مركز الحسين للسرطان
King Hussein Cancer Center

The 2021 WHO Classification of Tumours of the Central Nervous System (CNS5)

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Mutation vs. Epigenetic changes

Mutation theory

- Alteration of the DNA structure of the genome leading to the development of various diseases including cancer
  - Point mutations, insertions, deletions,….etc
- ATRT monosomy 22
- Oligo 1p/19q co-deletion

Epigenetic theory

- ‘epi’ means ‘above’ , and epigenetics means ‘above genetics’
- ‘Non-structural’ gene modifications without modifying the DNA structure
- Events which modify gene expression **without** modifying the structure of the genes themselves
- MGMT in GBM

Epigenetics

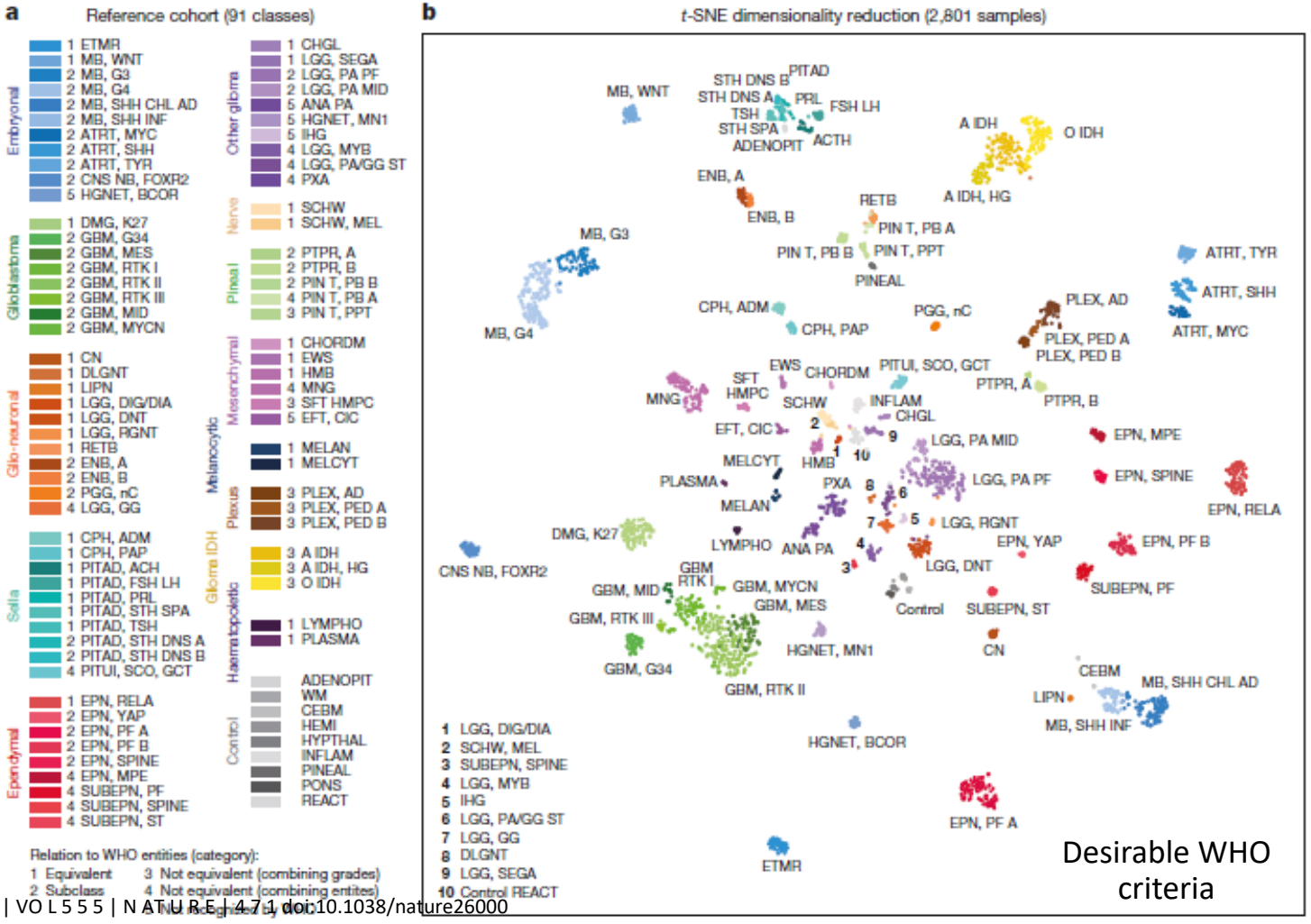
Different mechanisms for the epigenetic modification, including DNA methylation and histone modifications.

- **Hypermethylation:** the function of entire genes (including tumor suppressor genes) can be suppressed.
- **Hypomethylation:** silenced genes, as well as growth promoting genes can be activated.

An epigenetically modified DNA methylation landscape, is stable and can be transmitted from one generation to next generation.

Methylation Profile

Histological Diagnosis without Histology!



Desirable WHO criteria

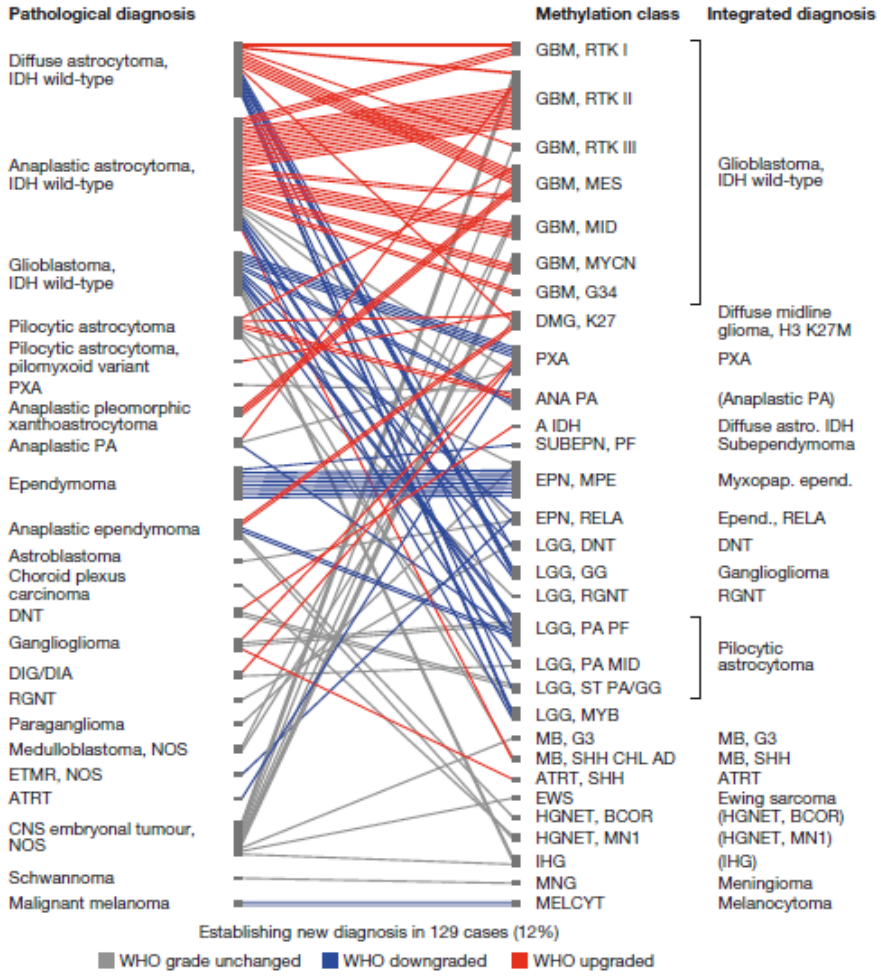


Figure 4 | Reassessment of discrepant cases and establishment of

2018 | VOL 555 | NATURE | 471 doi:10.1038/nature26000

1. Methylation profile is “desirable” in the classification of CNS tumors

Gliomas, Glioneuronal Tumors, and Neuronal Tumors

(1) Adult-type diffuse gliomas	• The majority of primary brain tumors in neuro-oncology practice of adults, eg, *glioblastoma, IDH-wildtype.*
(2) Pediatric-type diffuse low-grade gliomas	• Expected to have good prognoses.
(3) Pediatric-type diffuse high-grade gliomas	• Expected to behave aggressively.
(4) Circumscribed astrocytic gliomas	• "Circumscribed" referring to their more solid growth pattern, as opposed to the inherently "diffuse" tumors in groups 1, 2, and 3.
(5) Glioneuronal and neuronal tumors	• A diverse group of tumors, featuring neuronal differentiation.
(6) Ependymomas	• Now classified by site as well as histological and molecular features.

2.1.2: Pediatric-type diffuse low-grade gliomas

- 2.1.2.1: Diffuse astrocytoma, MYB- or MYBL1-altered
- 2.1.2.2: Angiocentric glioma
- 2.1.2.3: Diffuse low-grade glioma, MAPK-altered
- 2.1.2.4: Polymorphous low-grade neuroepithelial tumour of the young

2.1.3: Pediatric-type diffuse high-grade gliomas

- 2.1.3.1: Diffuse midline glioma, H3 K27M-mutant
- 2.1.3.2: Diffuse hemispheric glioma, H3 G34-mutant
- 2.1.3.3: Diffuse paediatric-type high-grade glioma, H3-wildtype and IDH-wildtype
- 2.1.3.4: Diffuse midline glioma, EGFR-mutant
- 2.1.3.5: Infant-type hemispheric glioma, H3-wildtype

2.1.4: Circumscribed astrocytic gliomas

- 2.1.4.1: Pilocytic astrocytoma
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2.1.5: Glioneuronal and neuronal tumours

- 2.1.5.1: Gangliocytoma
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- 2.1.3.13 Diffuse leptomeningeal glioneuronal tumor

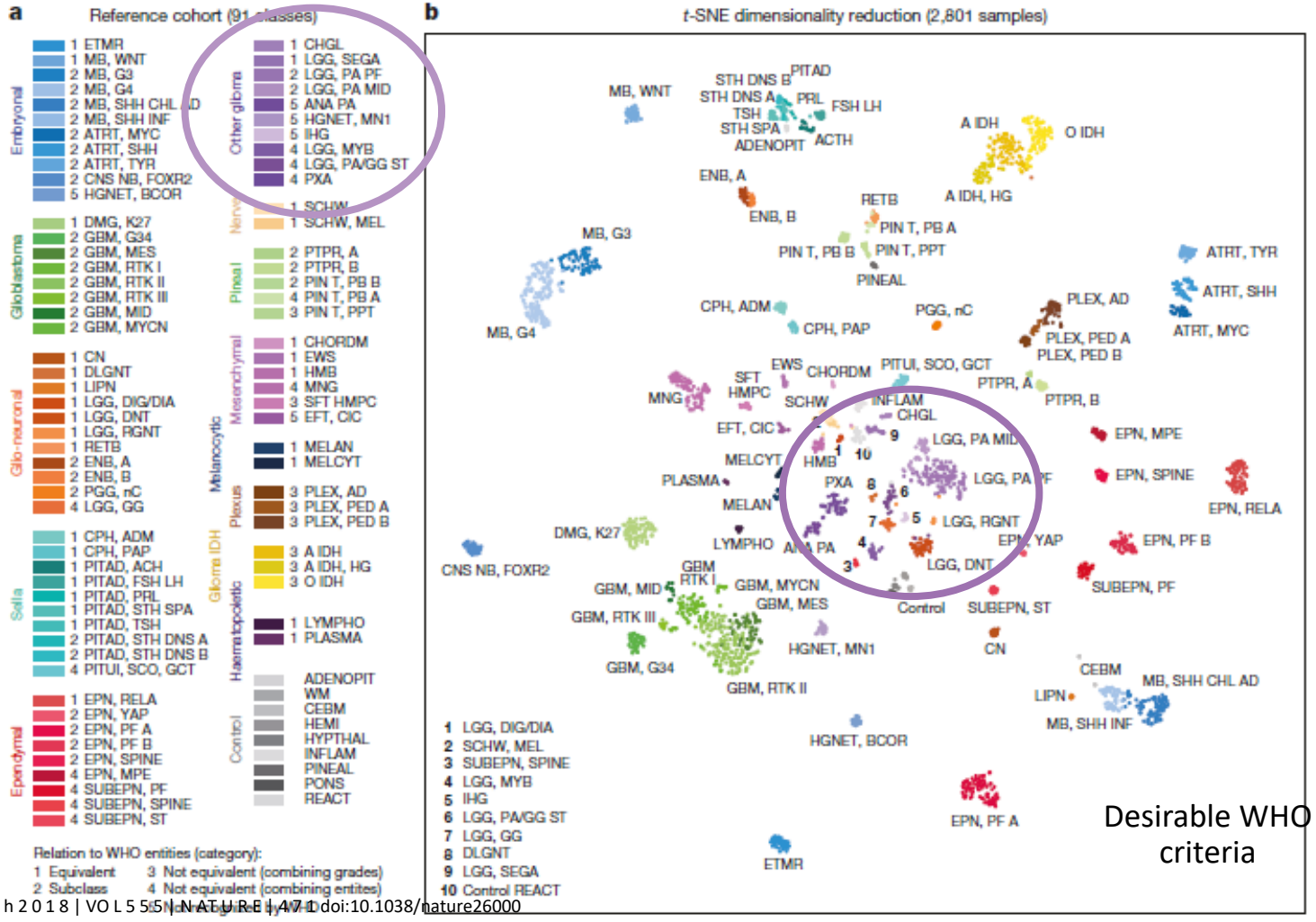
Many others.....

(2) Pediatric-Type Diffuse Low-Grade Gliomas

- Mostly hemispheric, diffuse gliomas.
- Carry distinct molecular alterations, despite histological similarities to adult gliomas.
- Appropriate molecular testing is therefore essential for accurate classification and the identification of potential therapeutic targets.
- Associated with good prognosis.
- All considered **grade 1.**

Methylation Profile

Low-grade Neuro-epithelial Tumors



Desirable WHO criteria

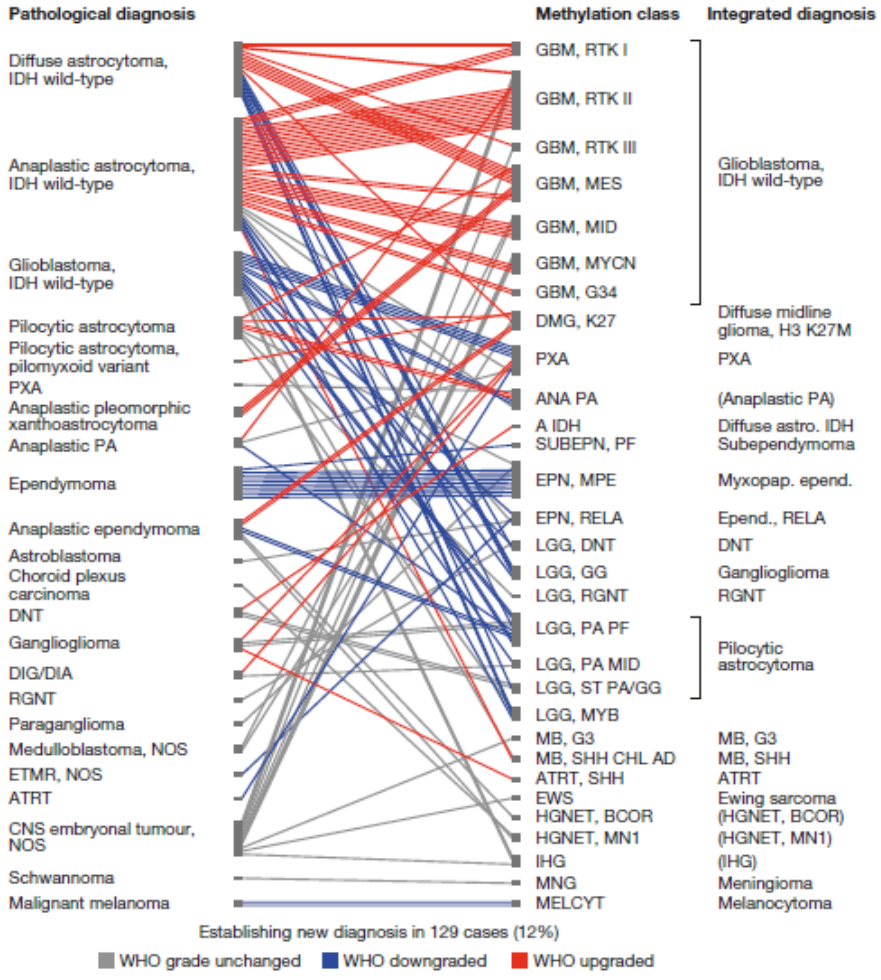
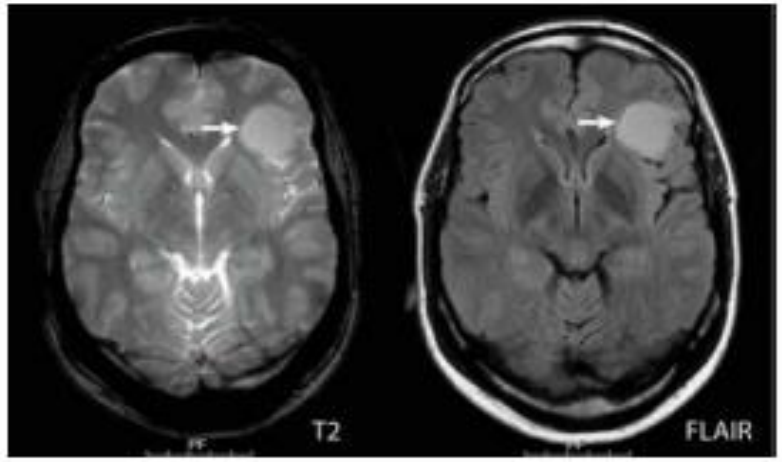
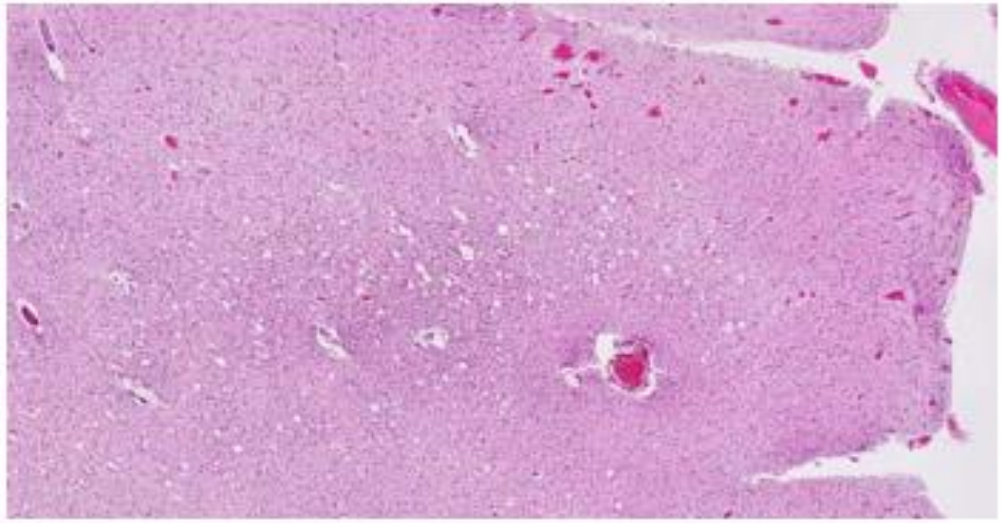


