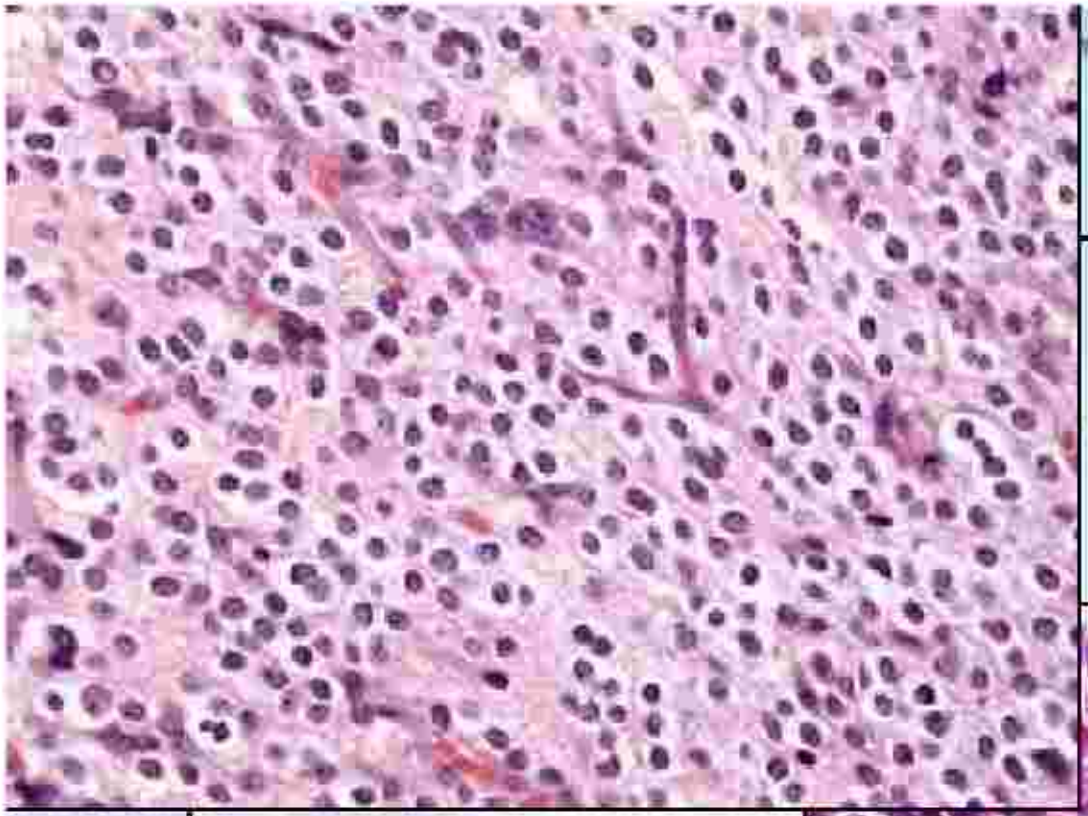


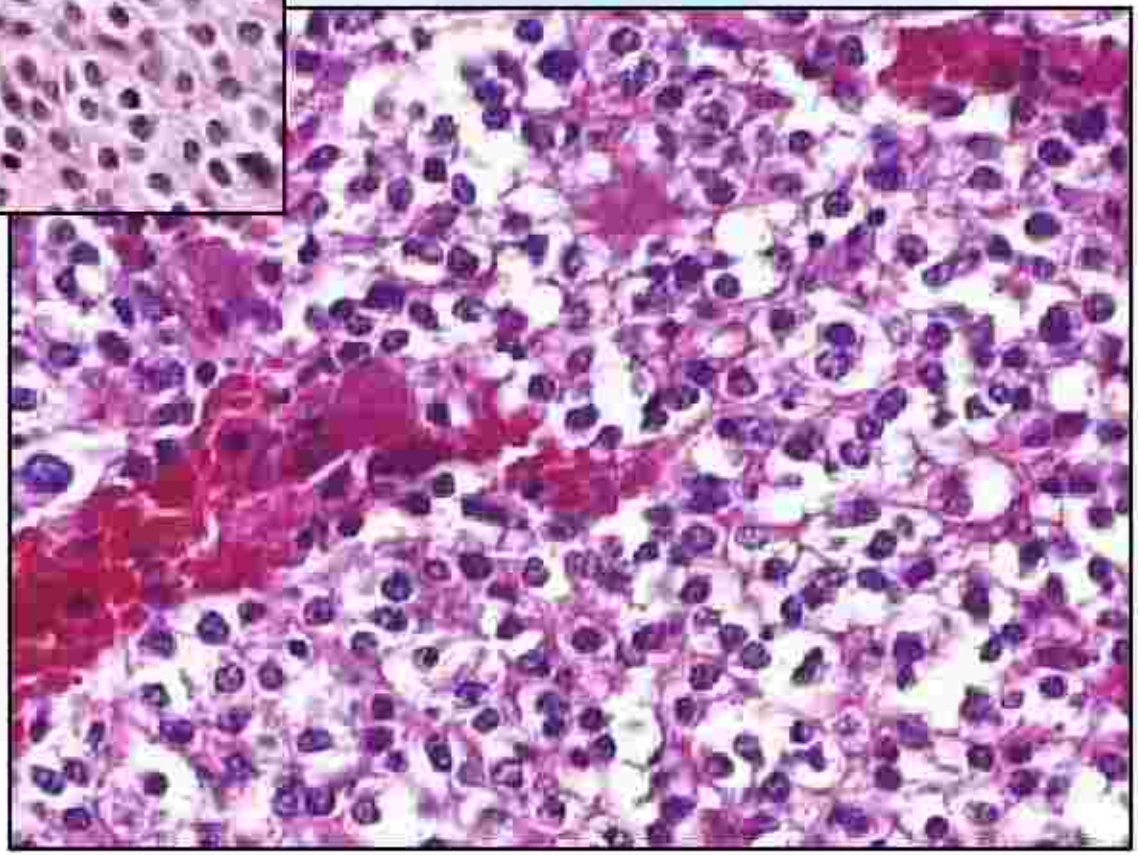
- *Mib-1 < 1%*

ASTROCYTOMA: 5 Year survival





OLIGODENDROGLIOMA



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OLIGODENDROGLIOMA

Good

- Age: < 40years
- Low grade
- Gross total resection
- 1p 19q del (a/w better chemoresponse)

Poor

- Mib-1 > 5%
- Anaplasia
  - Necrosis & mitosis > 6/ 10 hpf)
  - P53 immunoexp

MIXED GLIOMA

- ***OLIGOASTROCYTOMA (II)***
  - ***Conspicuous mixture of 2 distinct cell types***
  - ***At least one 100x field of oligo component***
  - ***Origin from bipotential glial precursor cells***