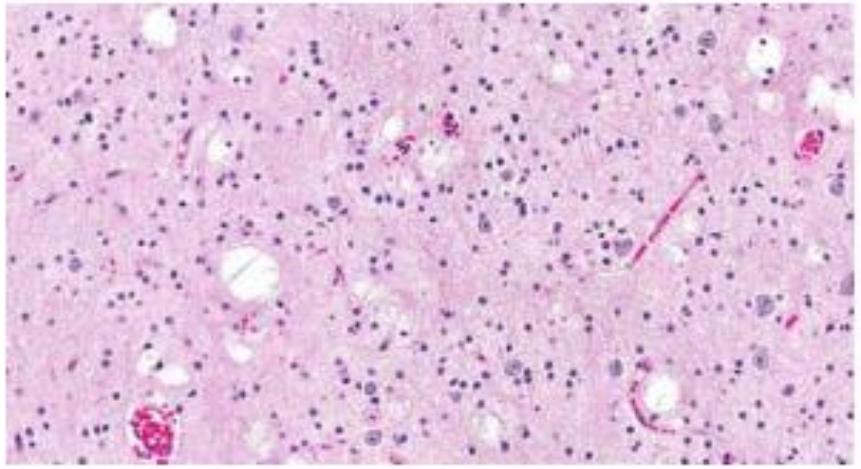
Figure 4 | Reassessment of discrepant cases and establishment of

22 march 2018 | VOL 555 | NATURE | 471 doi:10.1038/nature26000

Diffuse astrocytoma, MYB or MYBL1 altered

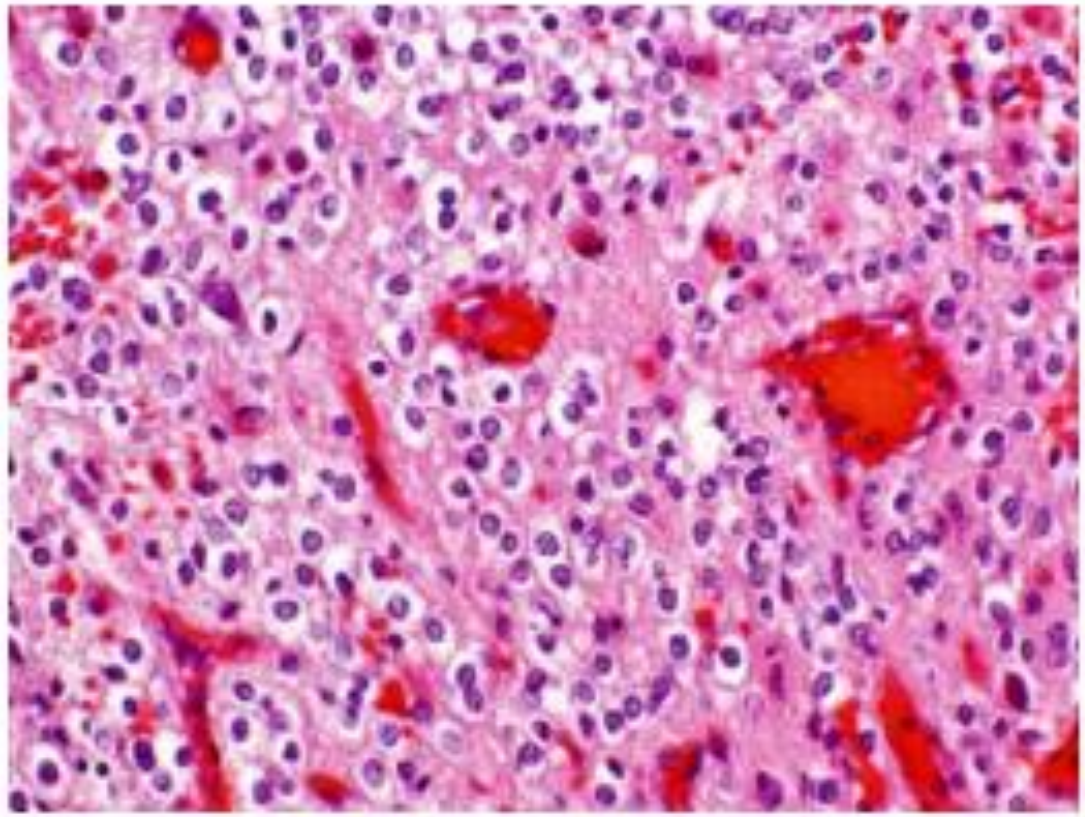


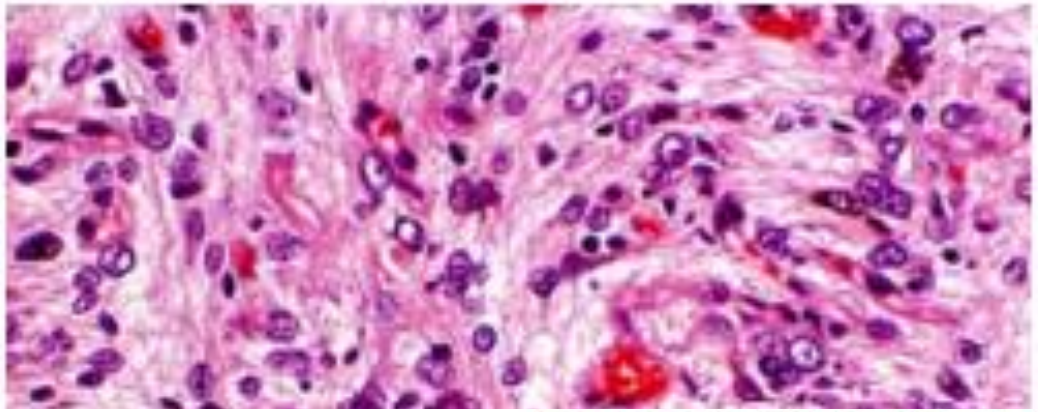


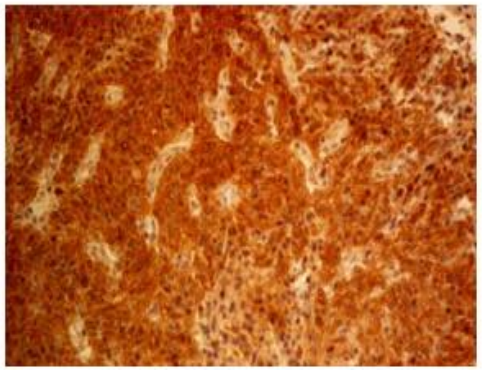


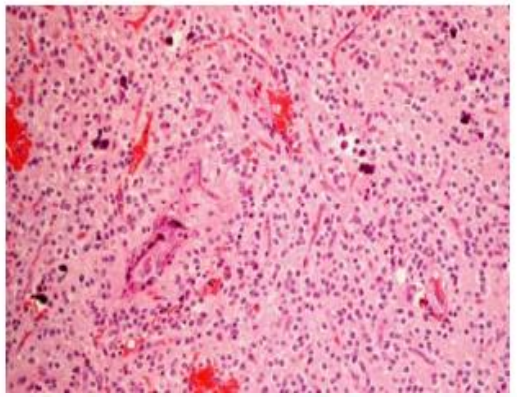
Considered grade-I glioma

Polymorphous low-grade neuroepithelial tumor of the young (PLTY)





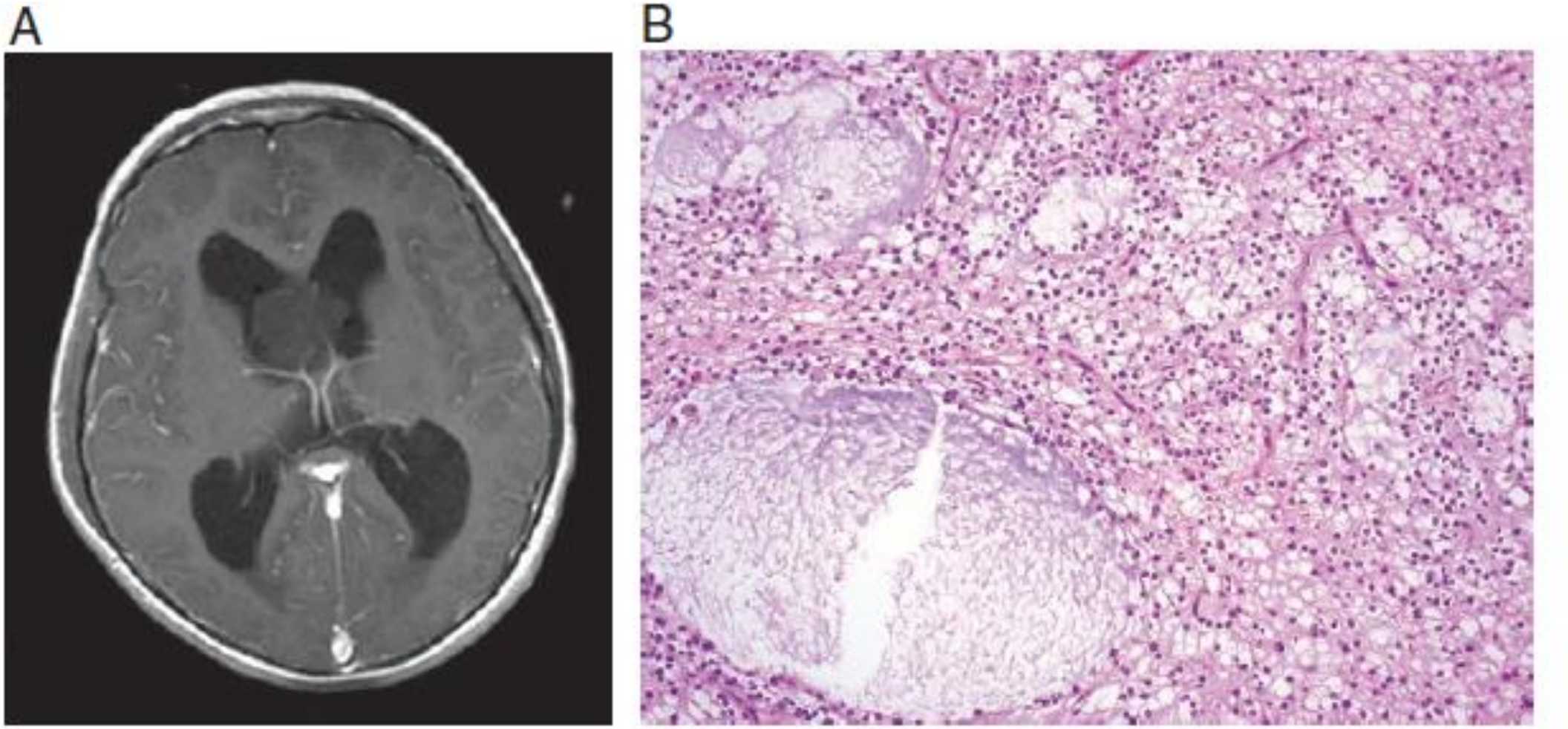




- Polymorphous low-grade neuroepithelial tumor of the young **(PLTY)** is a newly recognized, epilepsy-associated tumor type with MAPK alterations found in children and young adults

E. J. Rushing. MEMO. 2 February 2021. https://doi.org/10.1007/s12254-021-00680-x

Myxoid glioneuronal tumor



Louis et al. The 2021 WHO Classification of CNS Tumors. Neuro-oncology 2021

2. Pediatric-type diffuse low- grade gliomas are distinct, grade 1 tumors, associated with distinct molecular signature and good prognosis.

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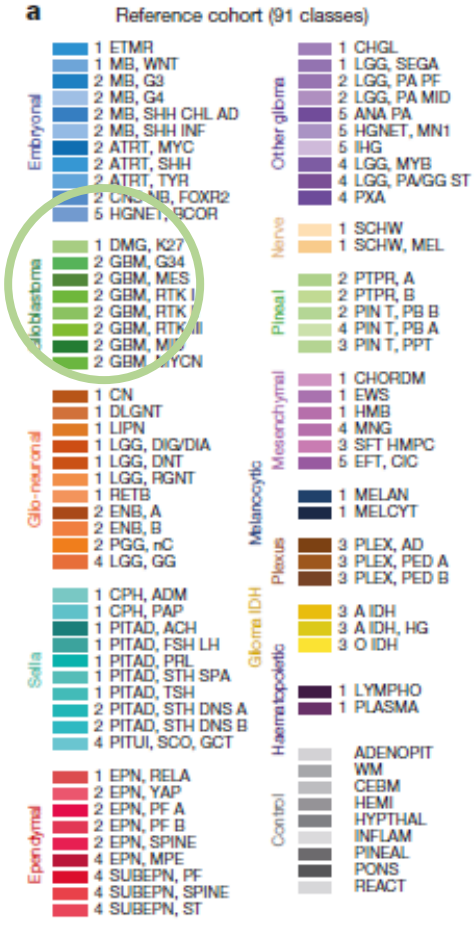
2.1.5: Glioneuronal and neuronal tumours

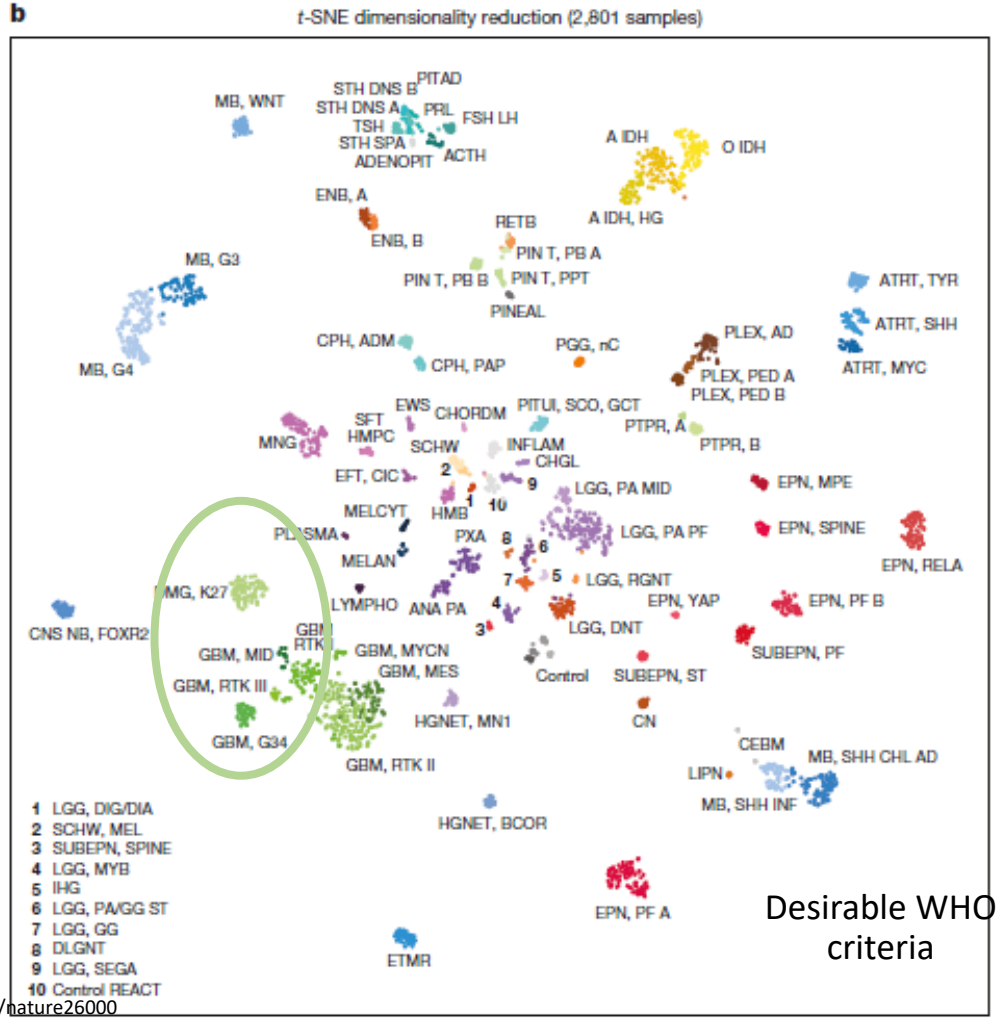
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Many others.....

Methylation Profile

DMG, H3 K27





Desirable WHO criteria

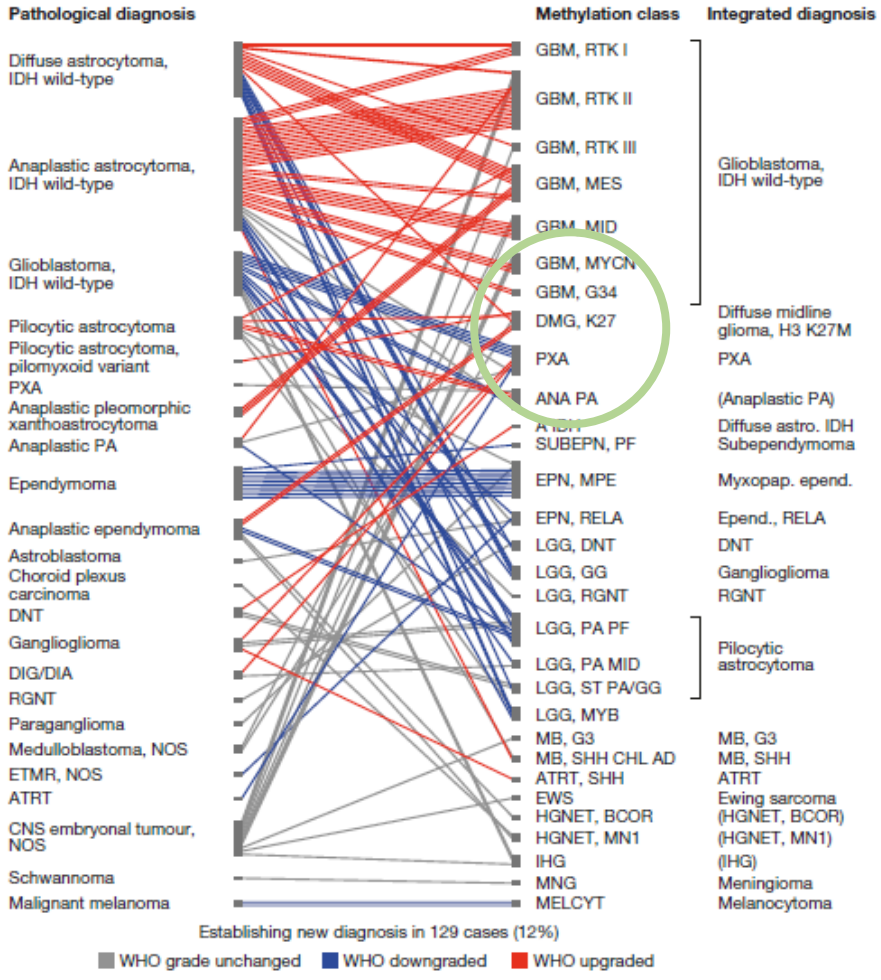
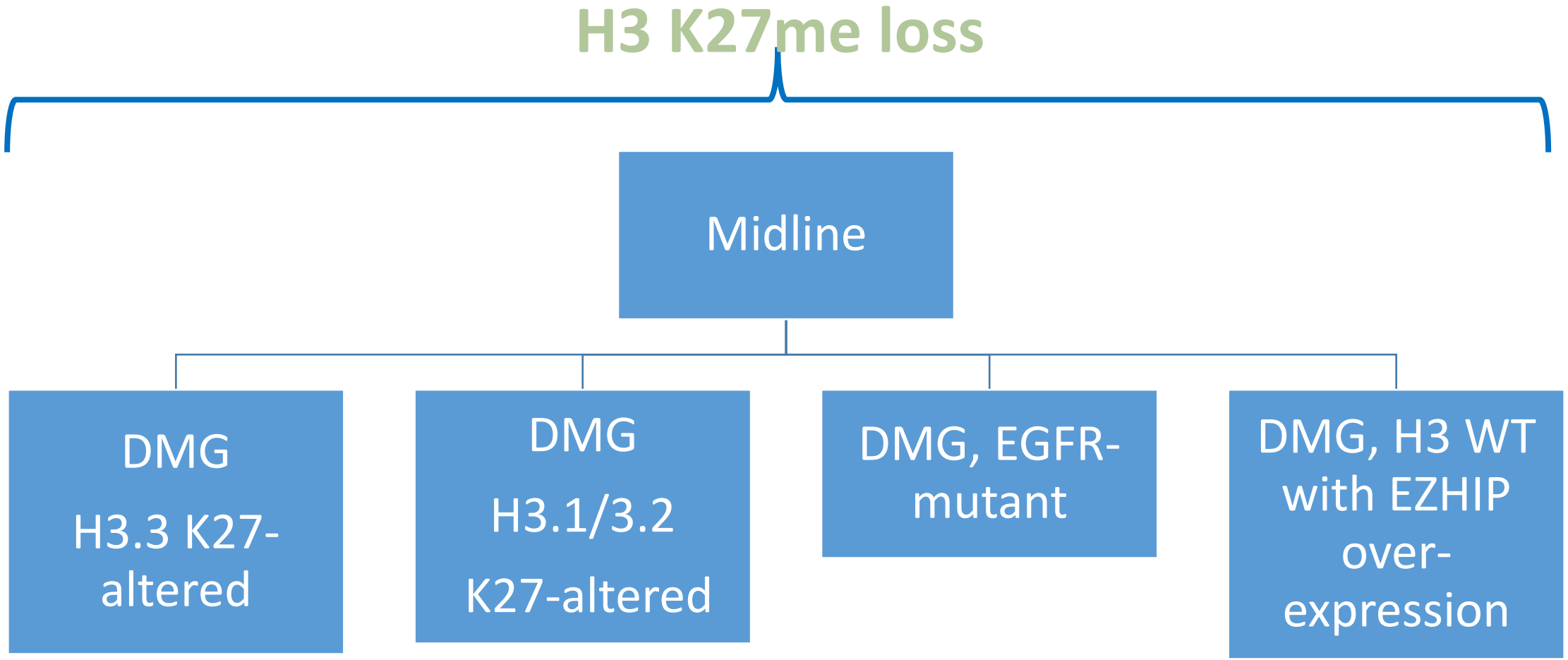


Figure 4 | Reassessment of discrepant cases and establishment of

DMG, H3 K27-altered



Diffuse midline glioma, H3 K27-altered , **WHO grade 4**

H3 K27M Mutation in Other Tumors/ Locations

- The prognostic significance of a H3 K27M mutation is unclear in
  - Unusual location or tumor entity
  - Ependymomas, pilocytic astrocytoma and ganglioglioma that were reported positive with H3 K27M mutation.

Two Immunostains

H3 K27M & H3 K27me

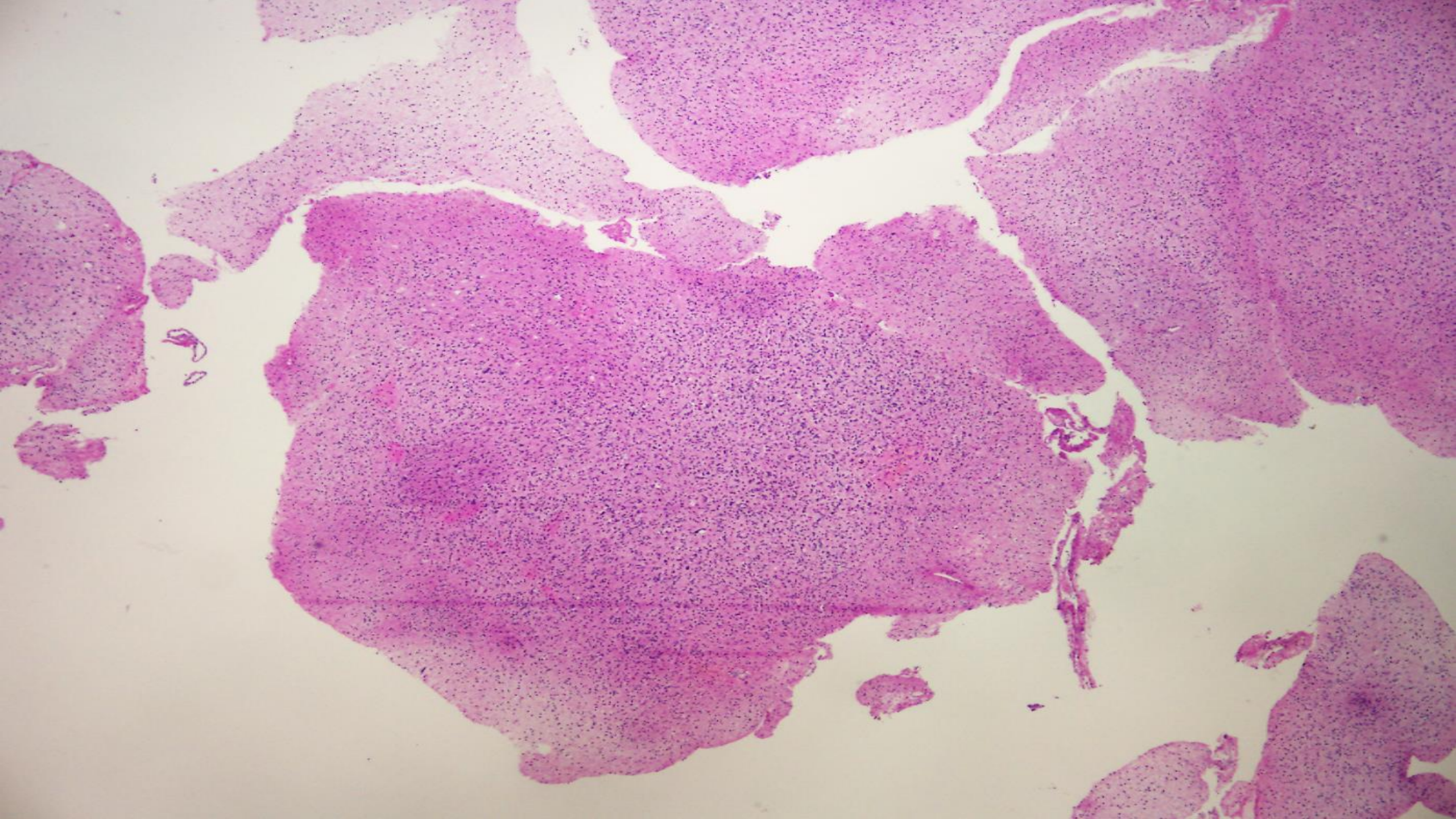
Positive (mutant) Negative(mutant)

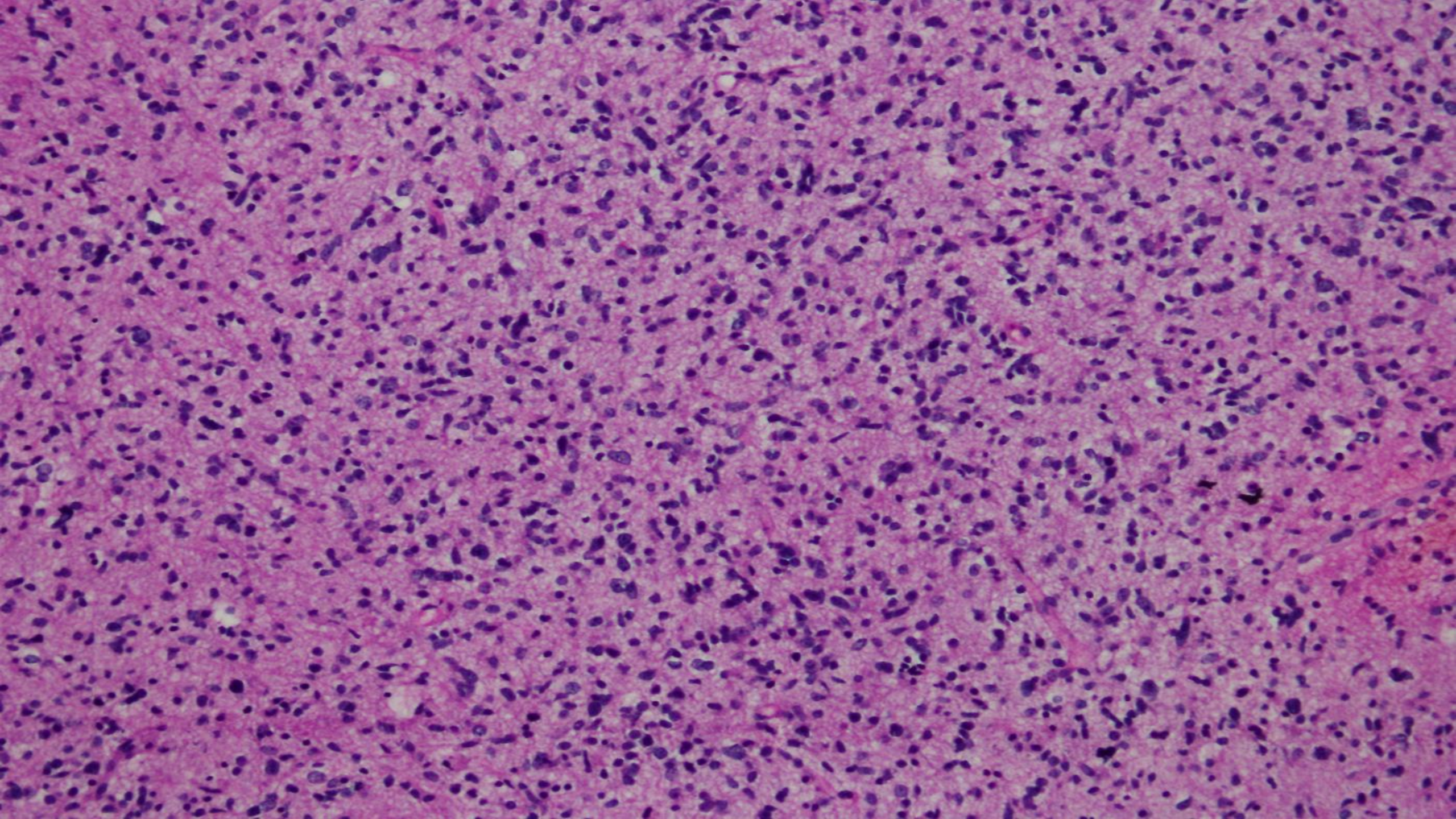
Internal Control (-) Internal Control (+)

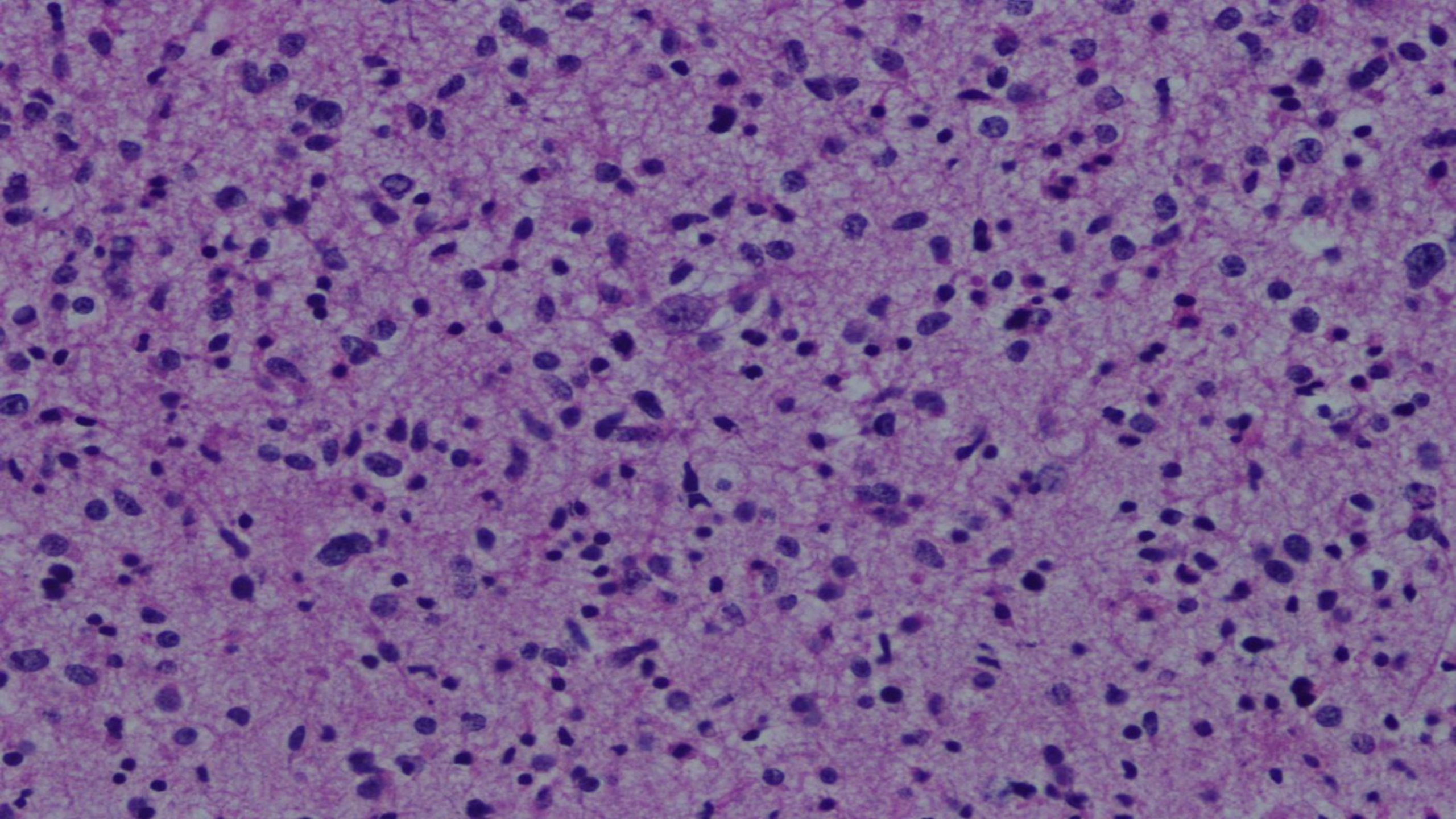
Histological grade is not important

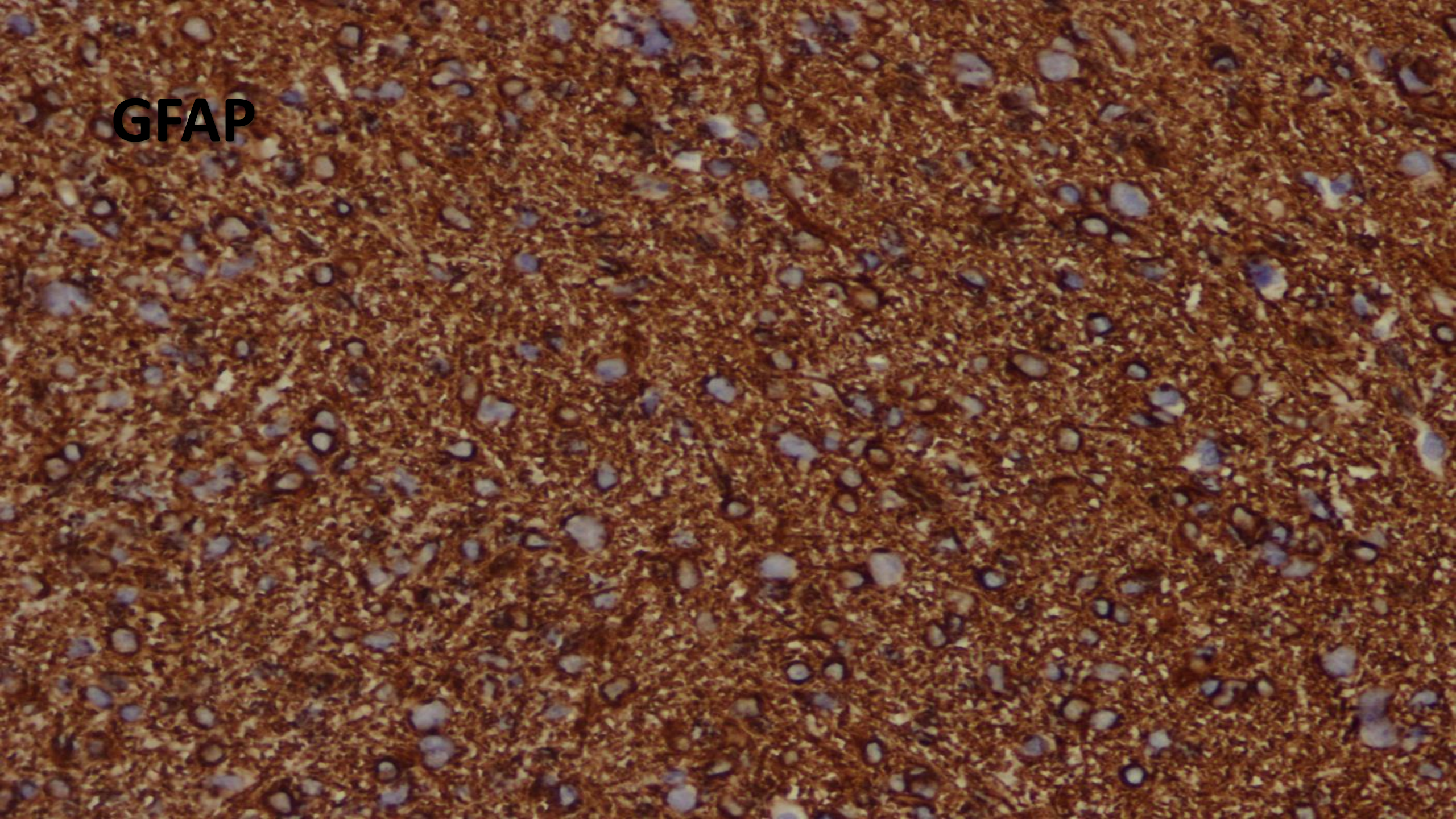
Case-1; 204288 P7305.21
A 5 year old male patient