CKDN 2A, occ EGFR amplificn

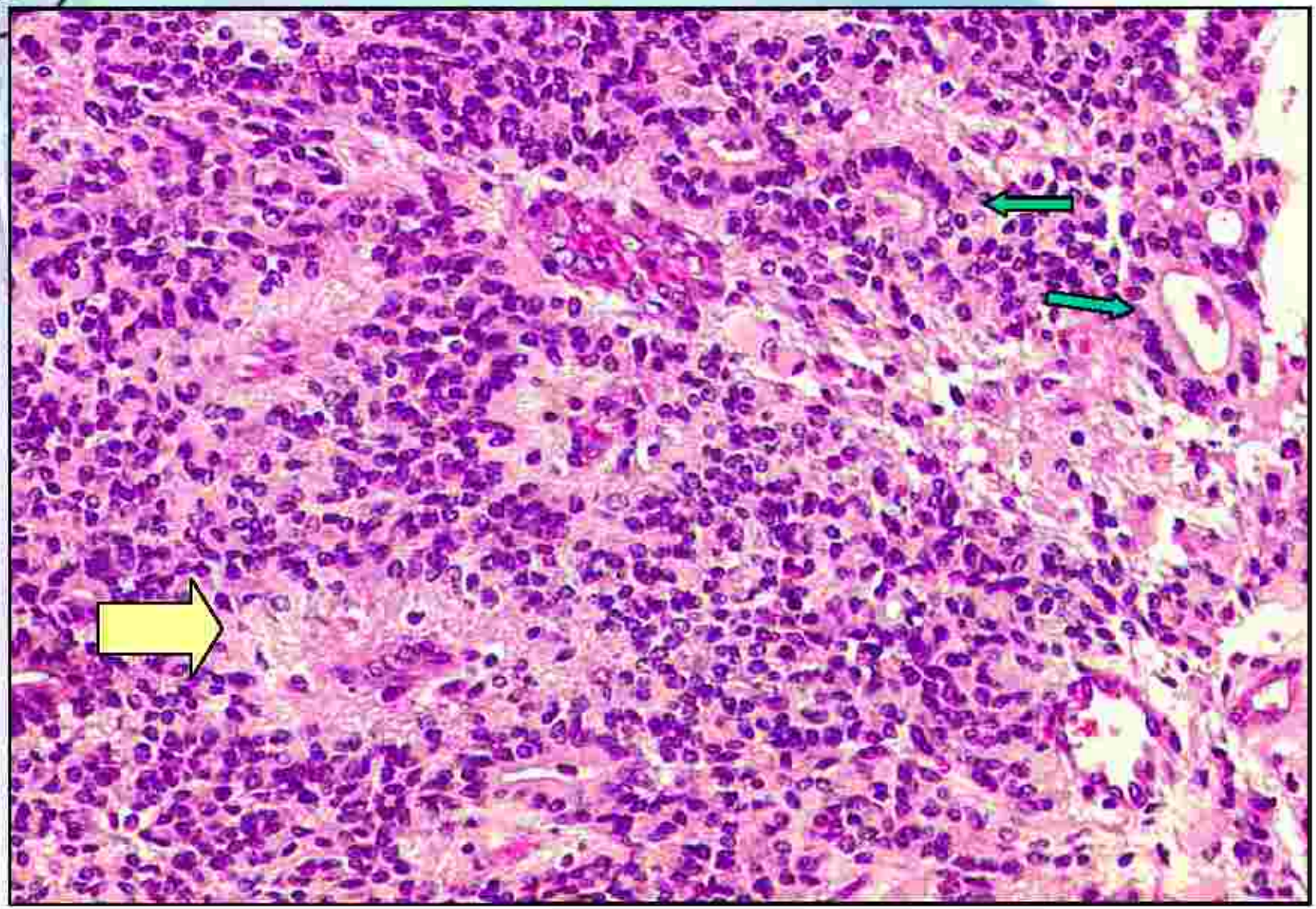
ANAPLASTIC OA (III)

EPENDYMOMA

- *Children- Infra/ supratentorial*
- *Adults- spinal cord*/ supratentorial*
- *Perivascular pseudorosettes/ True ependymal rosettes*
- *Poor prognosis-*
  - *Child < 3years; Post fossa*
  - *Incomplete resection*
  - *Anaplasia*
  - *Mib-1 > 4%*
  - *CSF seeding*

* Most common glioma at this site, a/w NF2

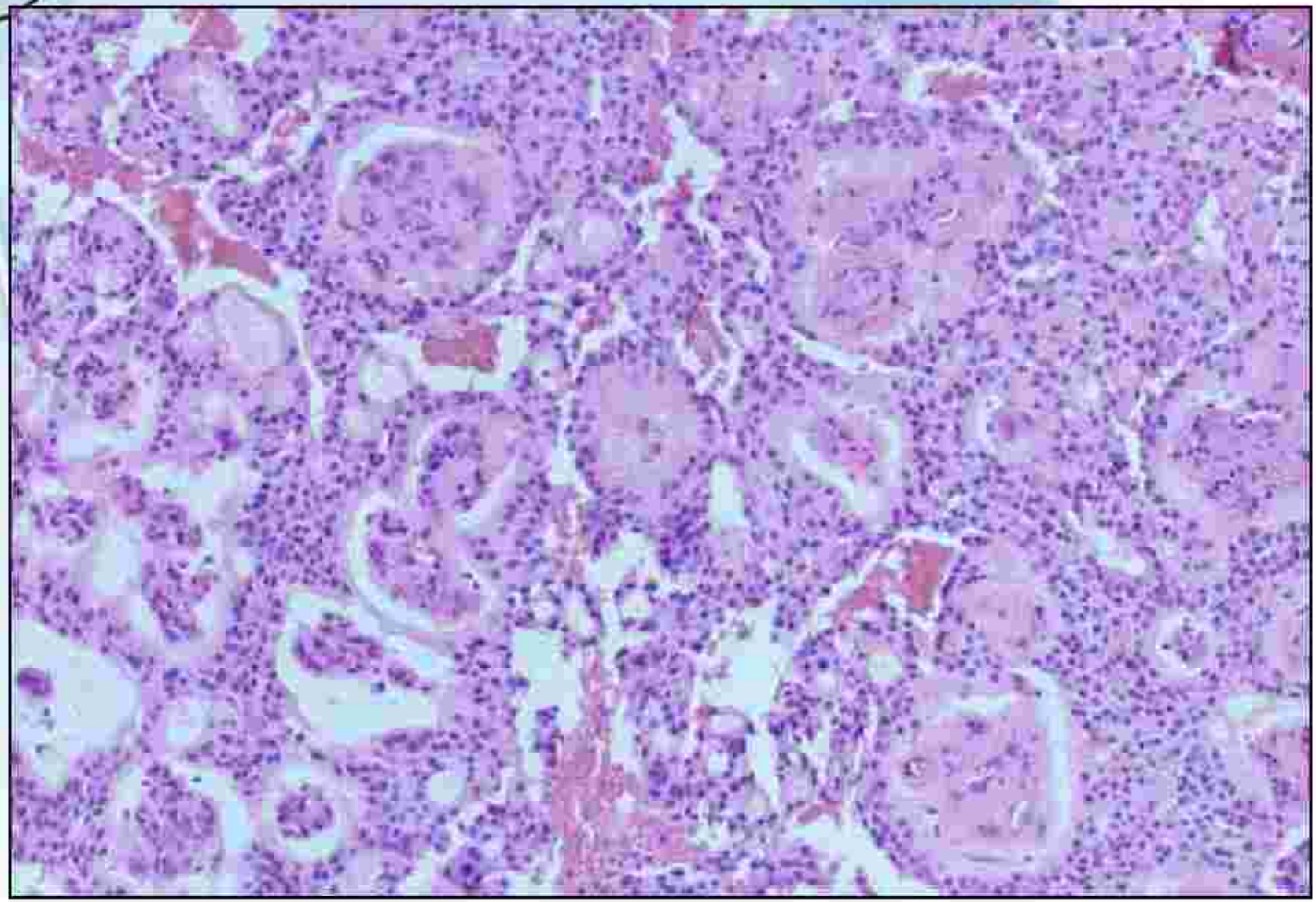
EPENDYMOMA



ANAPLASTIC EPENDYMOMA

- ***De novo or rarely progress from preexisting grade II***
- *MYXOPAPILLARY EPENDYMOMA [I]*
  - ***Almost exclusive in cauda equina/ filum terminale; good prognosis***
- *SUBEPENDYMOMA [I]*
  - ***Slow growing, intraventricular grade I, favorable prognosis***