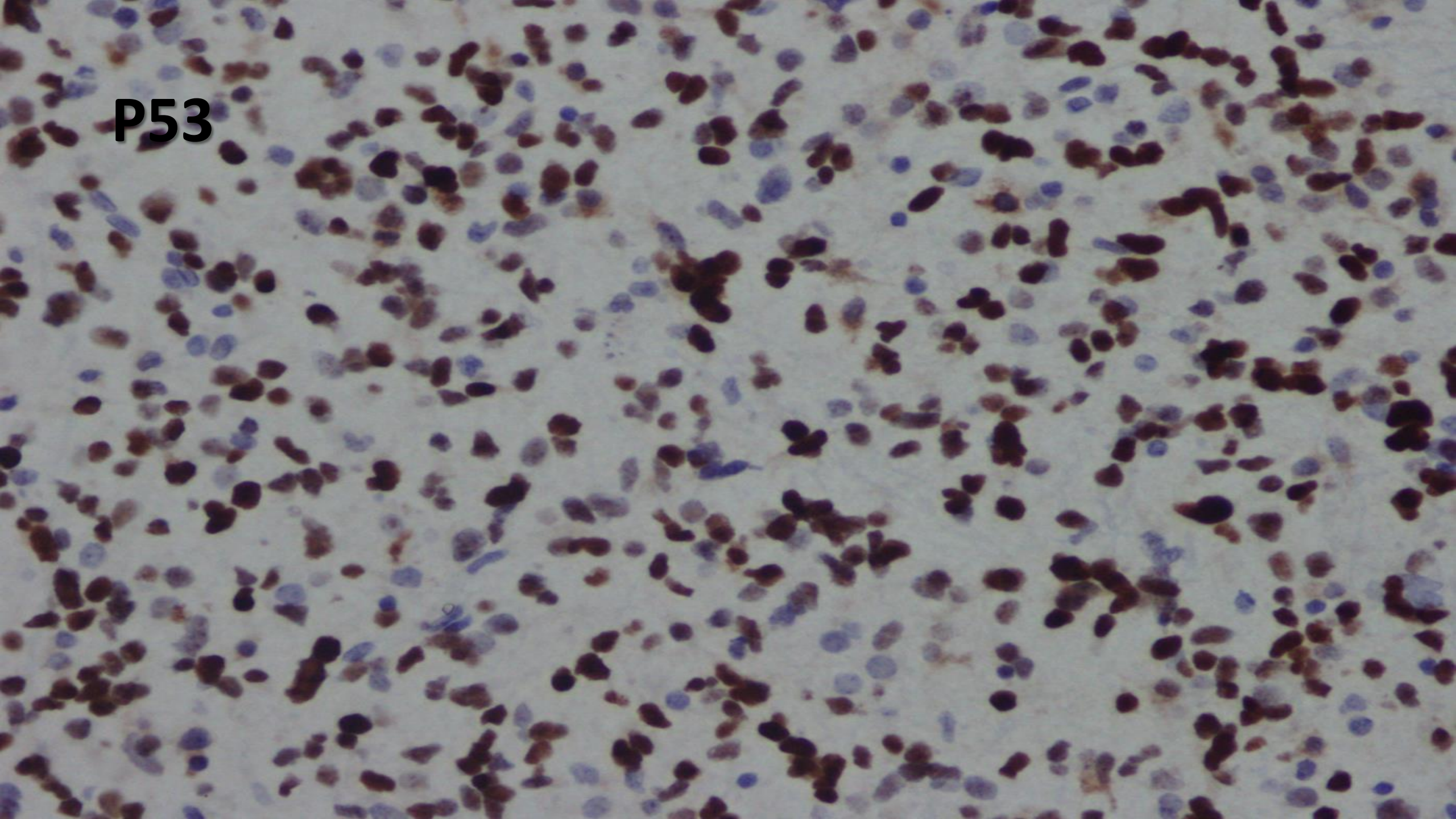


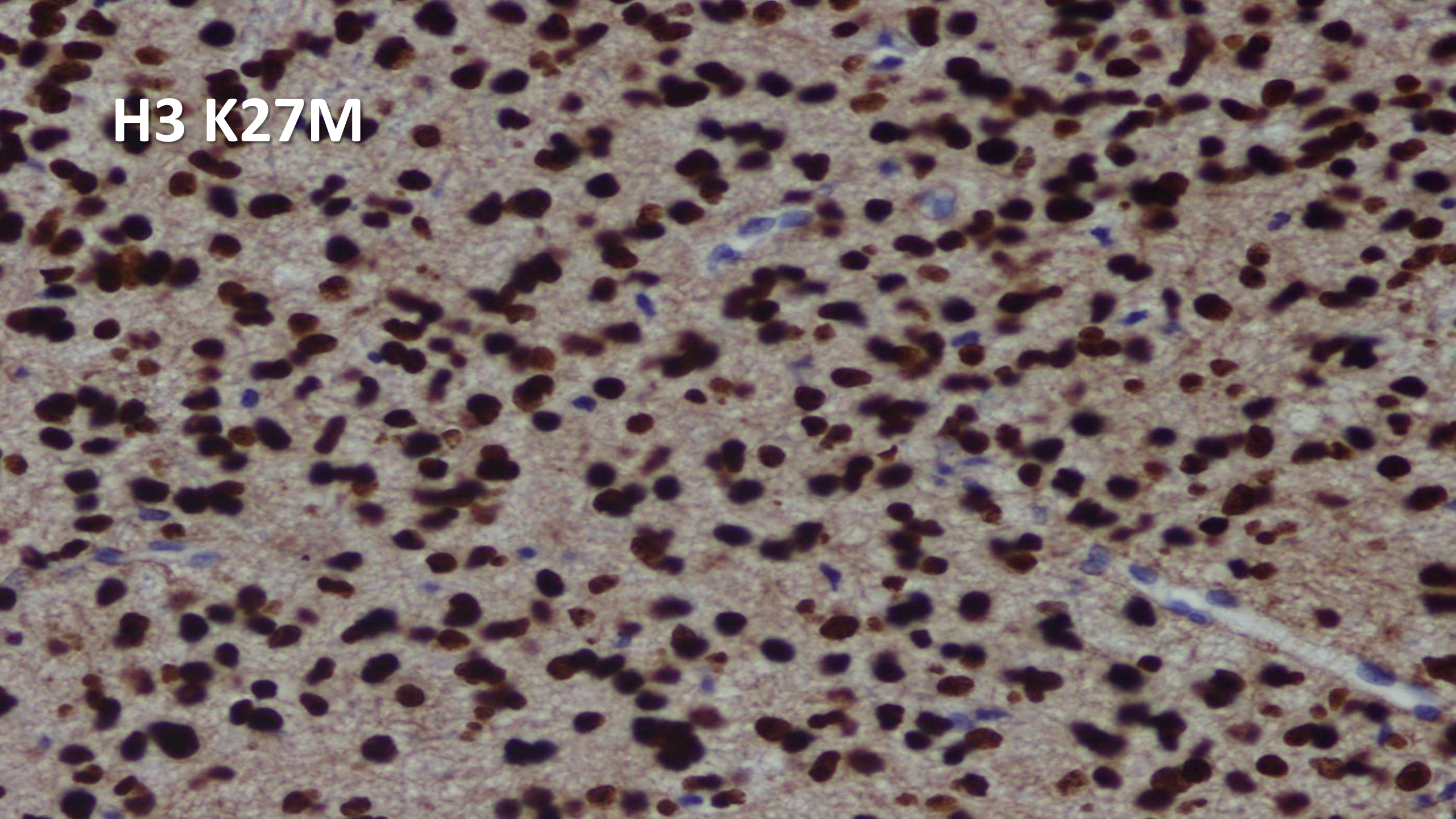


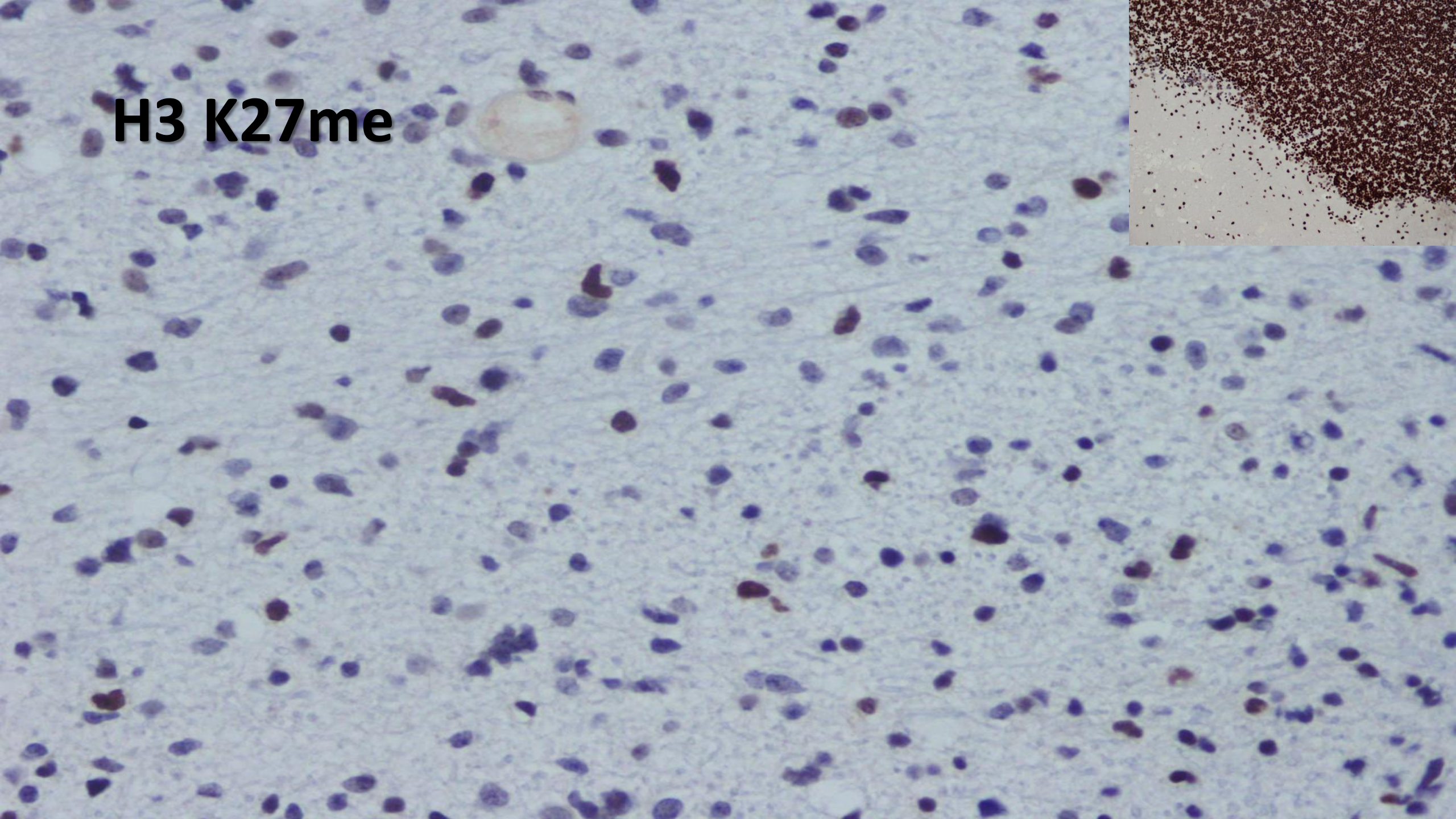




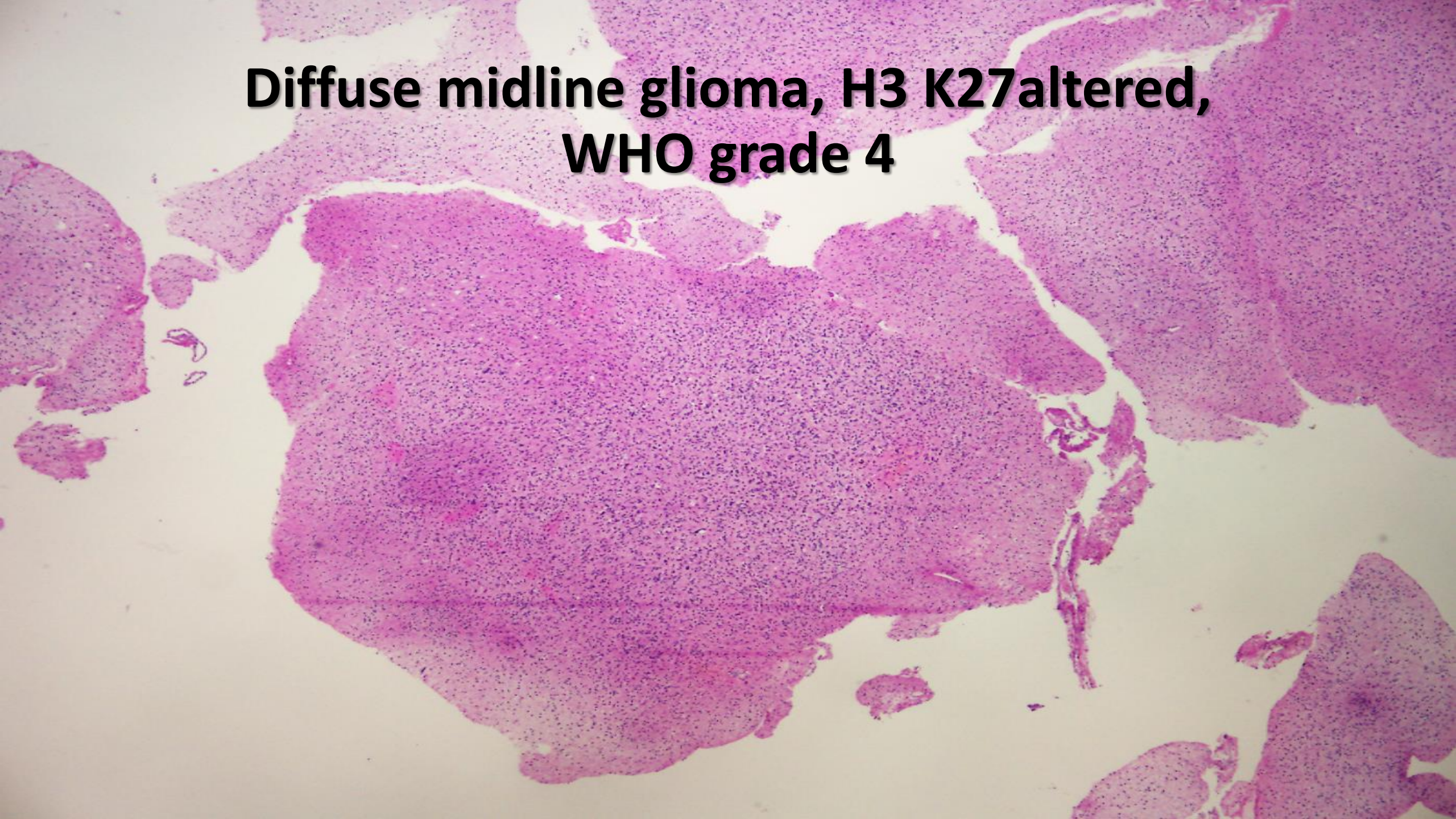

GFAP


P53

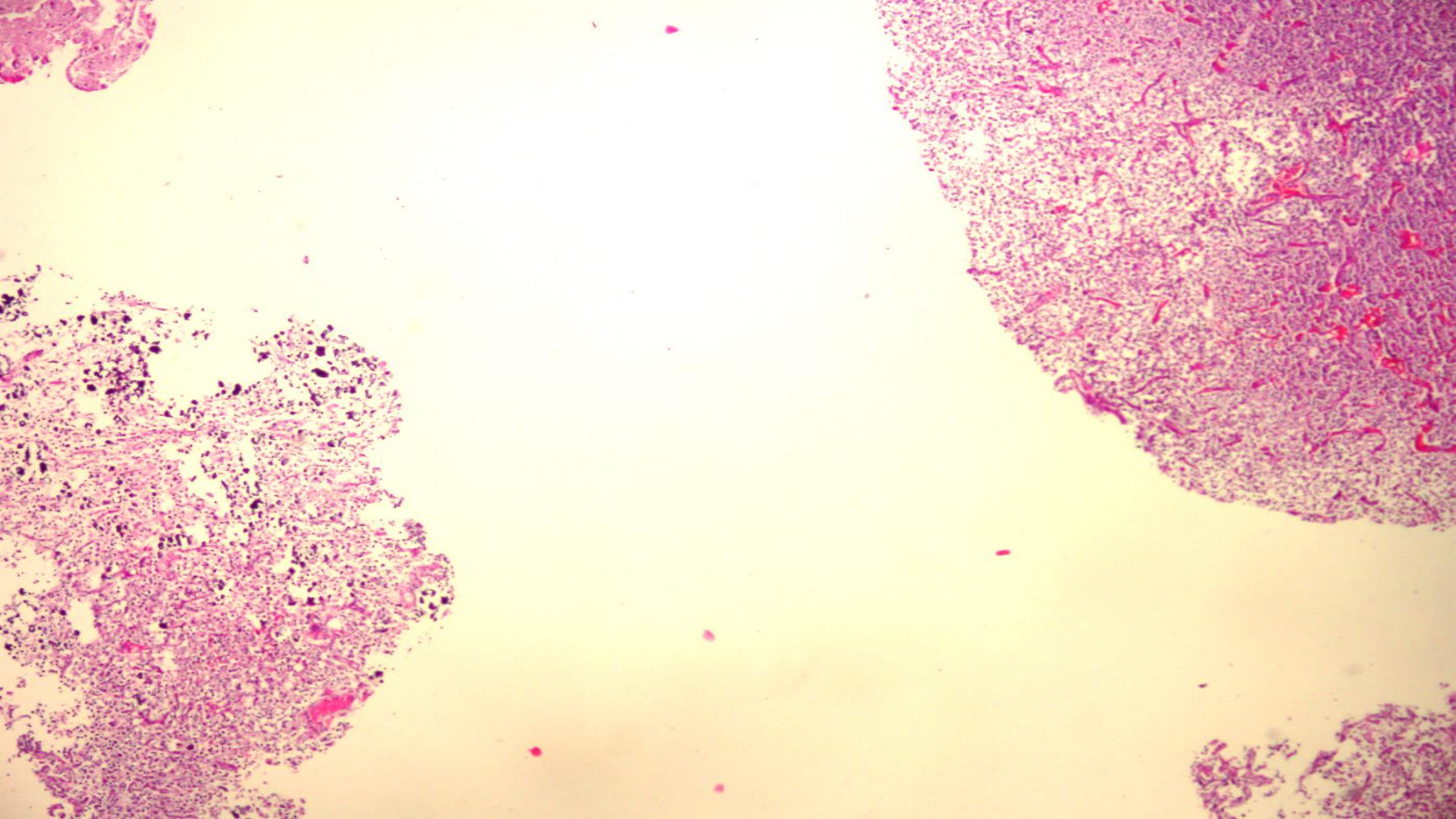

H3 K27M

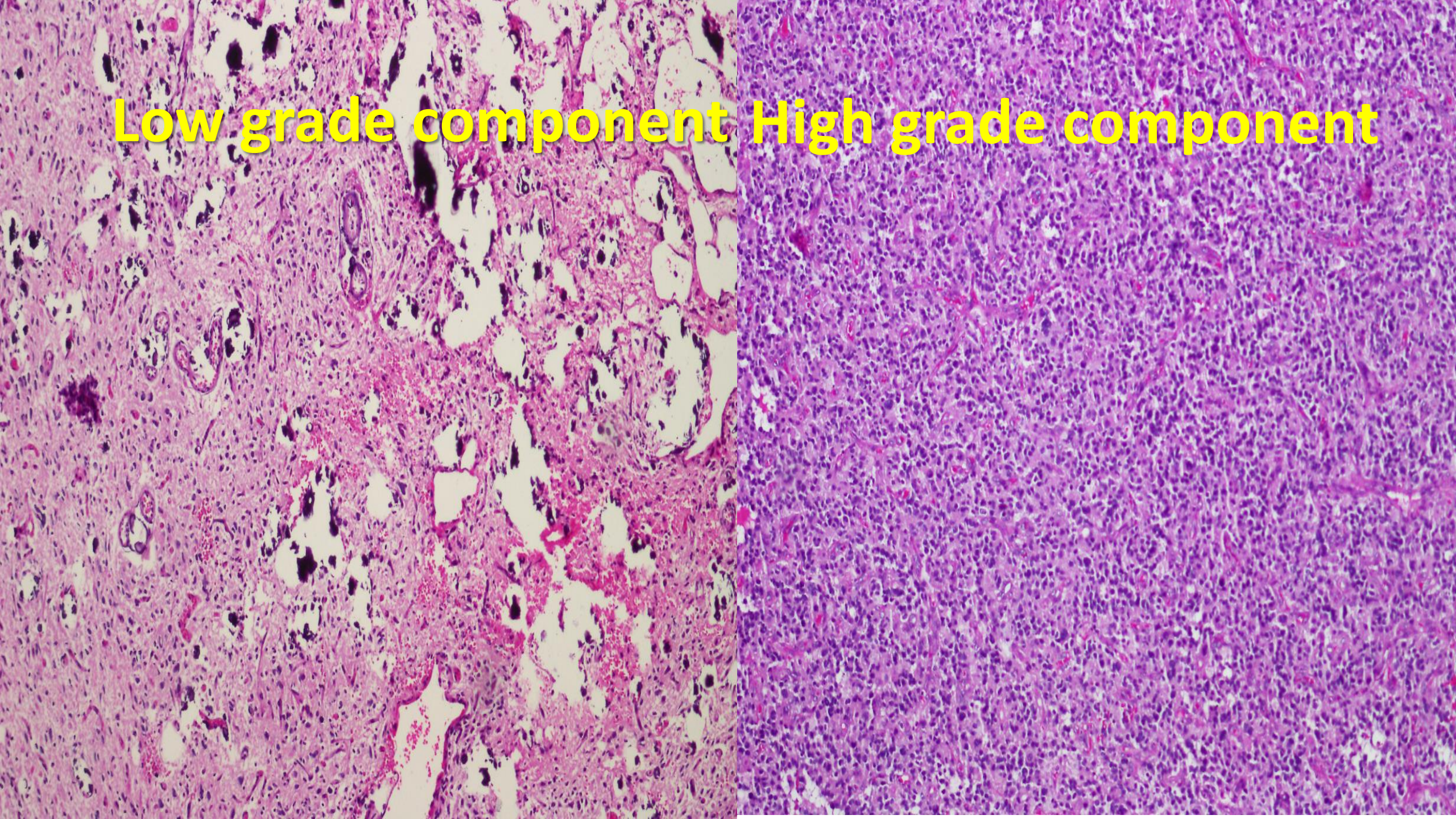