Myxopapillary EPENDYMOMA



NEURONAL/ MIXED GLIONEURONAL TUMORS

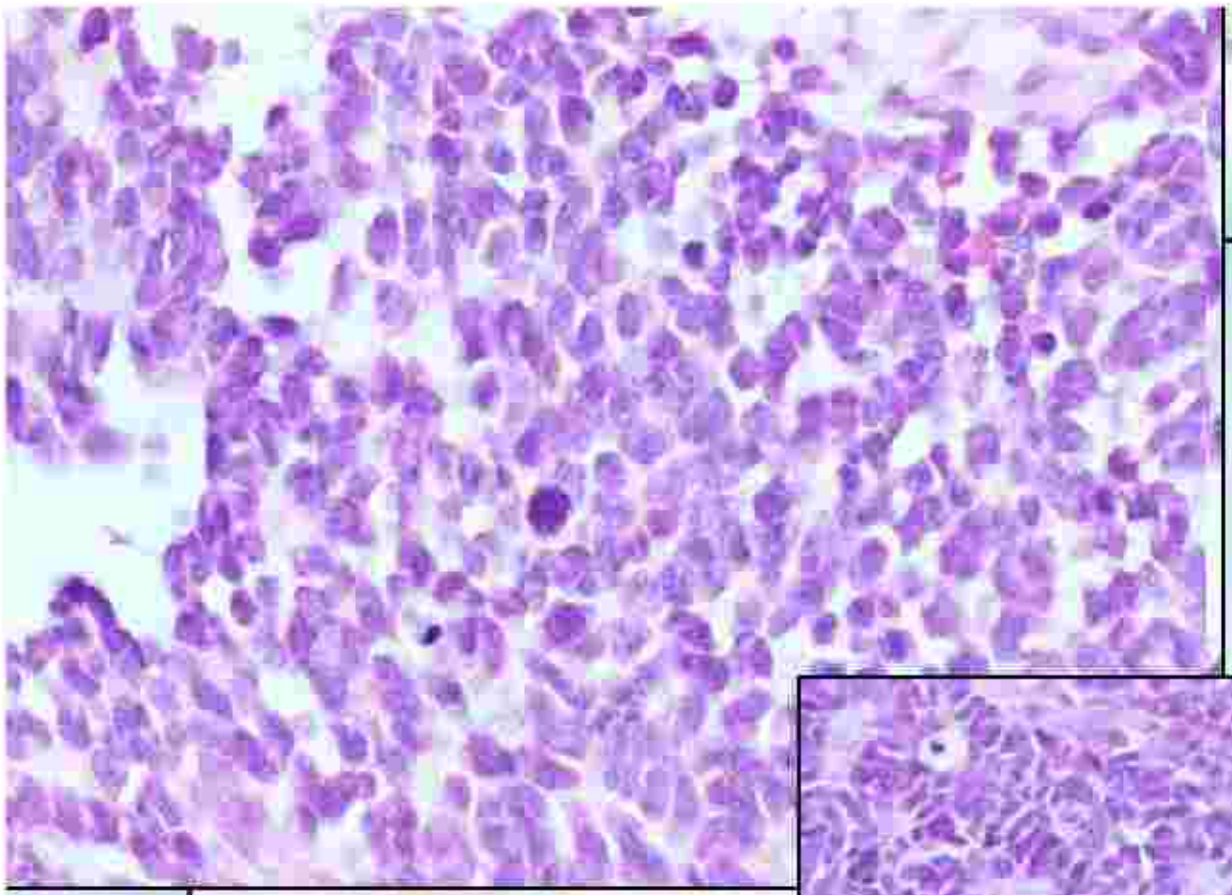
- *Rare*
- *Favorable prognosis; usually low grade I/ II*
- *Variable neuronal & glial differentiation*
- *Precise classification to avoid unnecessary RT/CT*

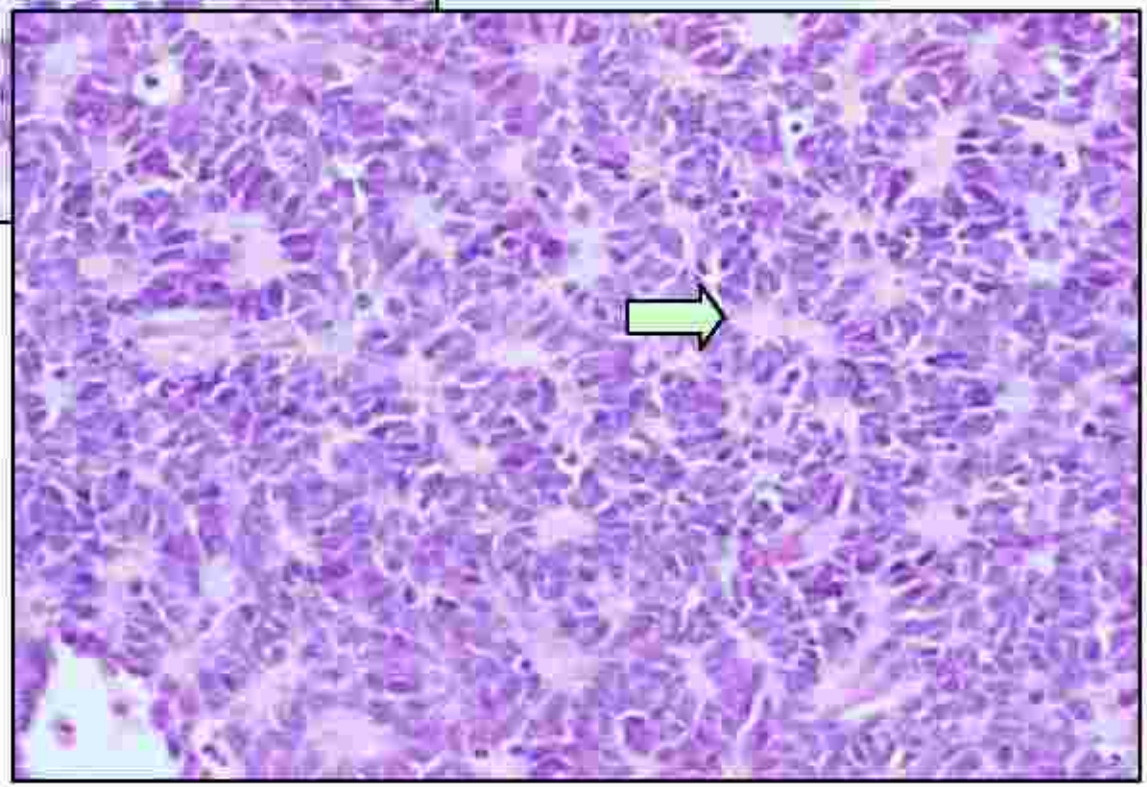
MEDULLOBLASTOMA- [IV]

- *Most common pediatric brain tumor (infratentorial)*
- *Std risk factors- > 3 years; cerebellar tumor; no mets at presentation; little/ no residual (<1.5 cm^3)*

All others are HIGH risk- + intense CT

- *M</S:*
  - *Cellular/ Round cell tumor*
  - *Homer-Wright rosettes*
  - *Desmoplastic & MBEN- good prognosis*
  - *Large cell variant- poor*
  - *IHC- Synaptophysin, chromogranin ++*
  - *Mib-1 : ↑↑*





Homer Wright rosette

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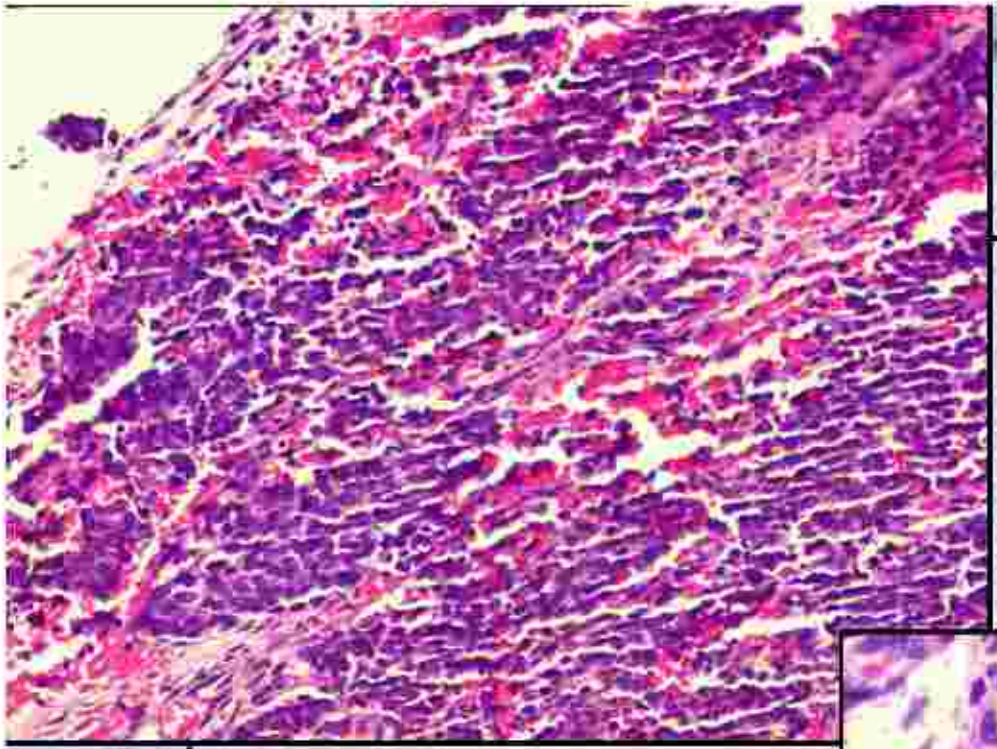
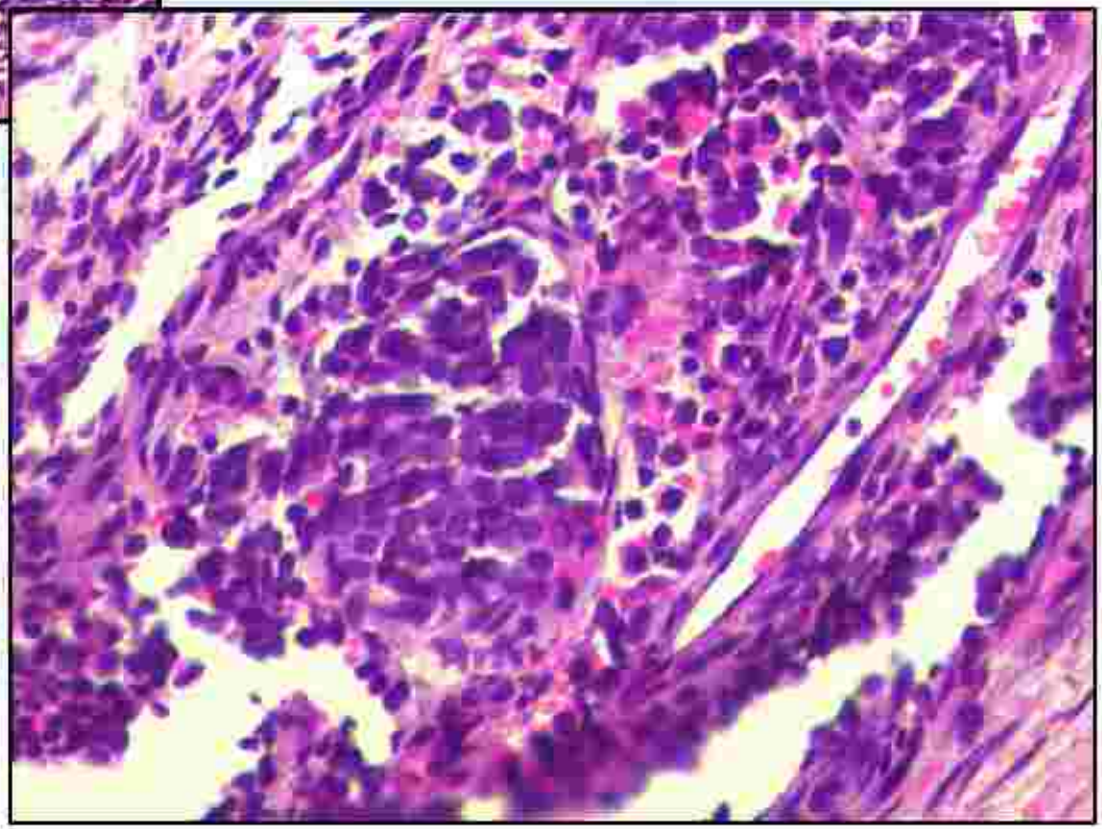
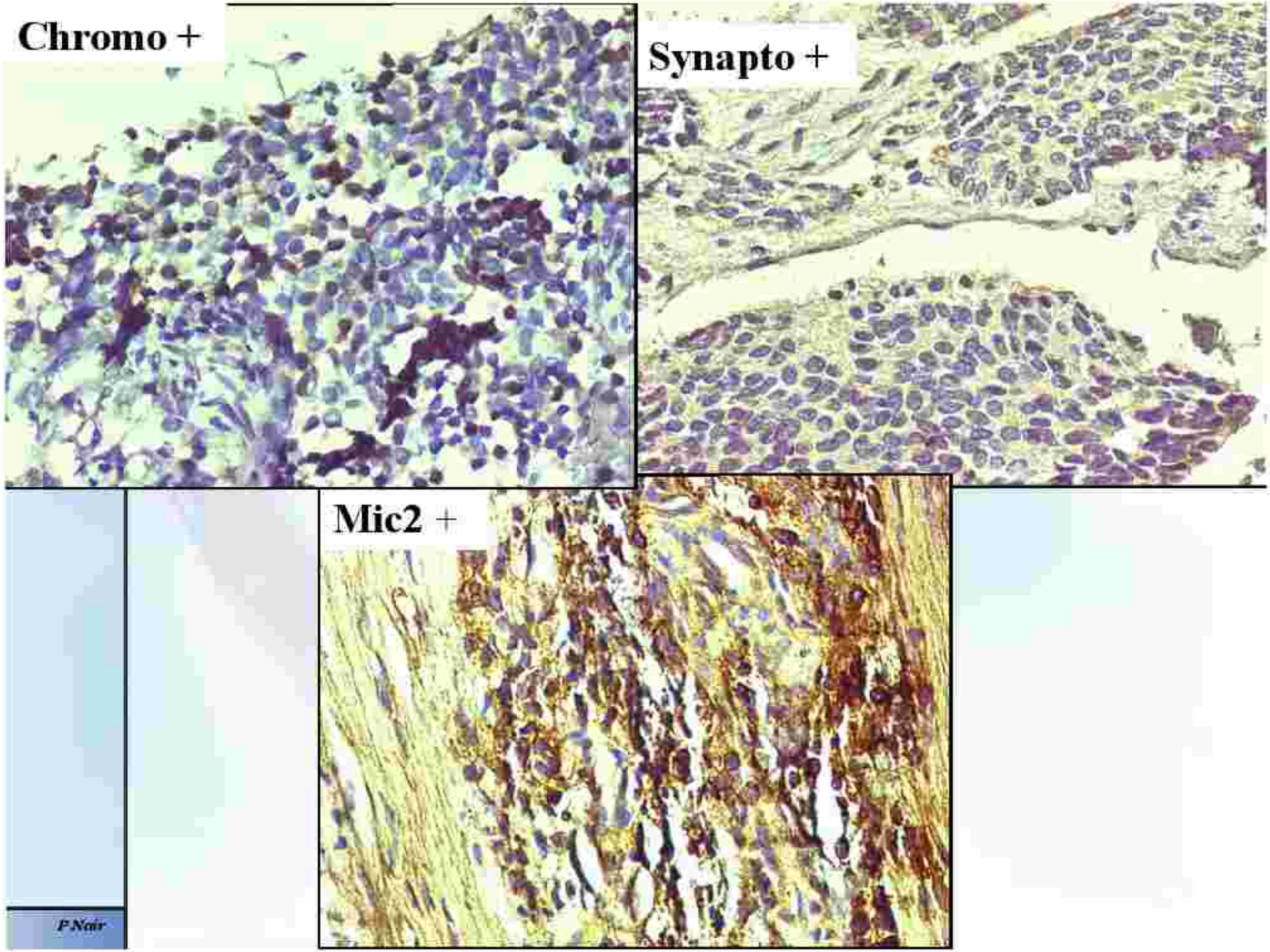