H3 K27me

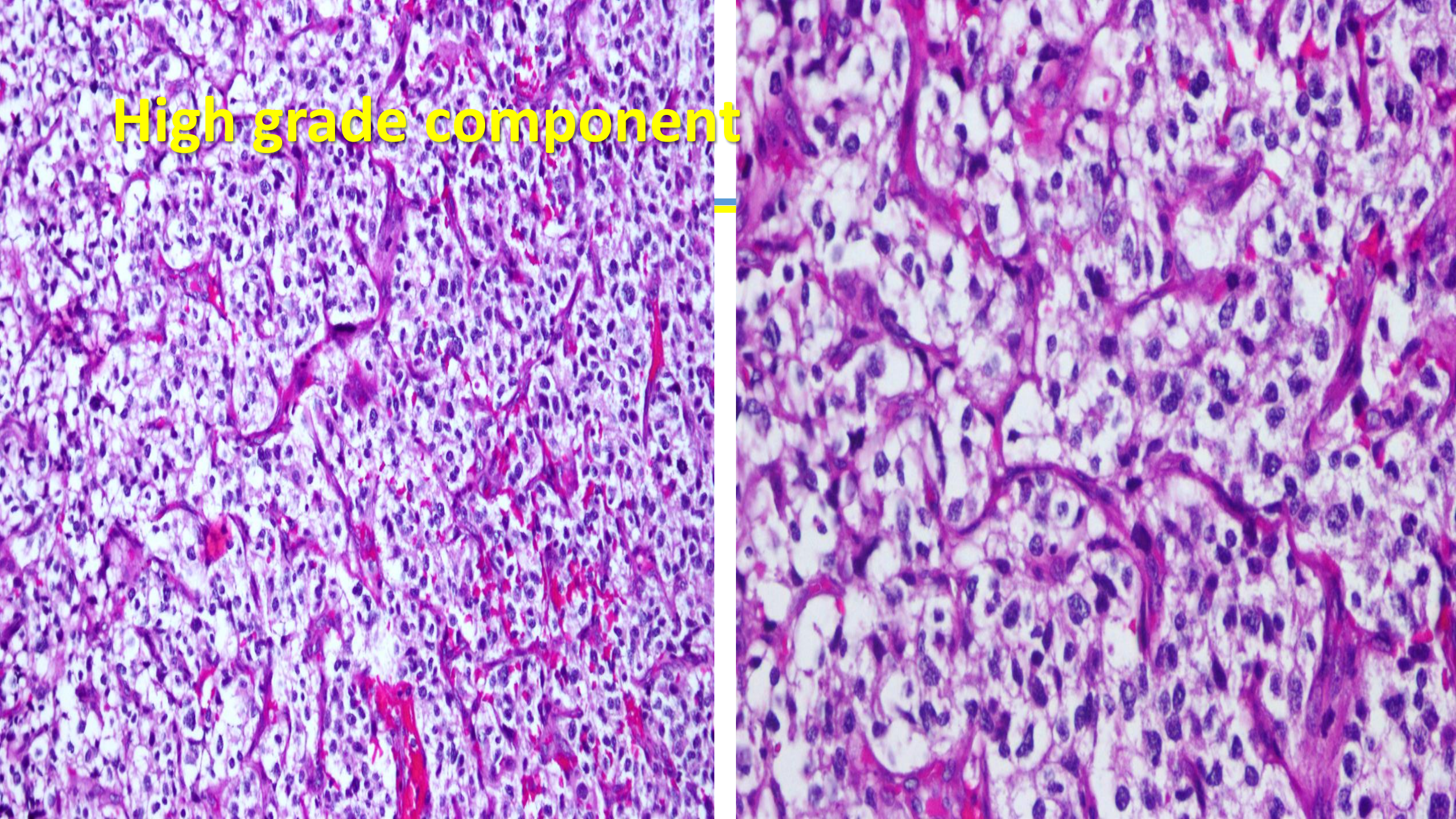
Diffuse midline glioma, H3 K27altered, WHO grade 4

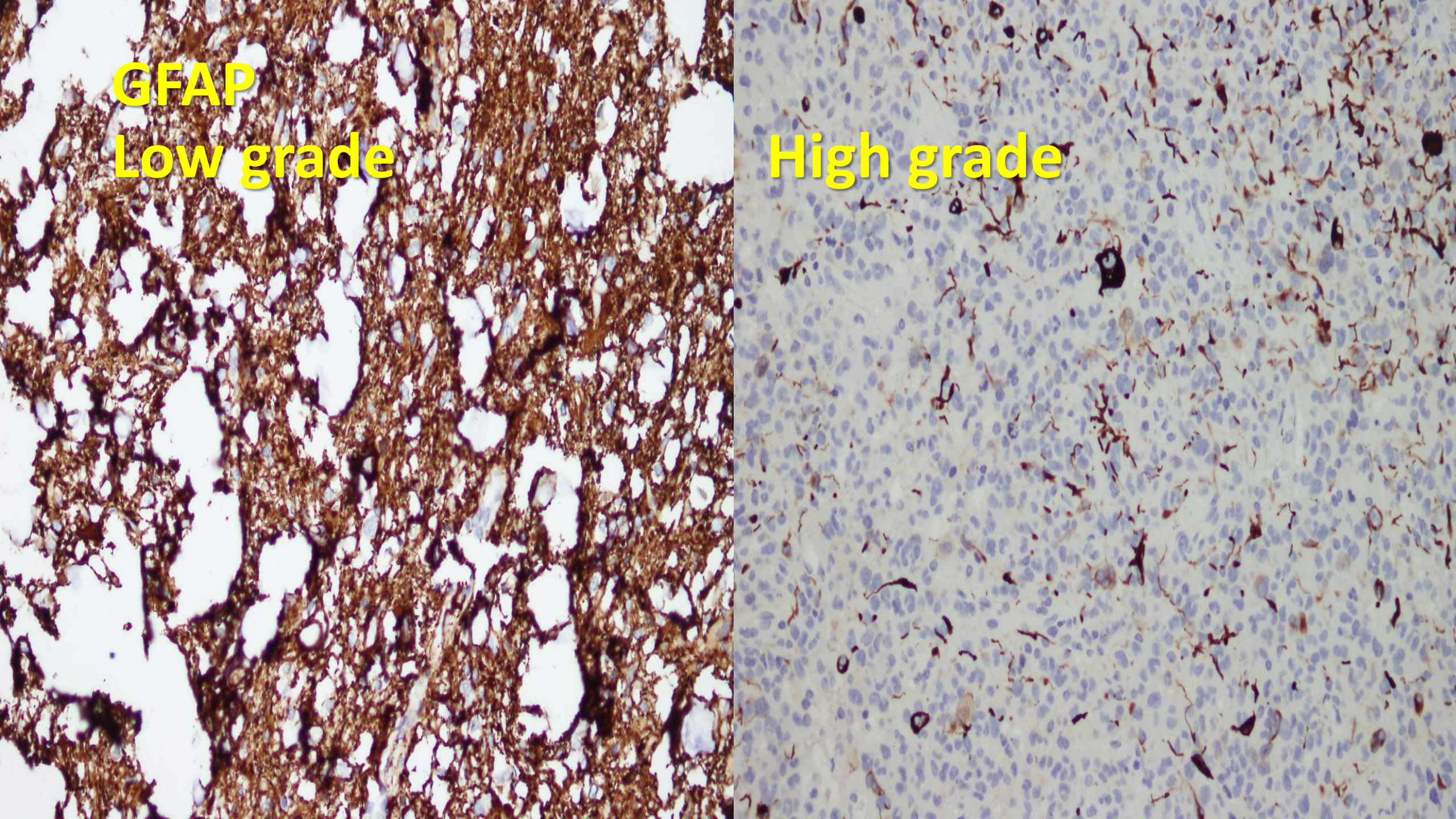


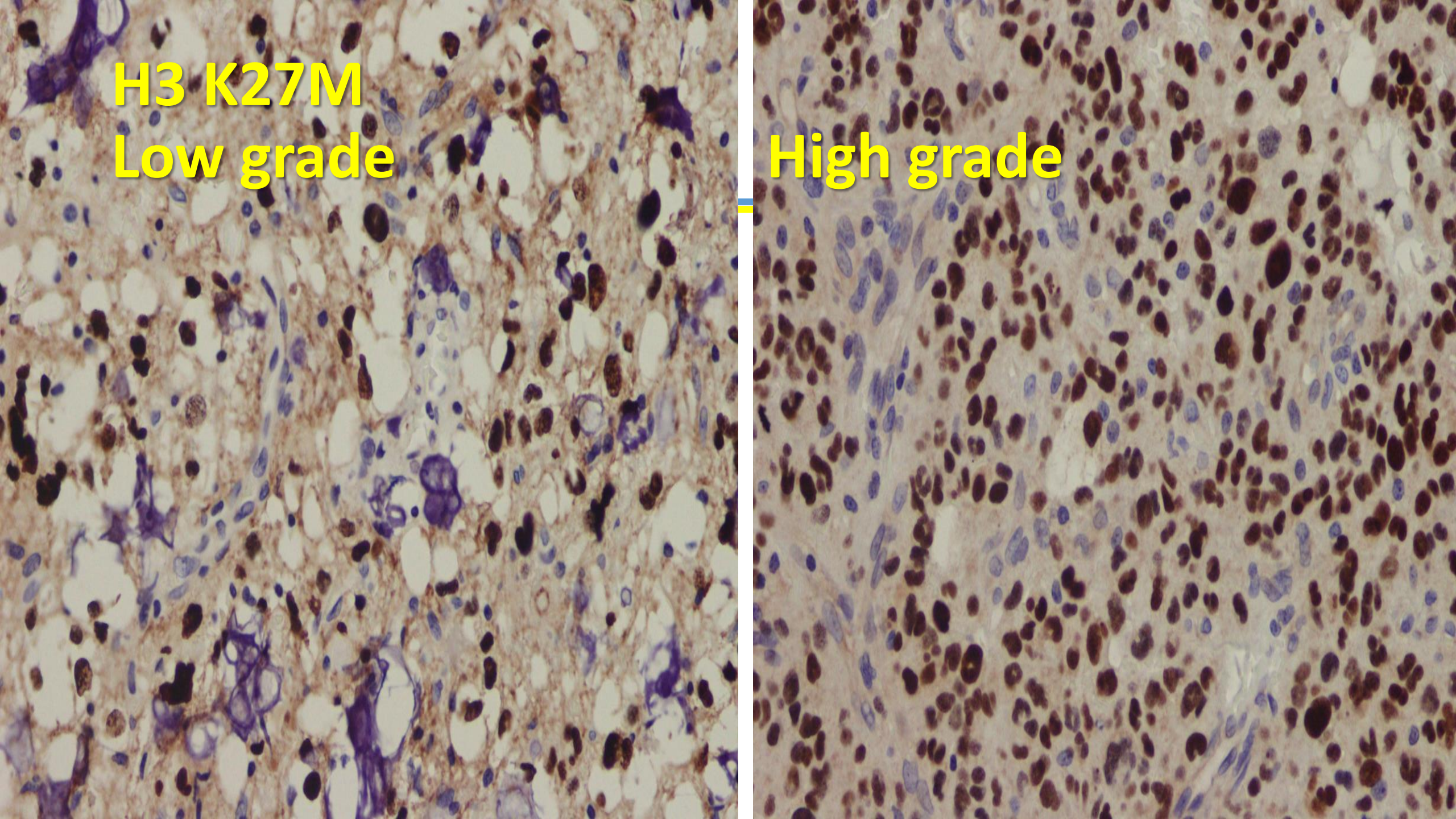
Case-2; P7310.21
A 17 year old male patient with a bithalamic tumor