Supratentorial - PNET




Chromo +
Synapto +
Mic2 +
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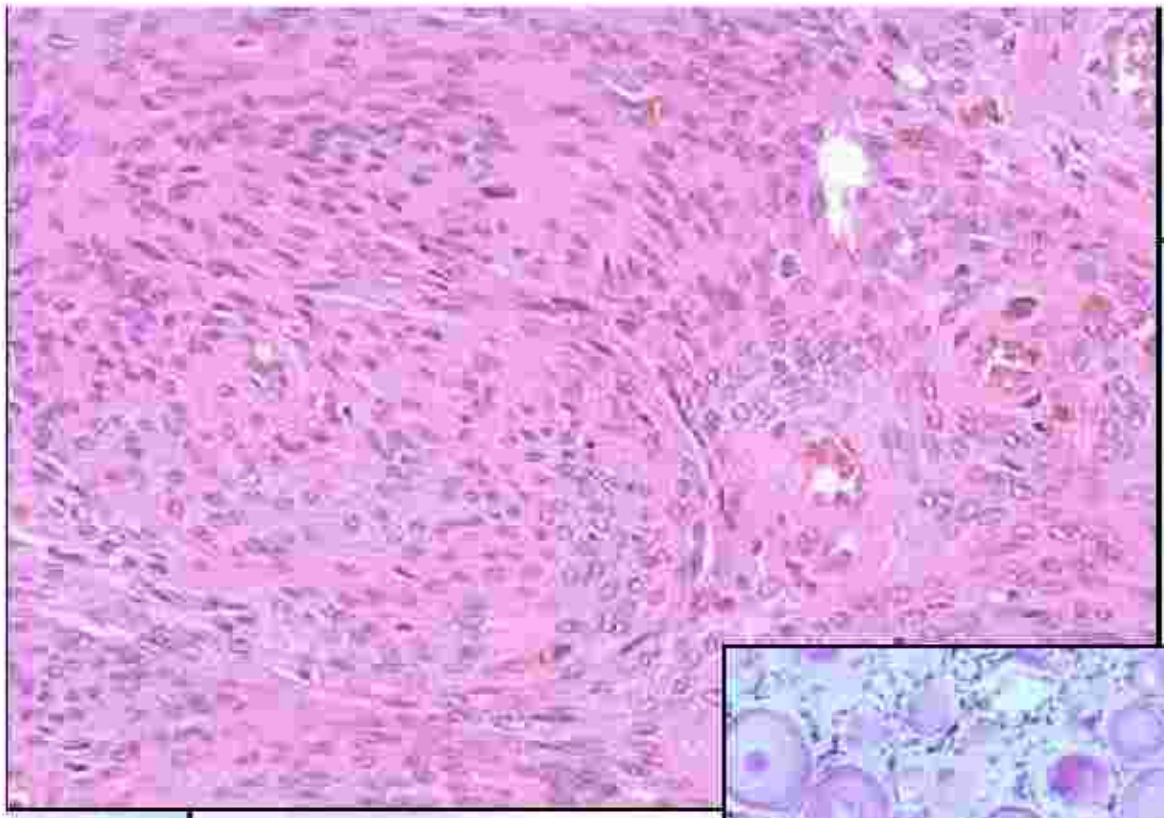
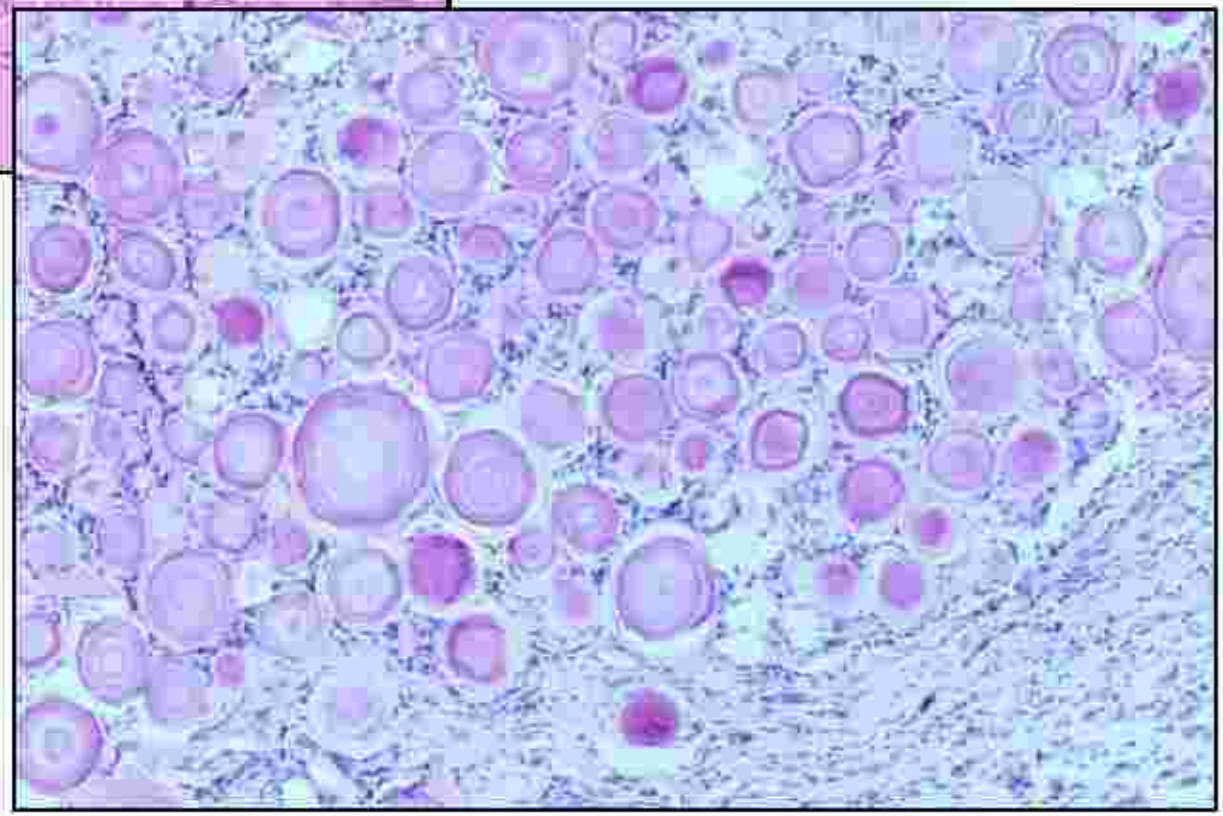
MENINGEAL TUMORS

- *MENINGIOMA:*
  - *Meningioma (typical) [I]*
  - *Atypical Meningioma [II]*
  - *Anaplastic (Malignant) Meningioma [III]*
- *MESENCHYMAL (non-meningothelial)*
- *Primary MELANOCYTIC Lesions*
- *UNCERTAIN Origin*
  - *Hemangiopericytoma*
  - *Hemangioblastoma*

MENINGIOMA

- *Arise from meningothelial cells of arachnoid granulations*
- *Adjacent to venous simuses*
- *Nodular, capsulated, slow growing- Benign*
- *Form whorls of cells, Psammoma bodies in the center*
- *Pressure effect*
- *No brain infiltration or metastasis (Benign)*