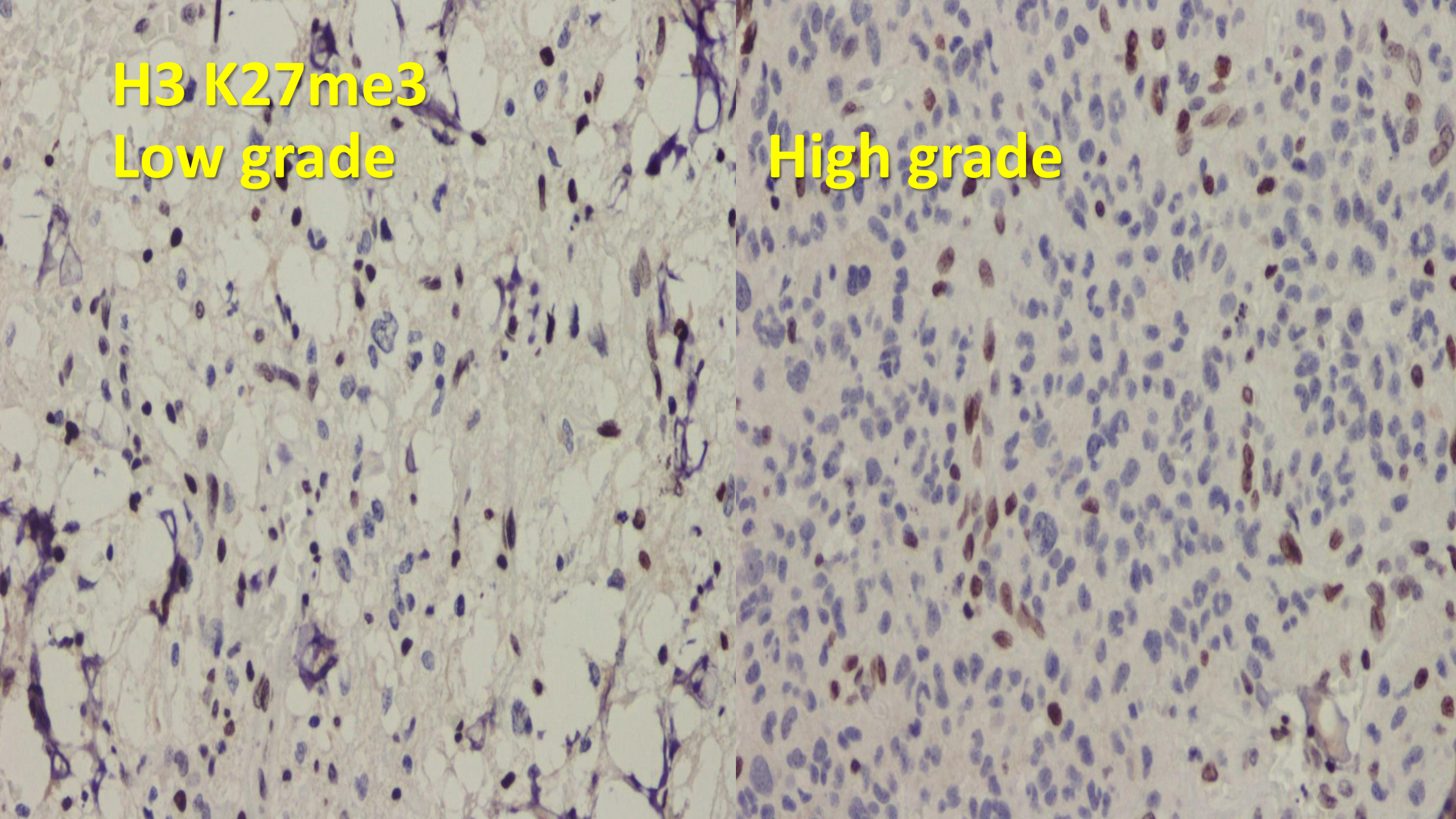


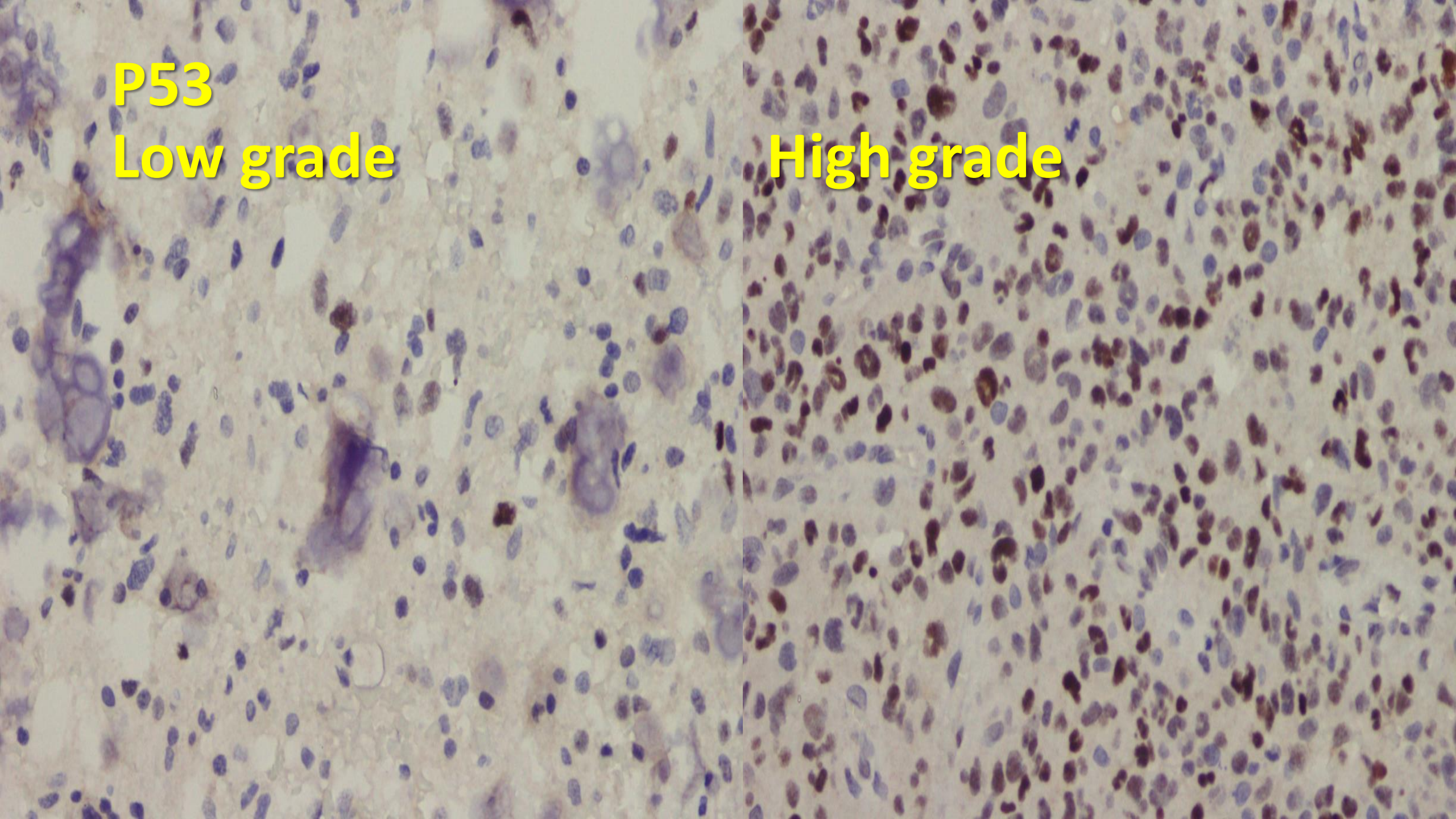

Low grade component
High grade component

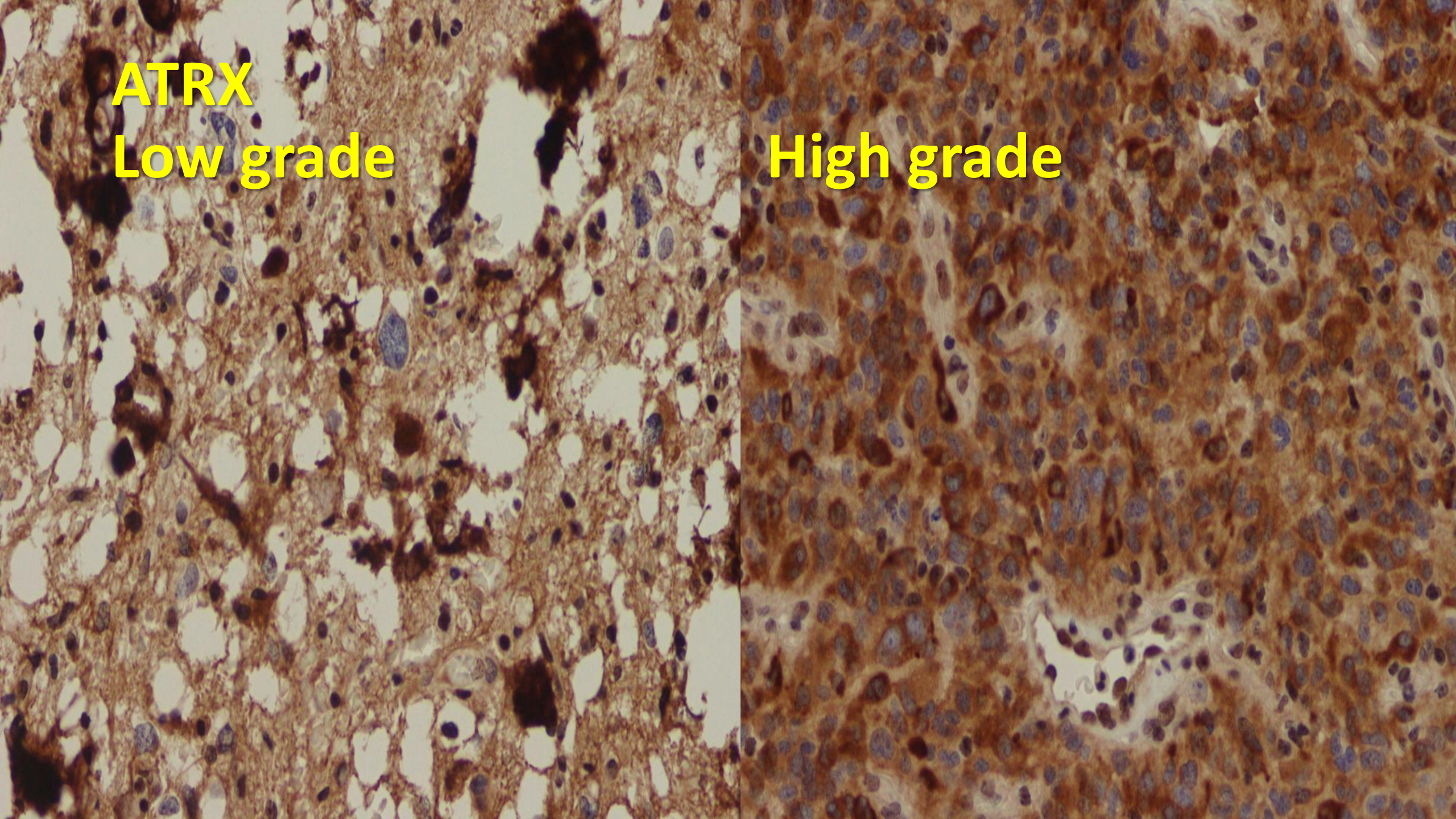

High grade component

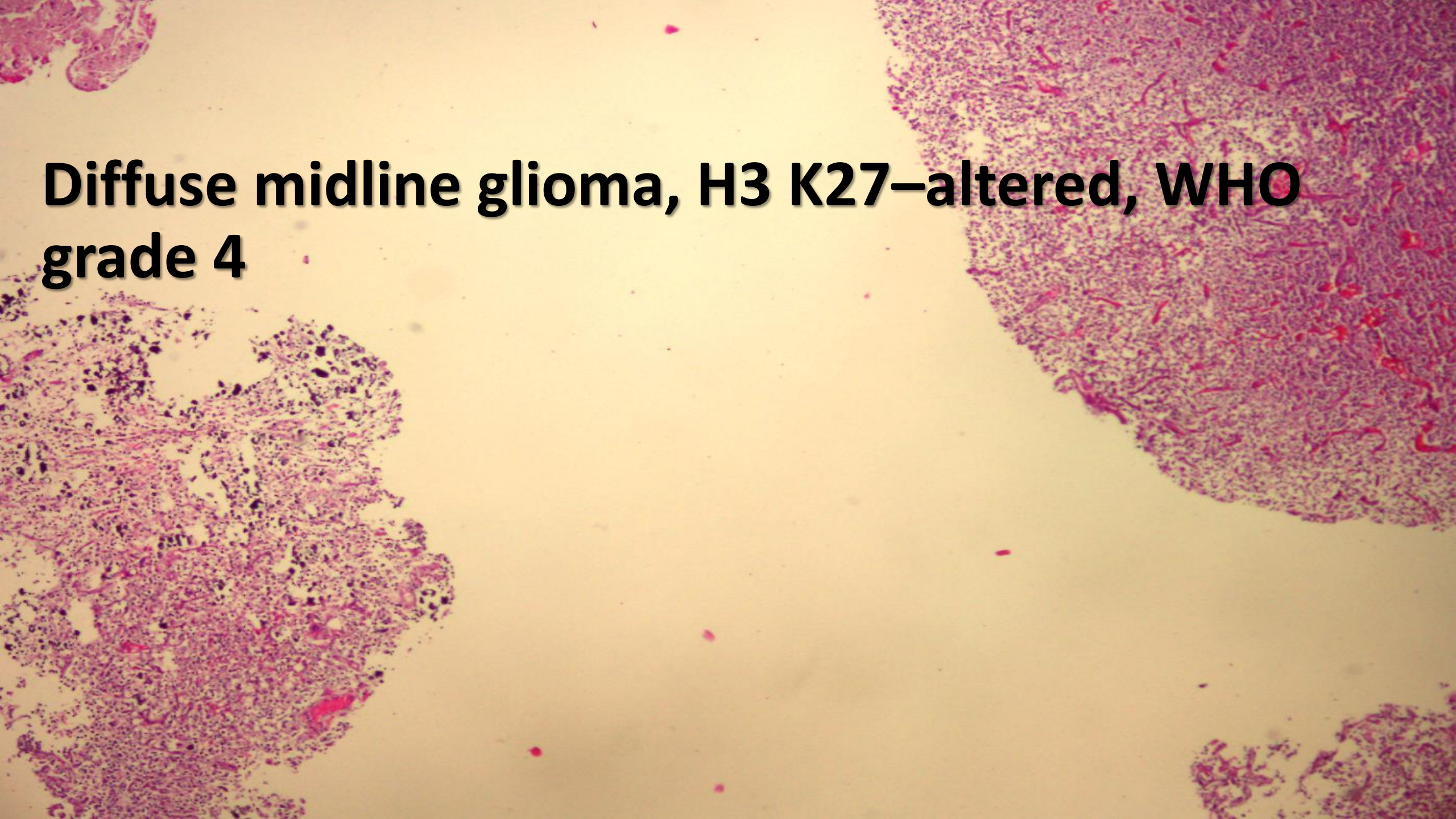

GFAP
Low grade
High grade


H3 K27M
Low grade
High grade


H3 K27me3
Low grade
High grade


P53
Low grade
High grade

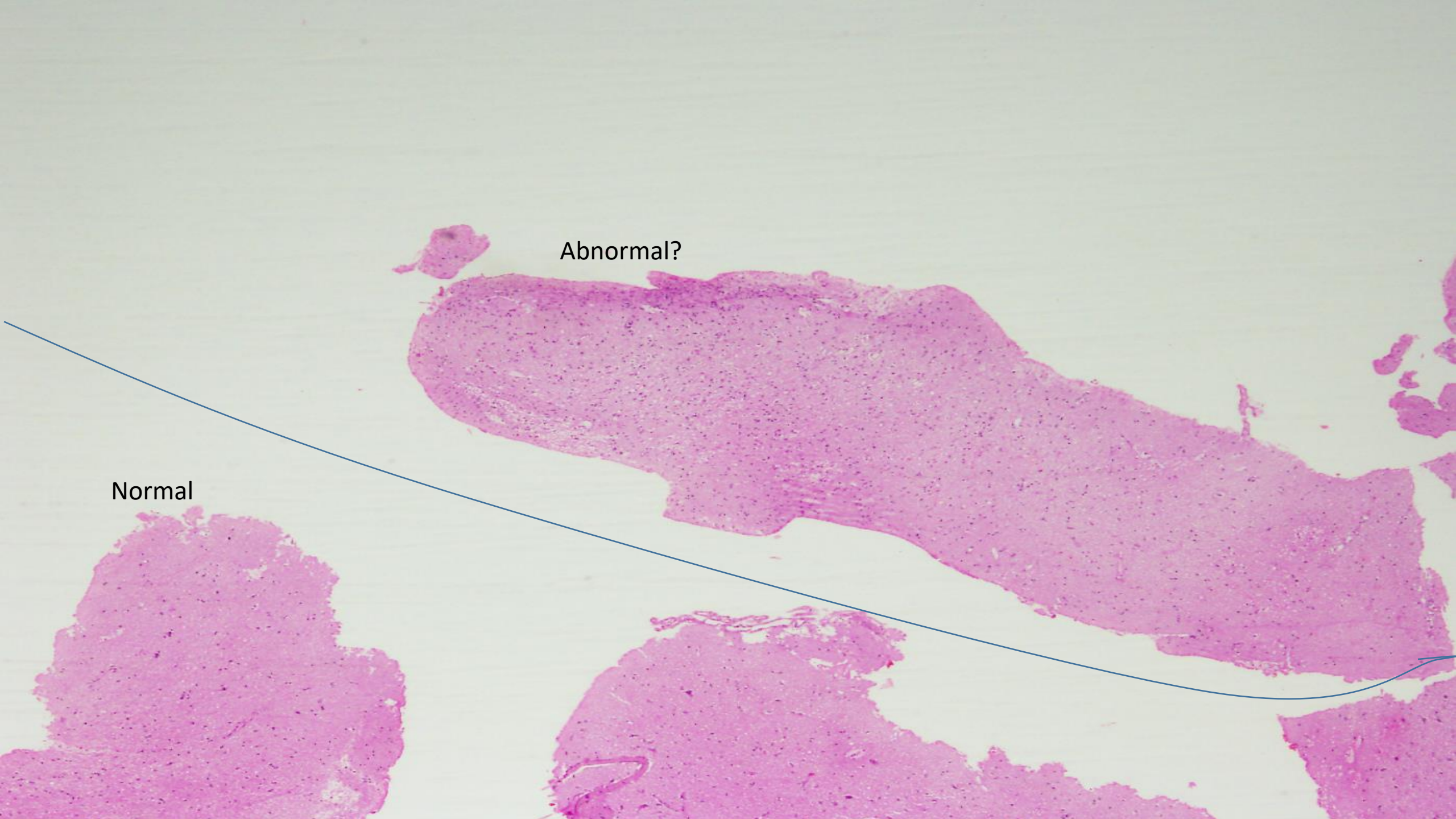

ATRX
Low grade
High grade

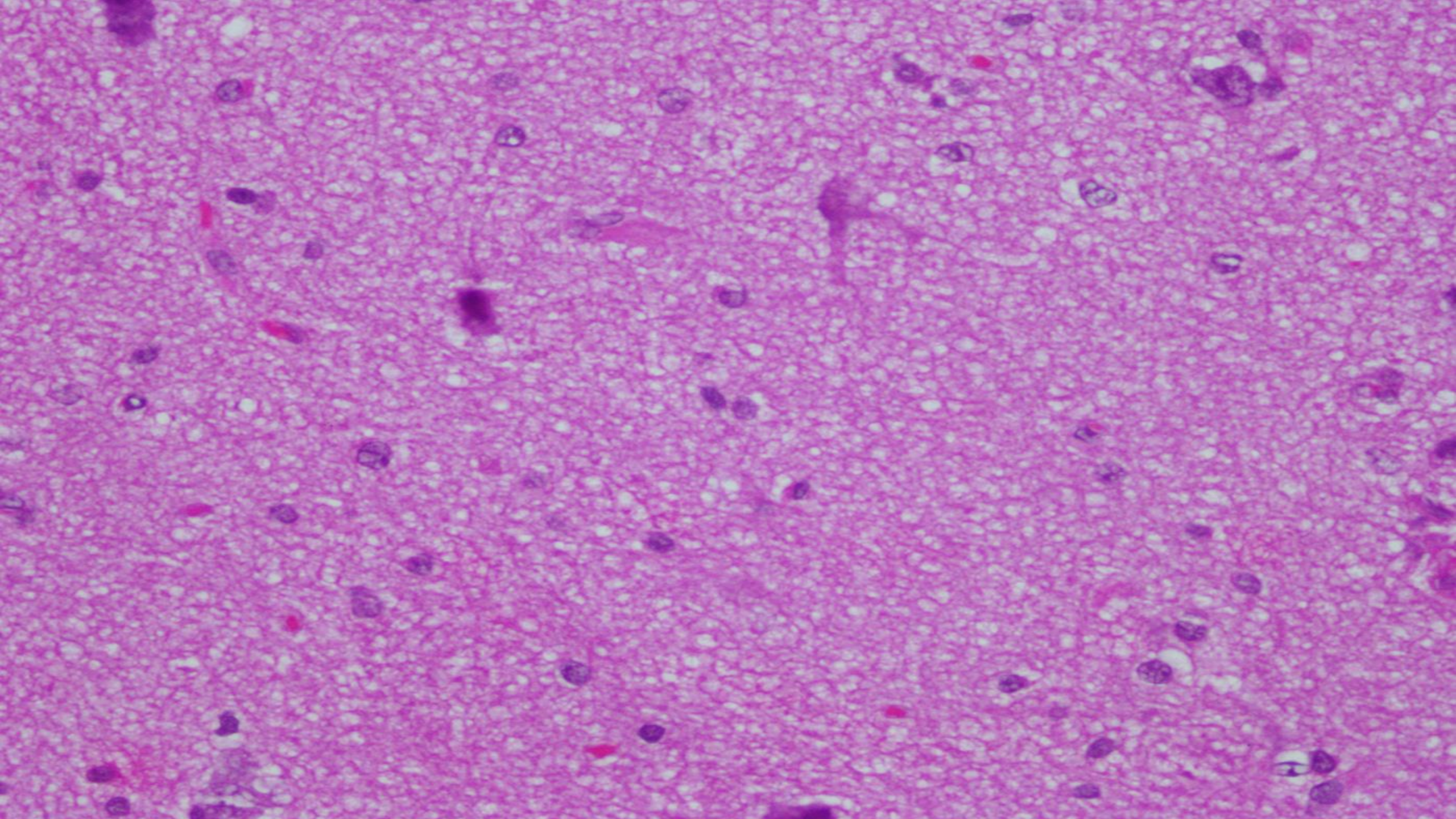


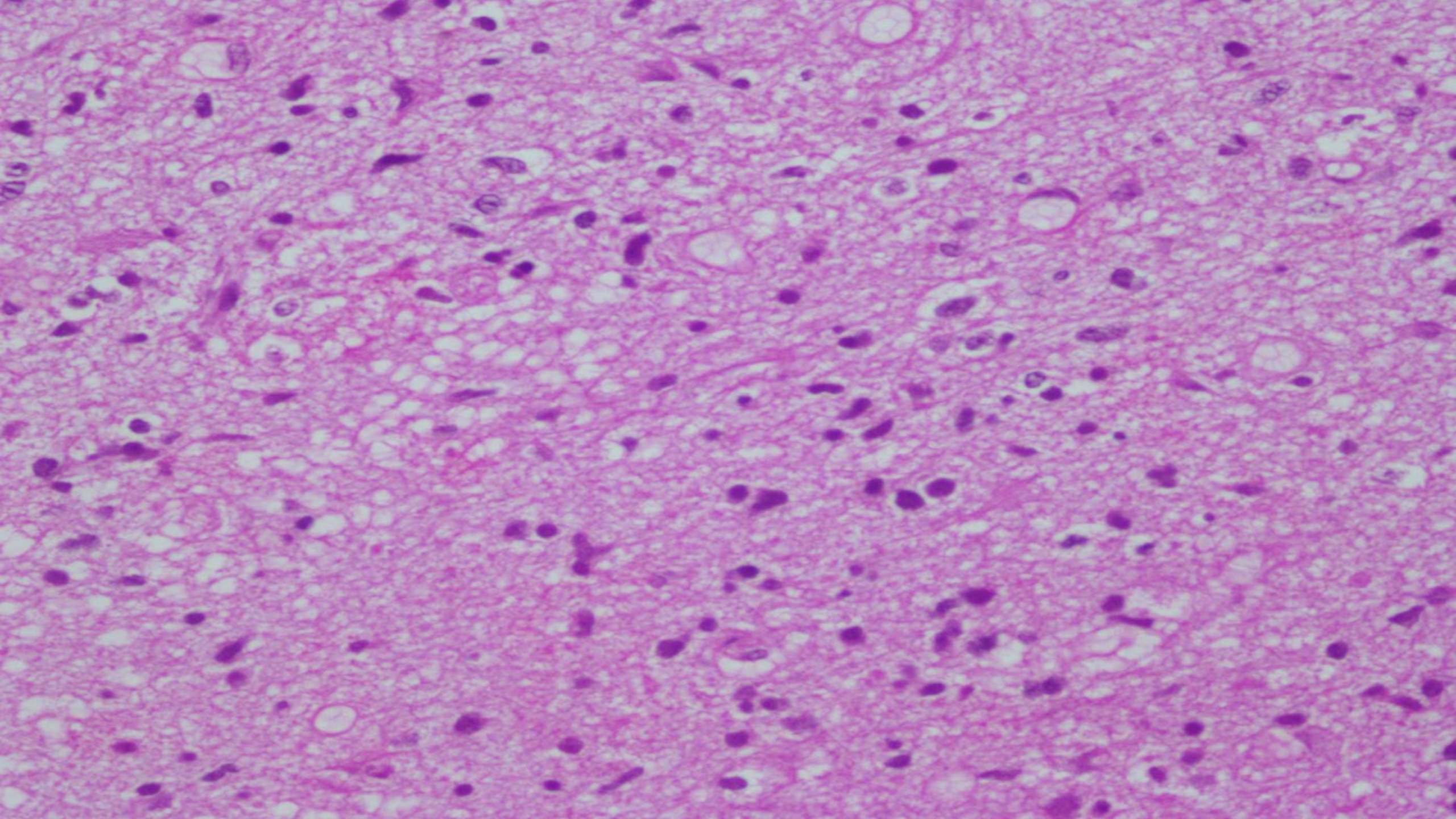
Diffuse midline glioma, H3 K27–altered, WHO grade 4

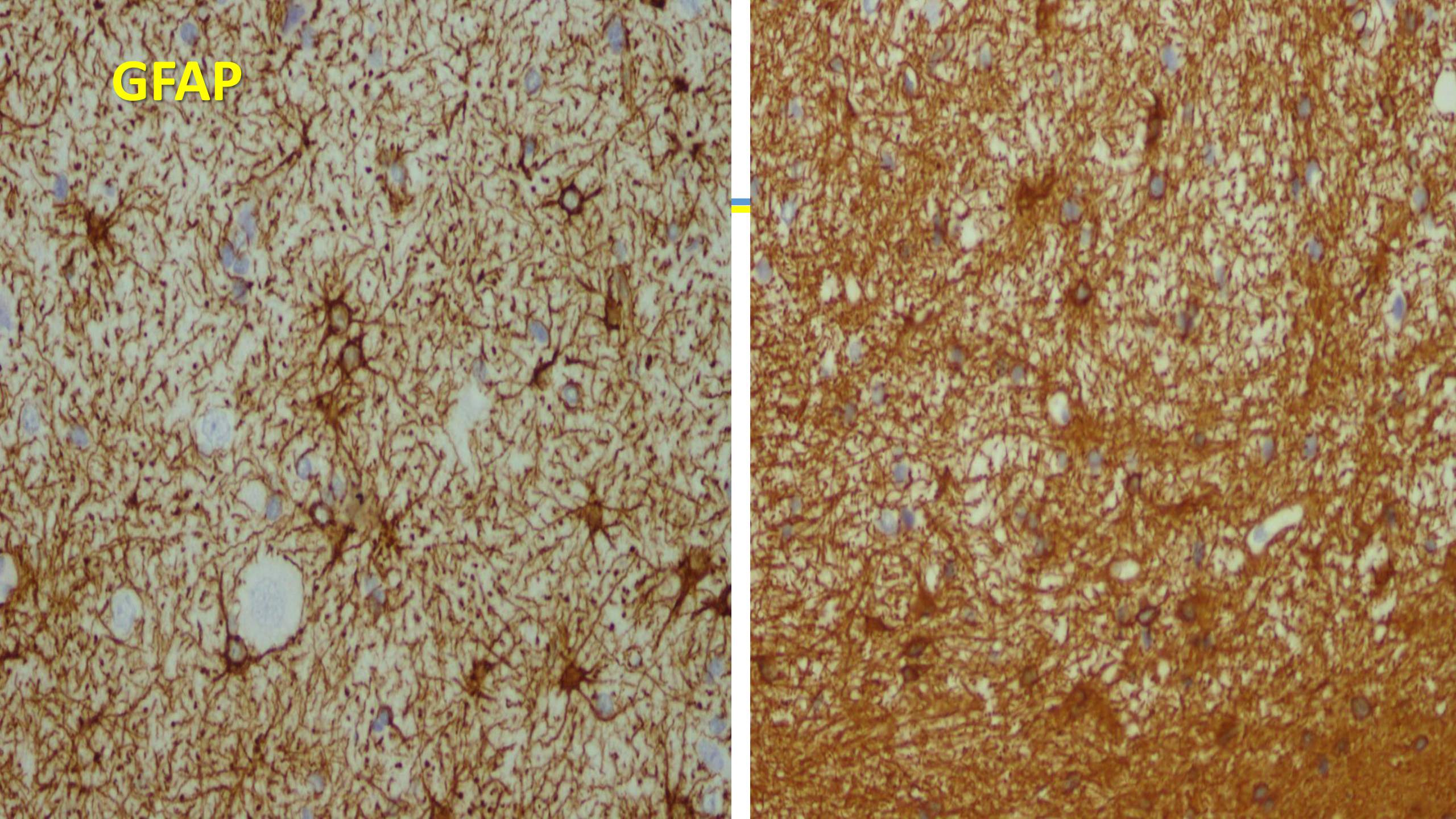
Case-2; Low grade component can exist with high grade component. ATRX can be mutant in a subset of cases (15%)

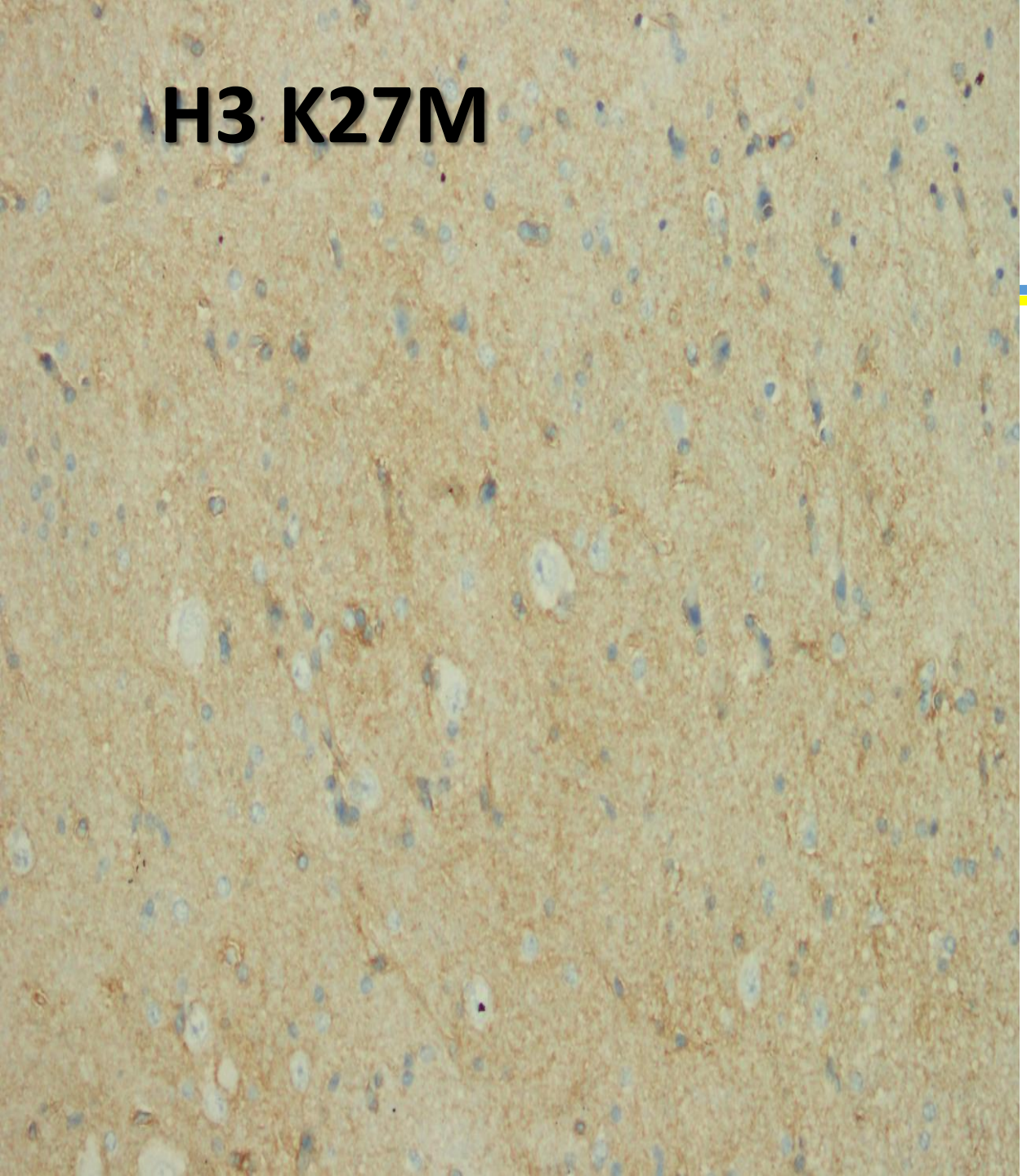
Case-3;
MRN 86537 P1852.2014. A 7 year old female patient with midbrain mass invading the pons and the thalamus

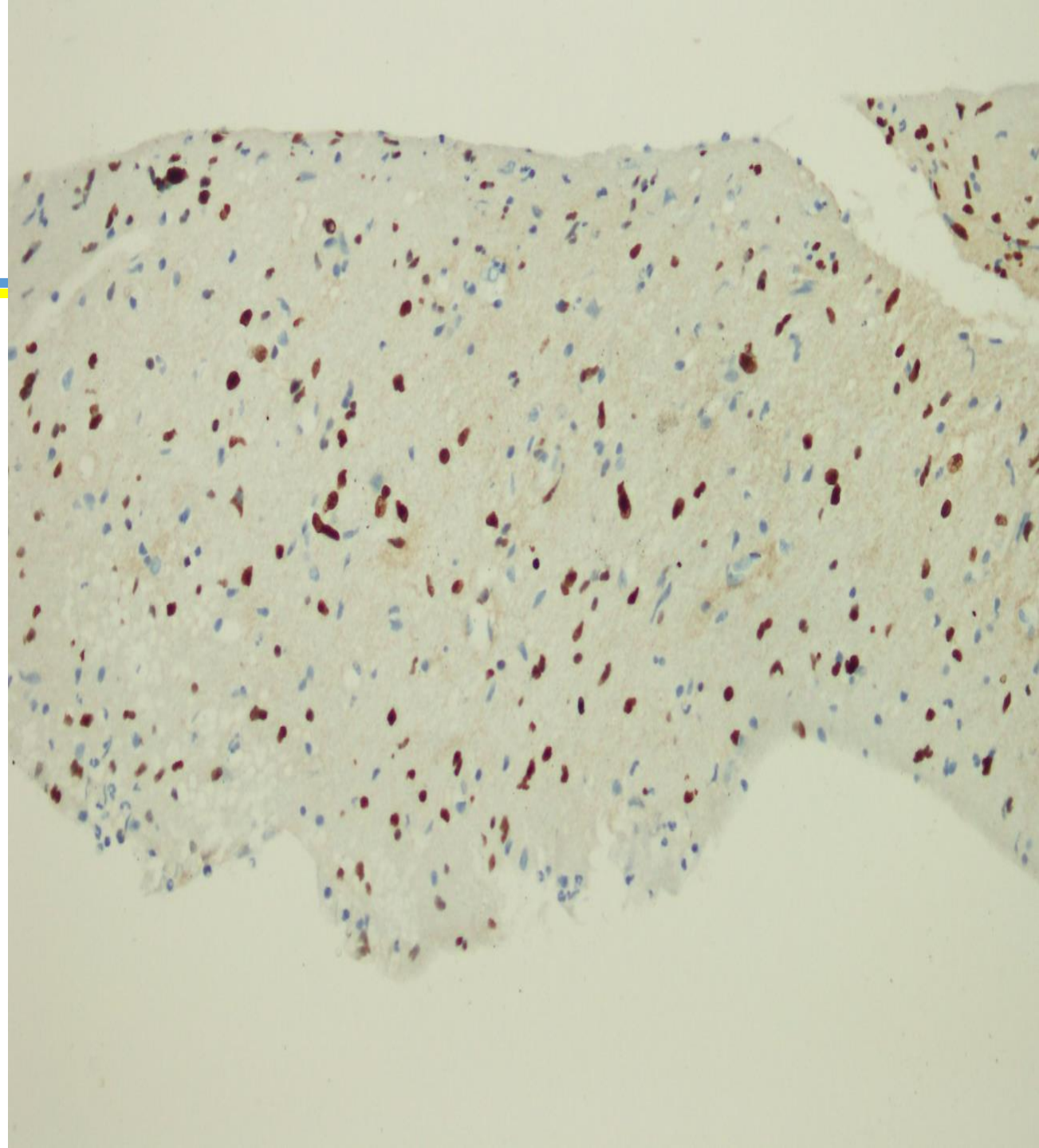

Abnormal?
Normal

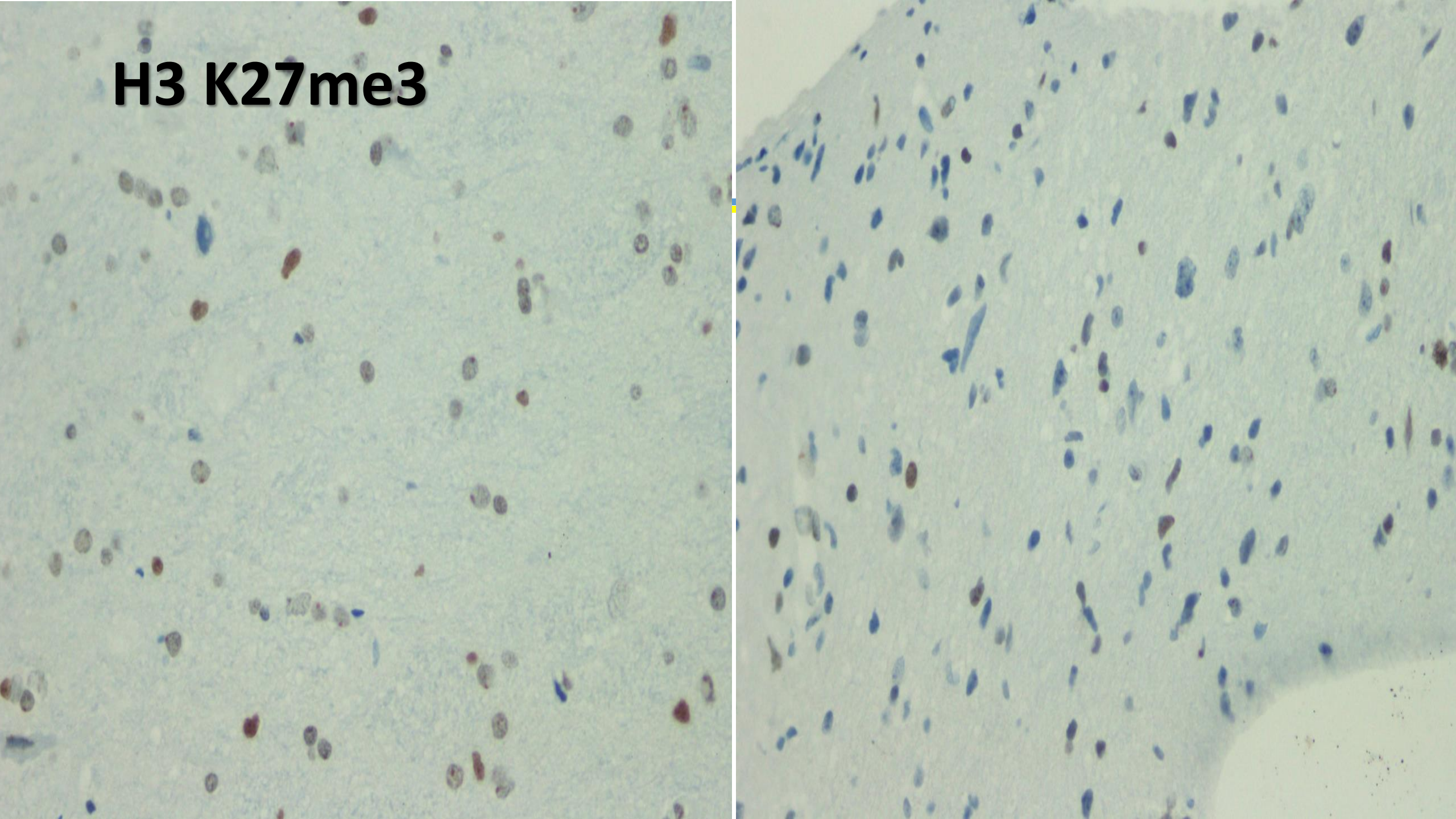




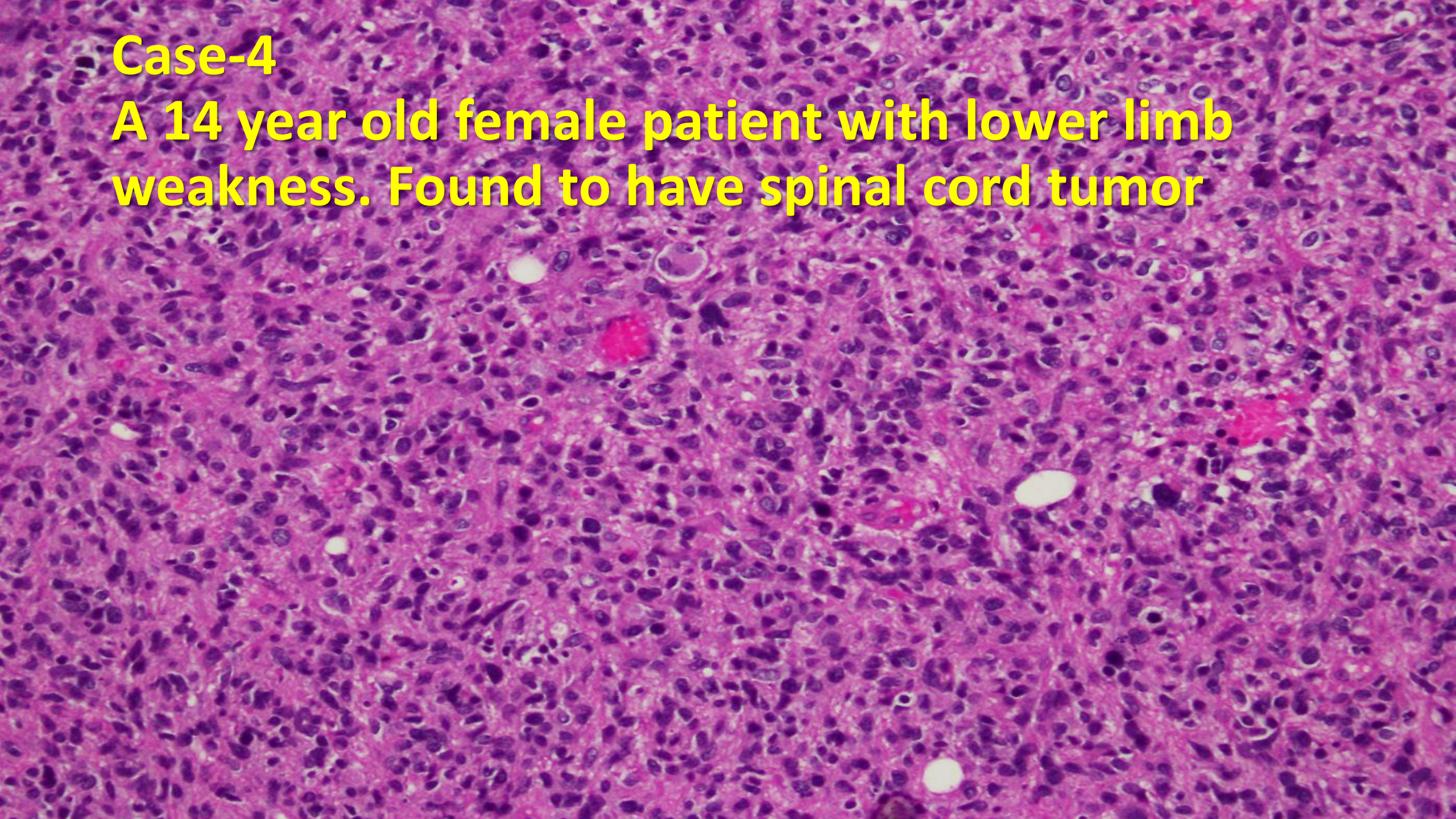

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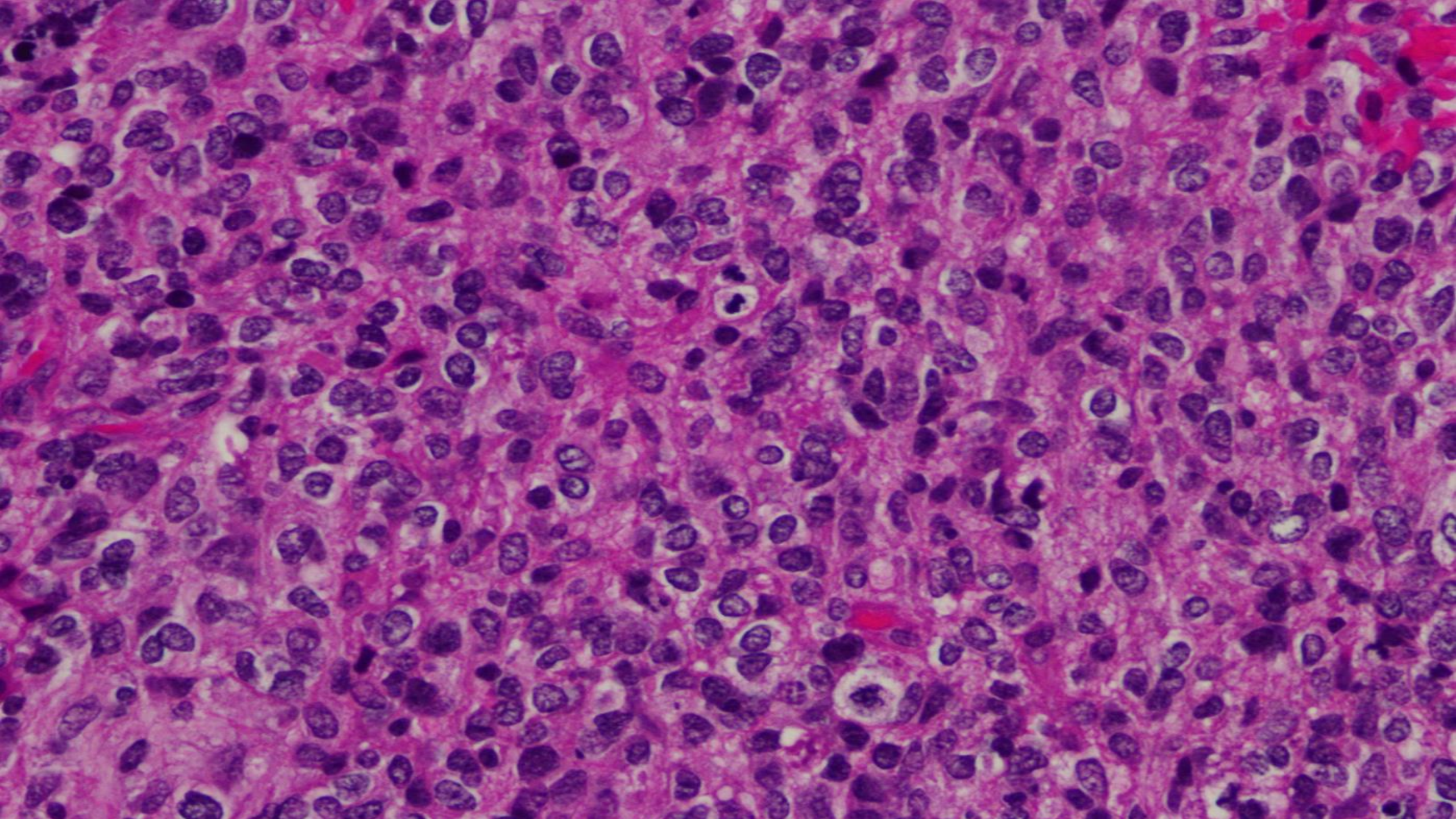