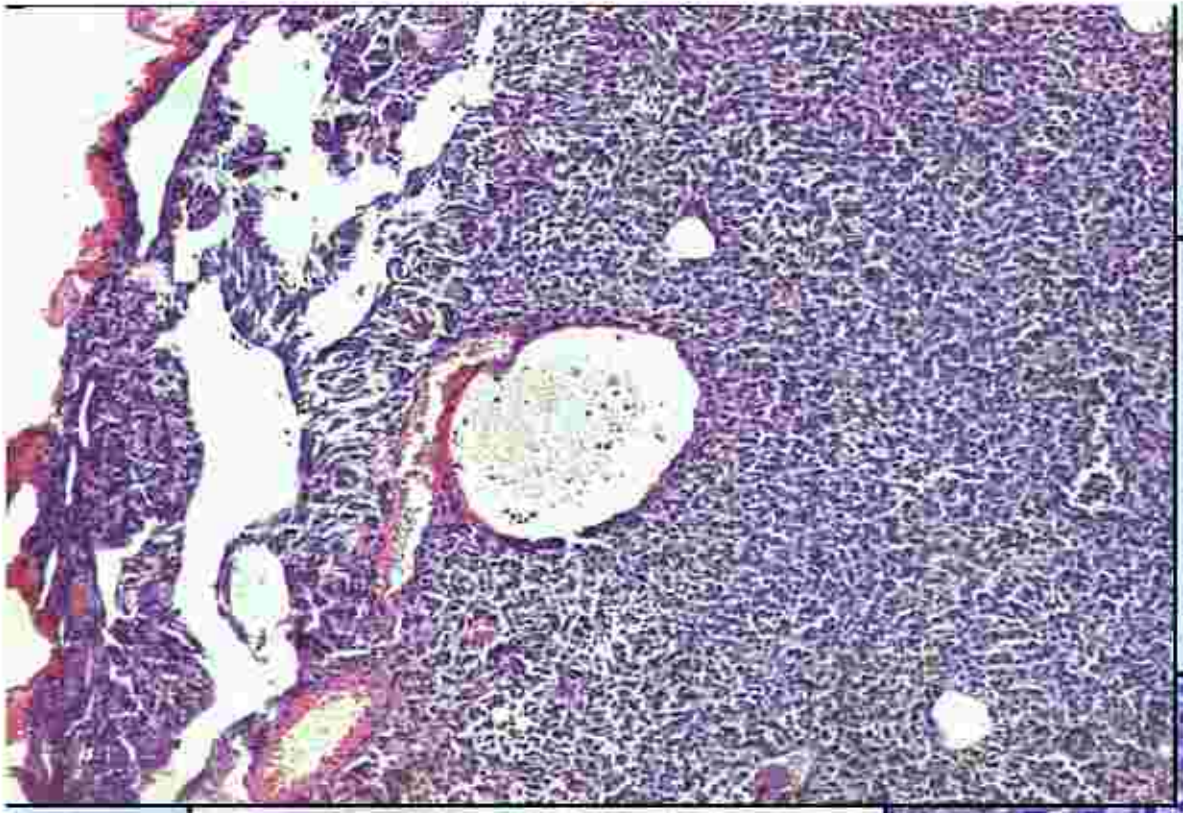
P Nair

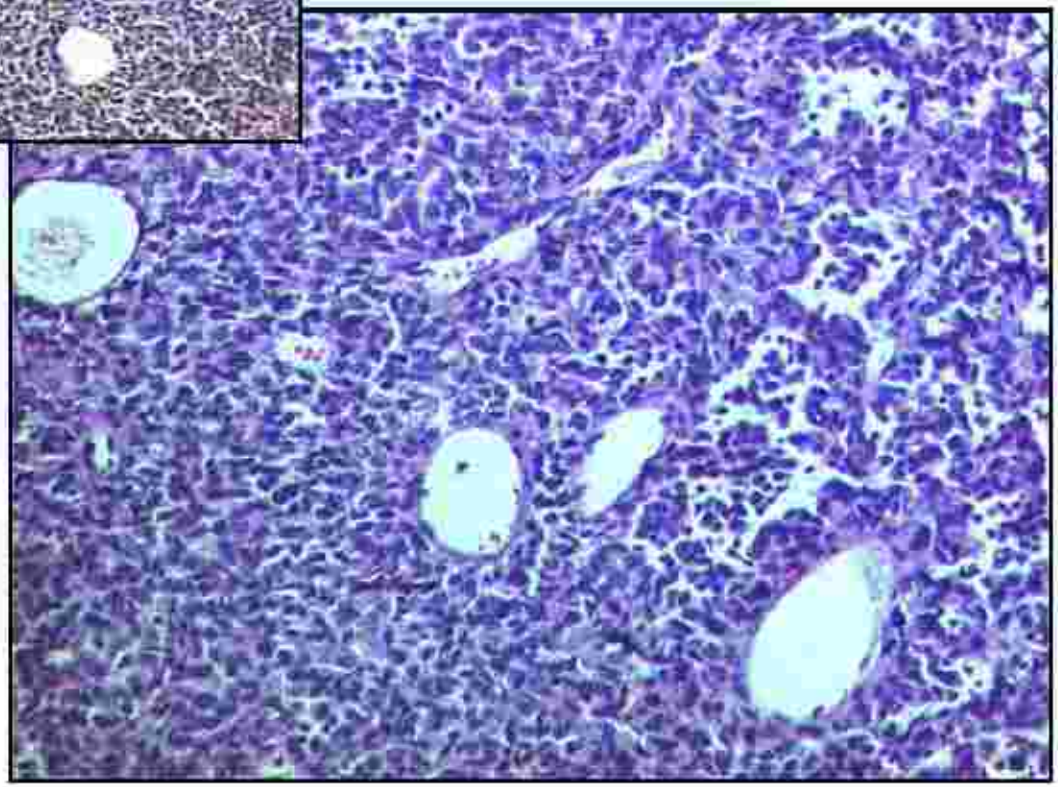
MENINGEAL TUMORS

TYPE	GRADE
MENINGIOMA	***I***
ATYPICAL MENINGIOMA	***II***
+ ***Clear cell; chordoid***	
(↑mitosis 4 - 19/10HPF; OR 3 of foll- ↑cellularity, ↑N:C, prominent nucleoli, patternless growth, spontaneous/ geographic necrosis)	
ANAPLASTIC MENINGIOMA	***III***
+ ***Papillary; rhabdoid***	
(↑mitosis > 20/10HPF; appearance like carcinoma/ sarcoma/ melanoma)	

Meningioma

- *IHC: EMA +; Mib-1< 4 / 8 / 15 %*
- *EM: Interdigitating cell processes*
- *Surgery if feasible-*
- *RT*
  - *Incomplete resection*
  - *Recurrent disease*
  - *Atypical / invasive features*





Hemangiopericytoma

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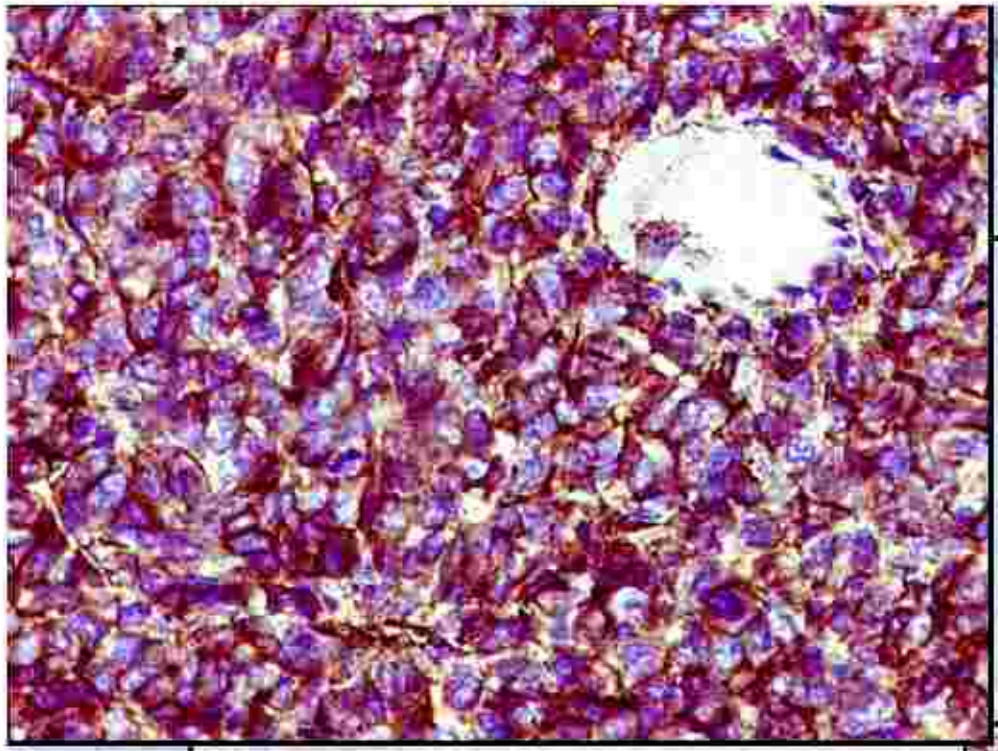
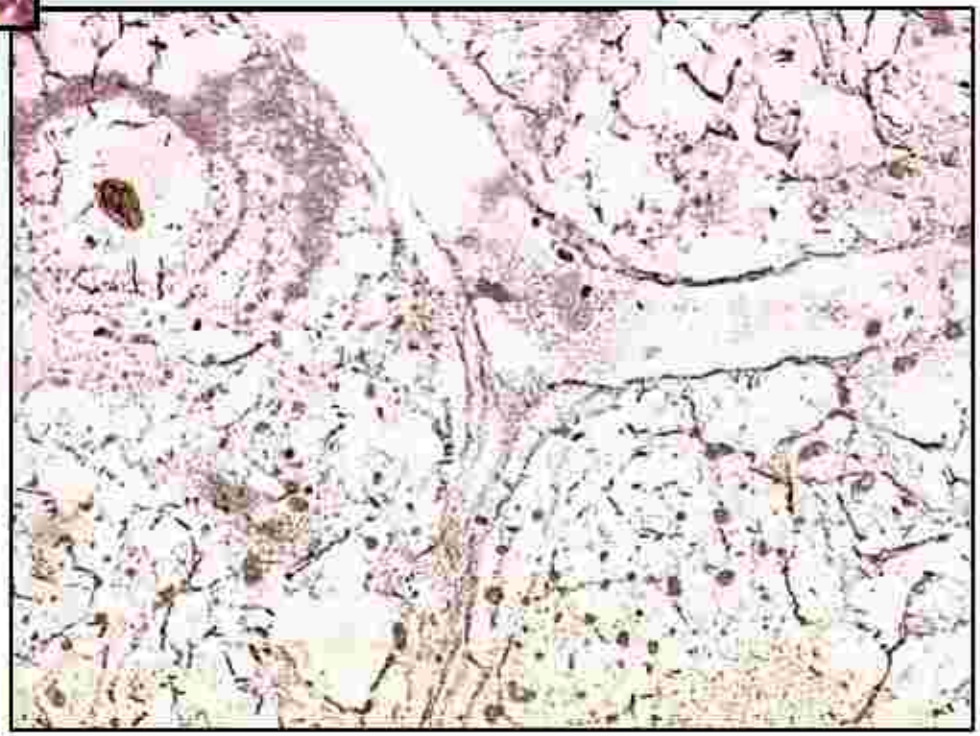
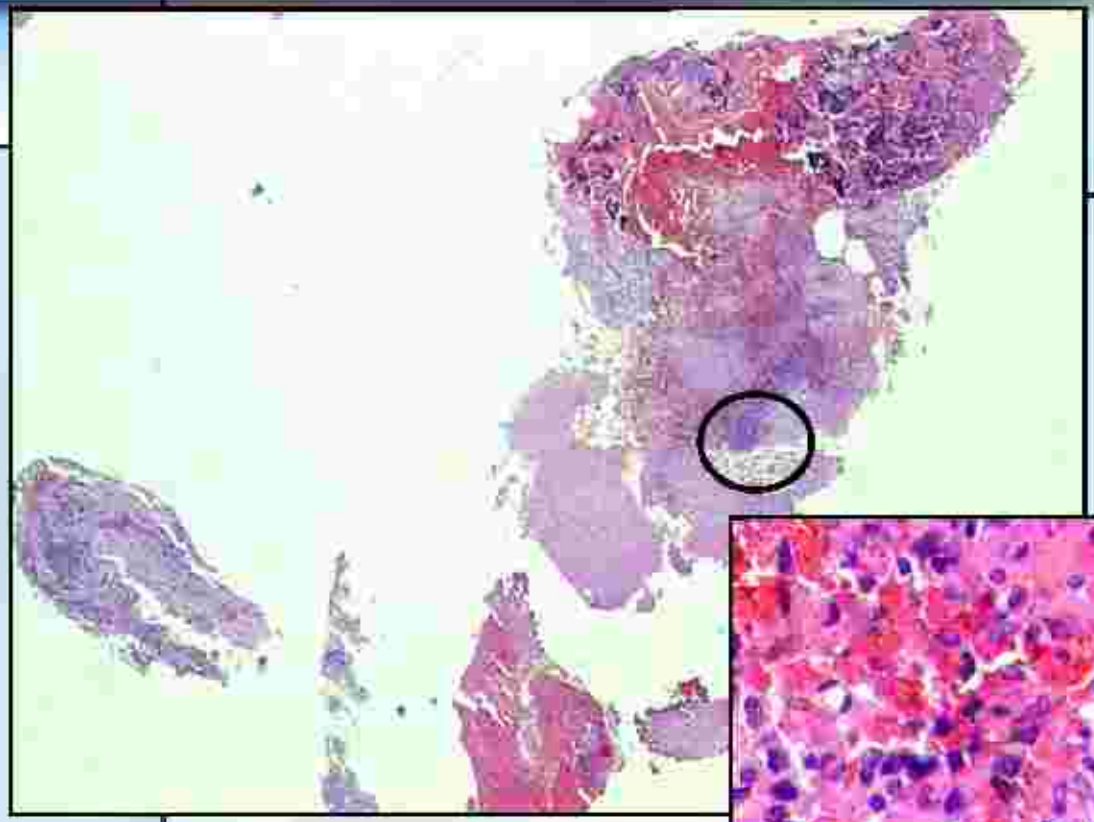


CD34 +

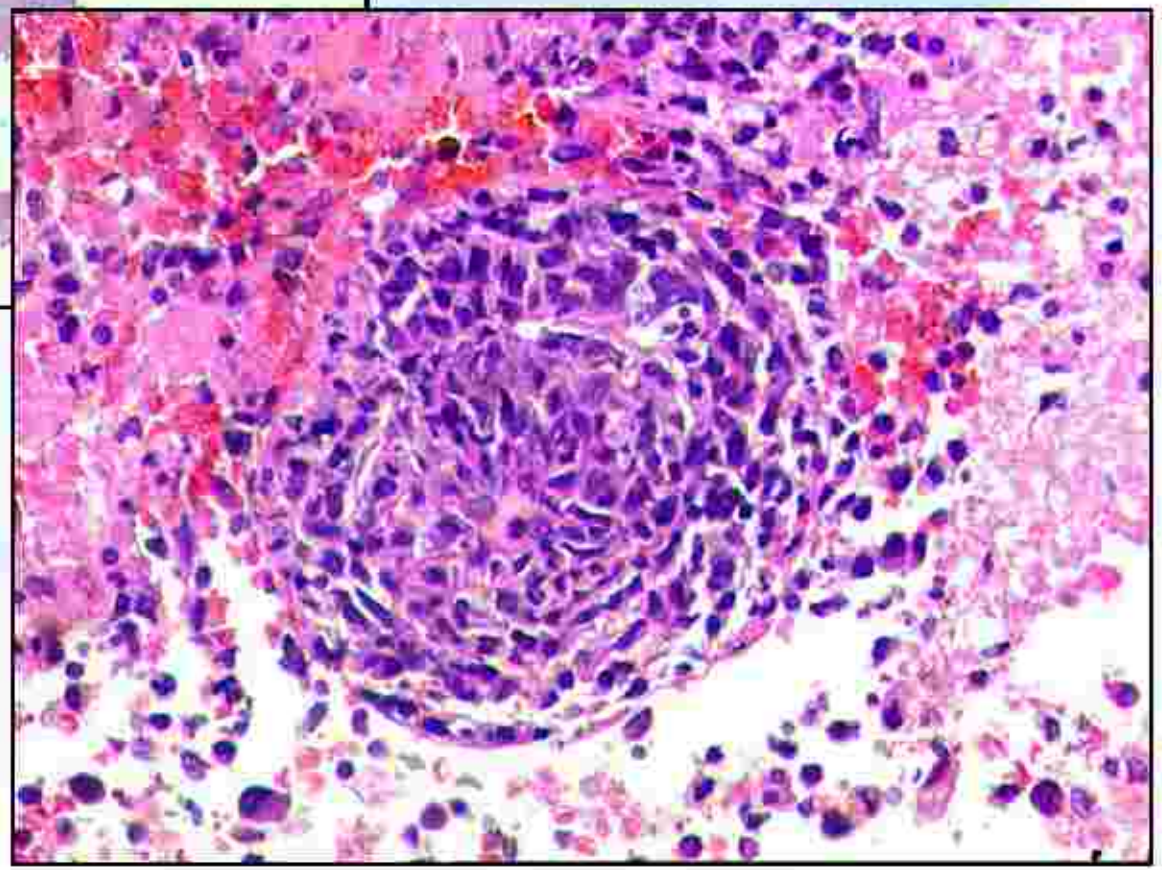
Hemangiopericytoma



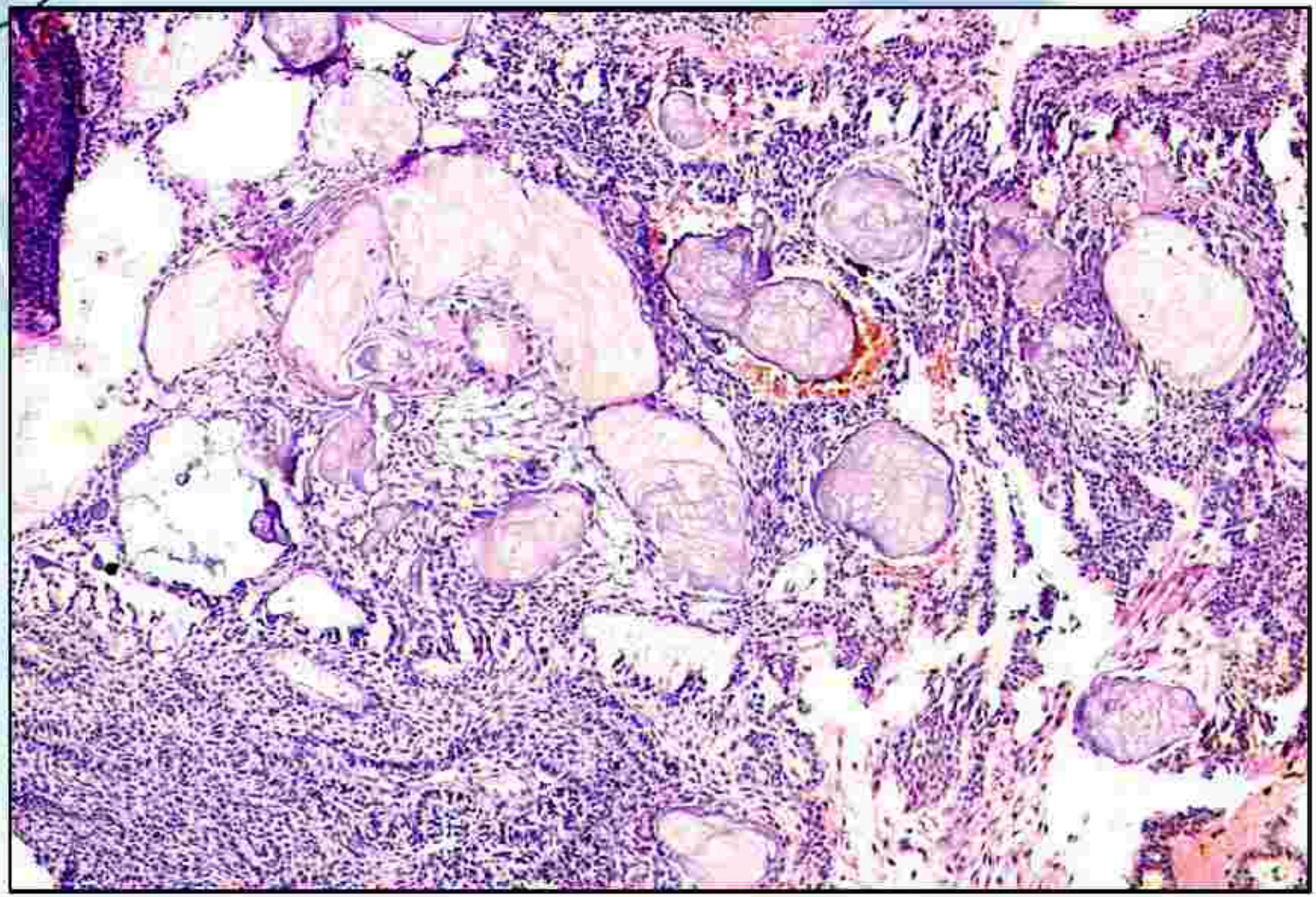
Reticulin



Primary Brain
LYMPHOMA



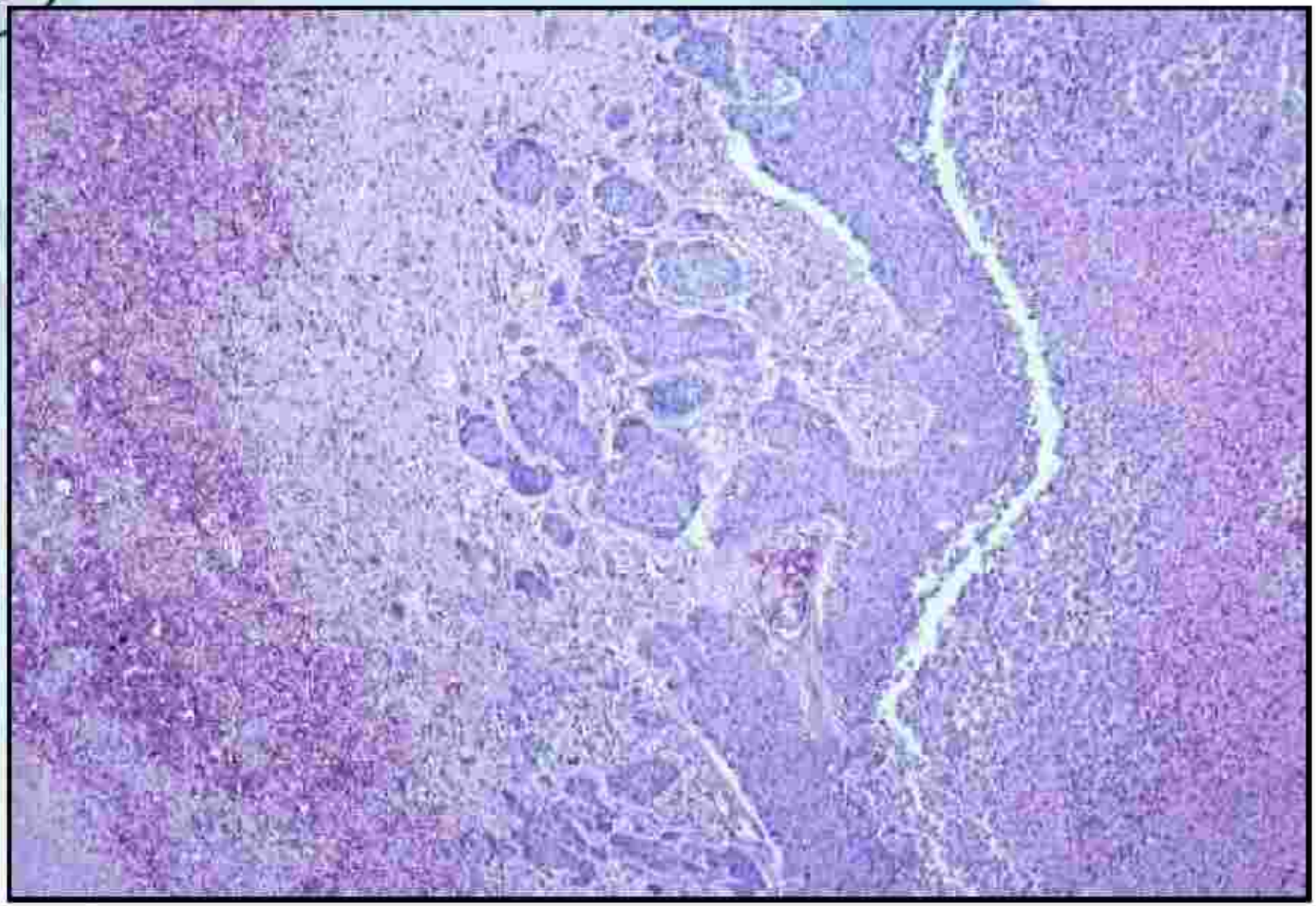
Craniopharyngioma [WHO I]



Metastasis

- *Most common brain tumor in adults*
- *Common primary sites: breast, lung, GI tract, kidney & melanoma*
- *Most are in cerebrum (MCA territory); at the grey-white junctions due to vascularity*
- *Discrete, globoid, sharply demarcated tumors*

Metastatic carcinoma



- *Tumor heterogeneity*
- *Limited biopsy material*
- *Team effort-*
  - *Surgeon*
  - *Radiologist*
  - *Pathologist*
  - *Radiation oncologist*

Thank you!!