H3 K27M

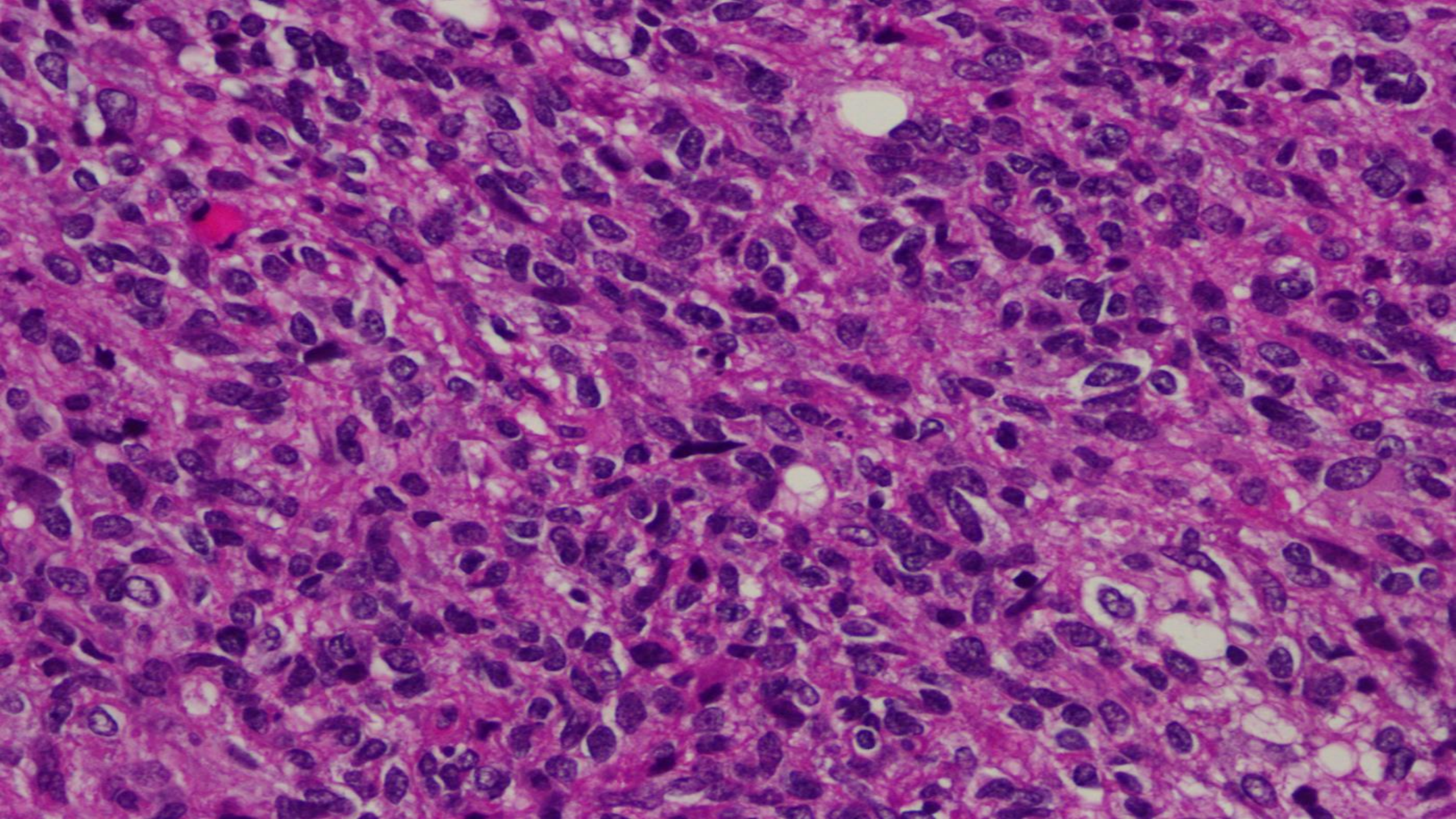


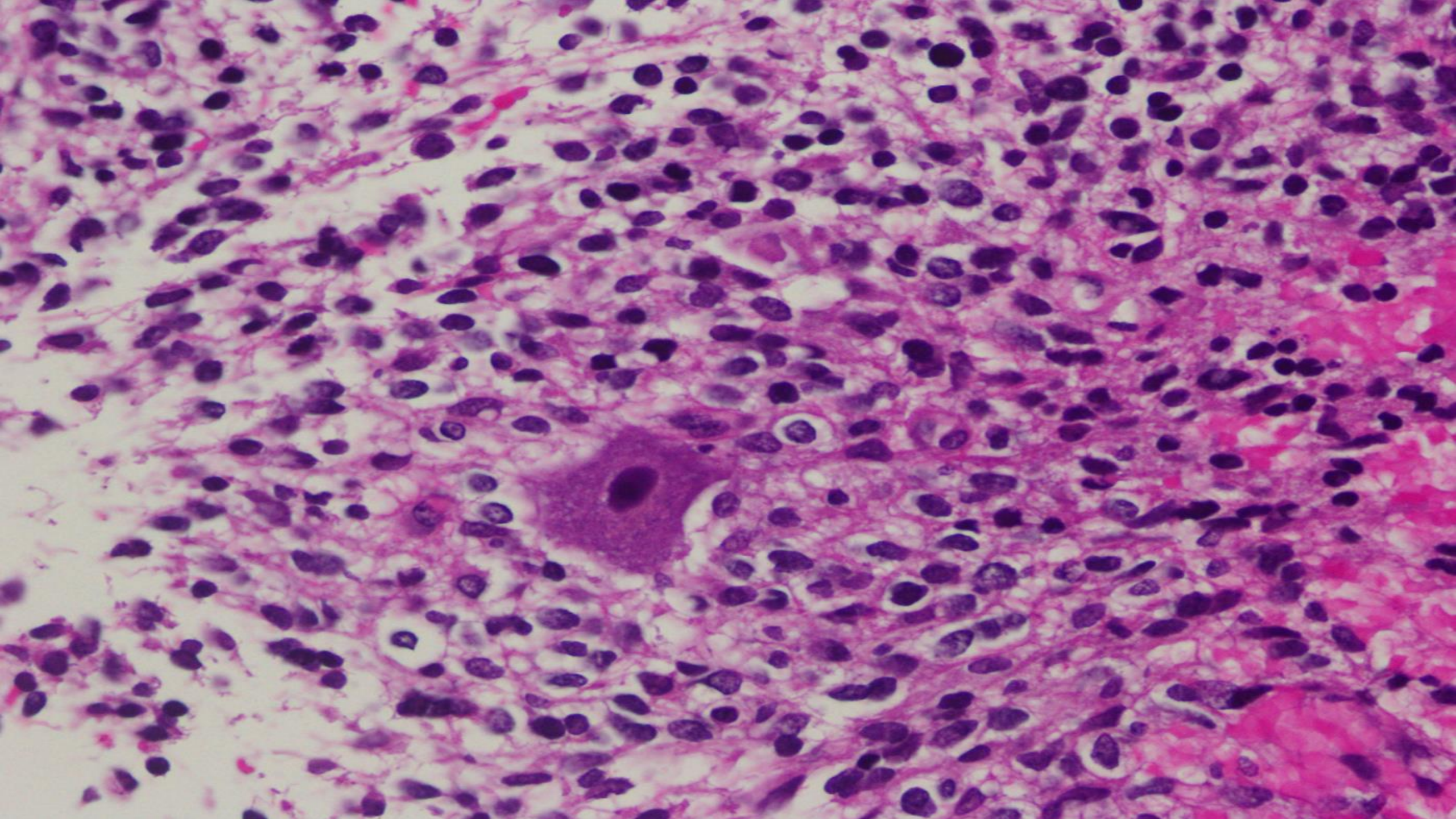

H3 K27me3

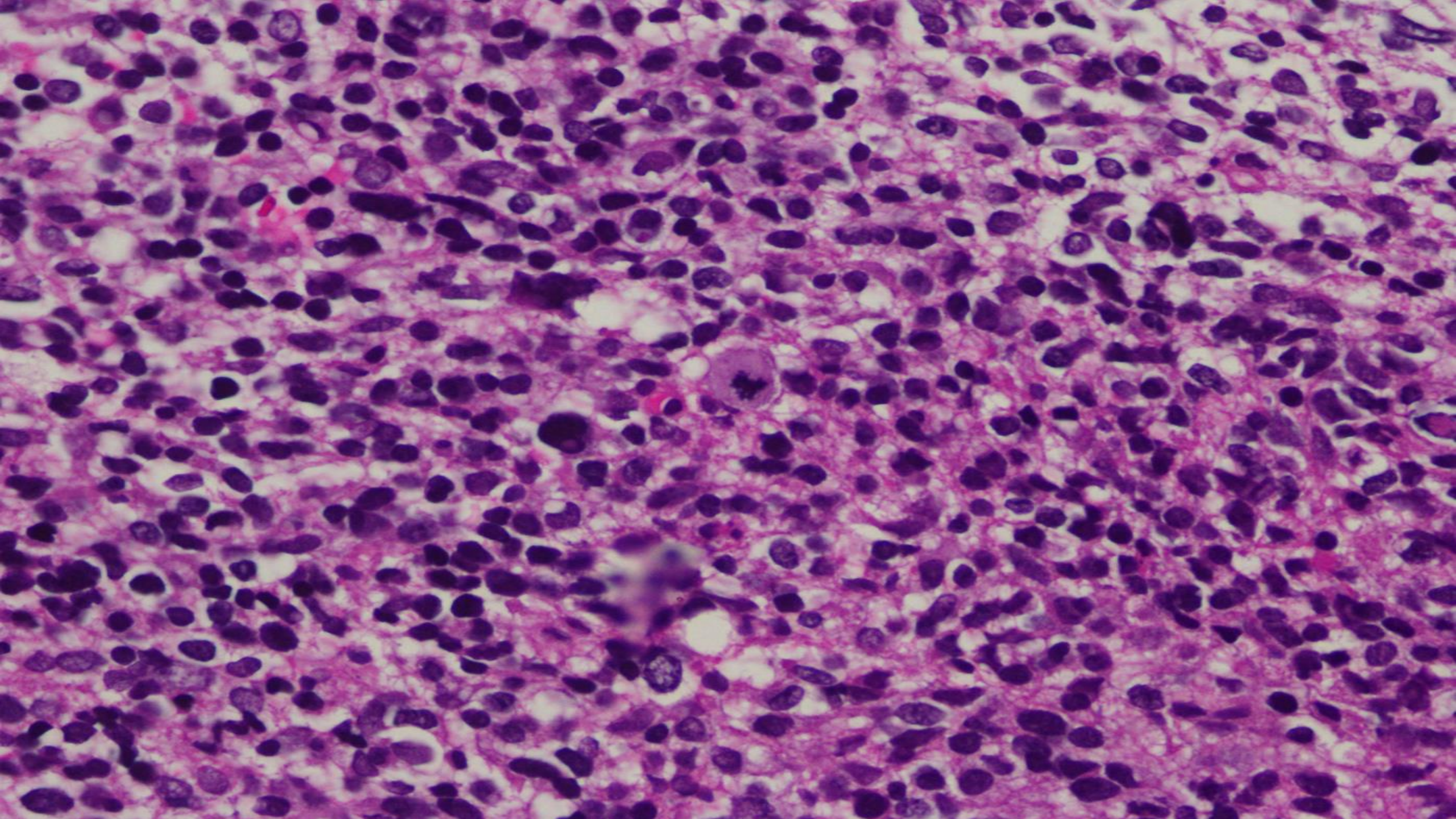
Case-3; Diffuse low grade glioma can be the only “component” sampled. If mutant (positive H3 K27M and/ or H3 K27 me negative), this is considered grade 4, regardless of the actual grade.

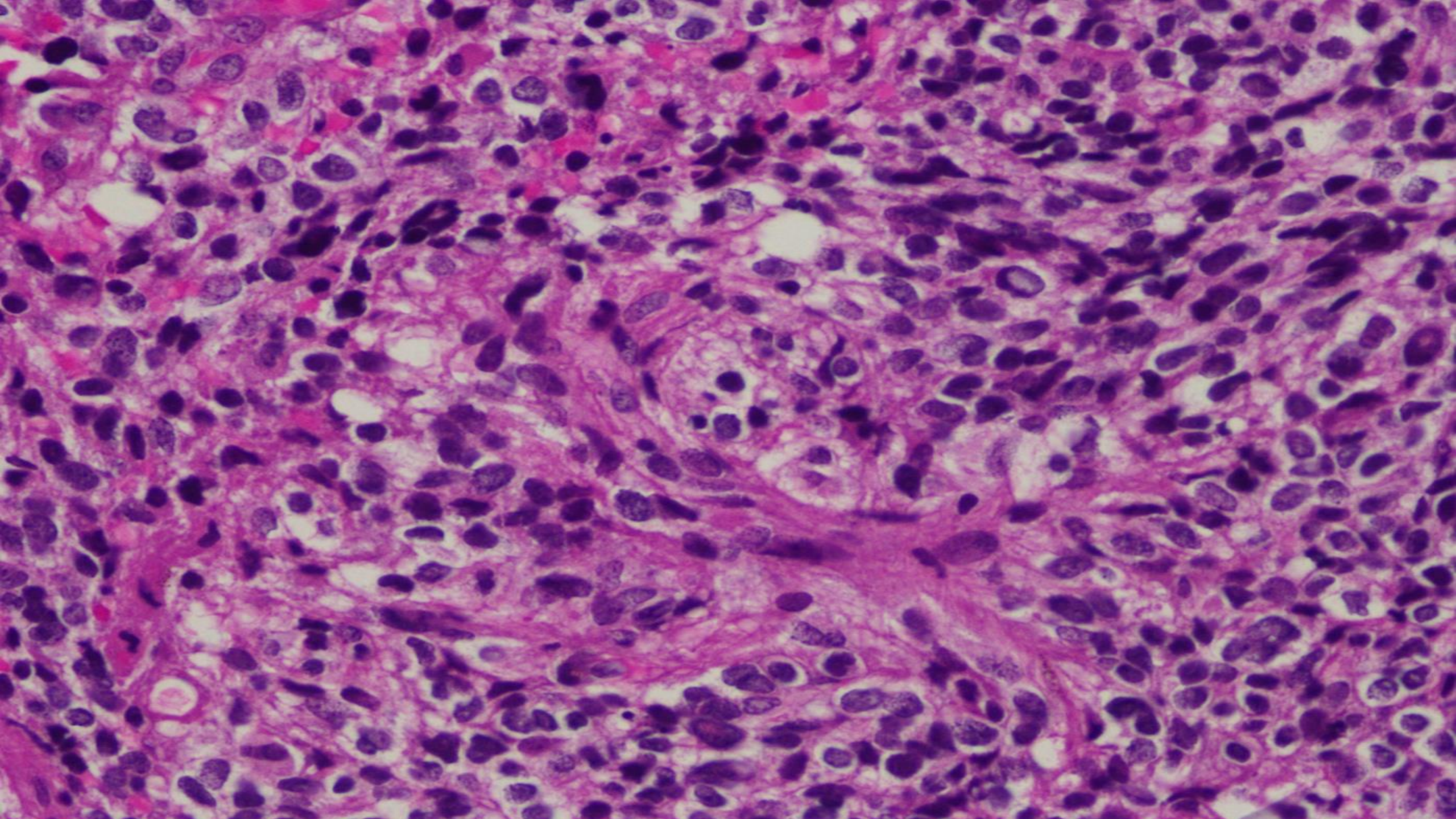

Case-4
A 14 year old female patient with lower limb weakness. Found to have spinal cord tumor

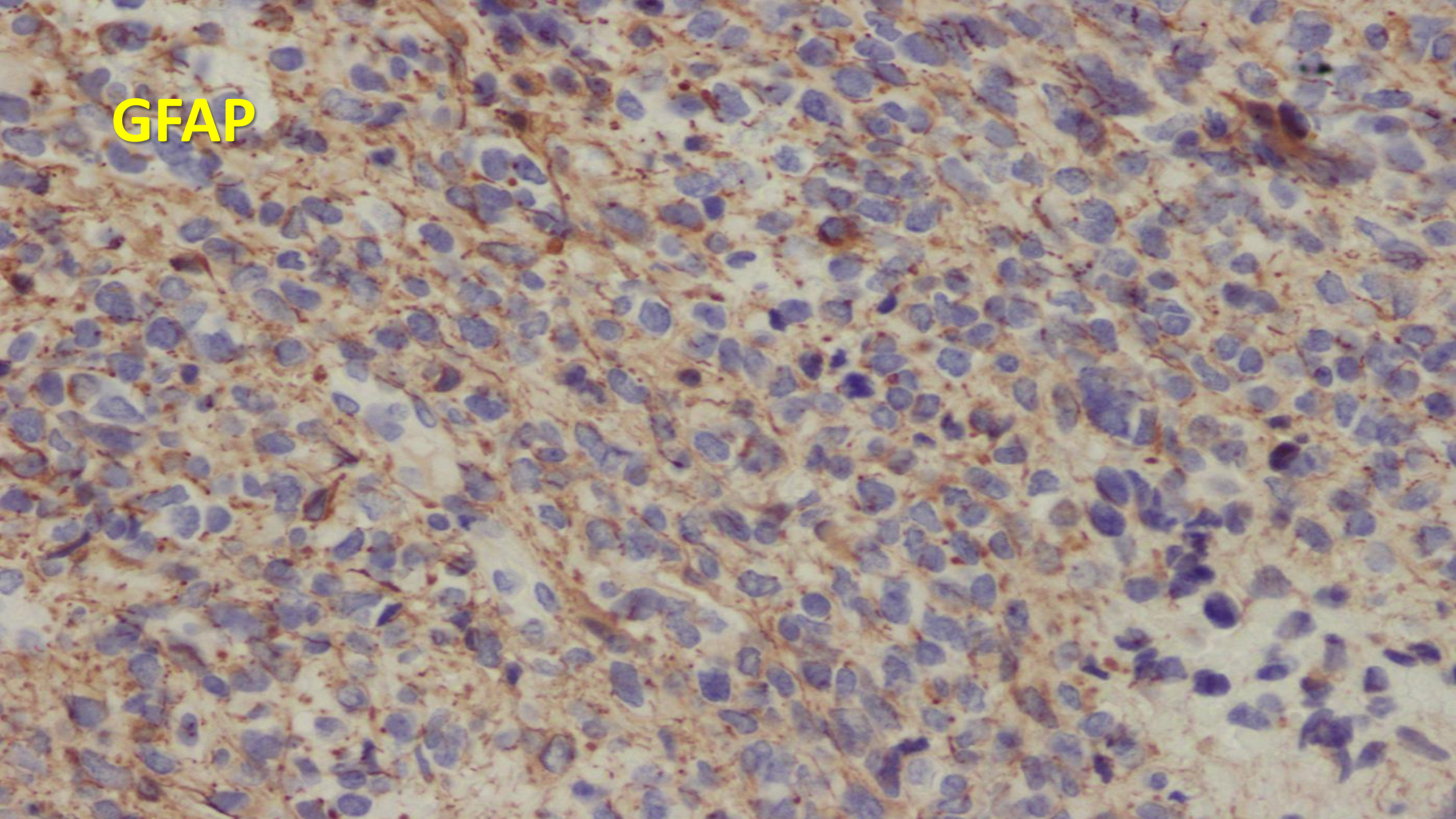


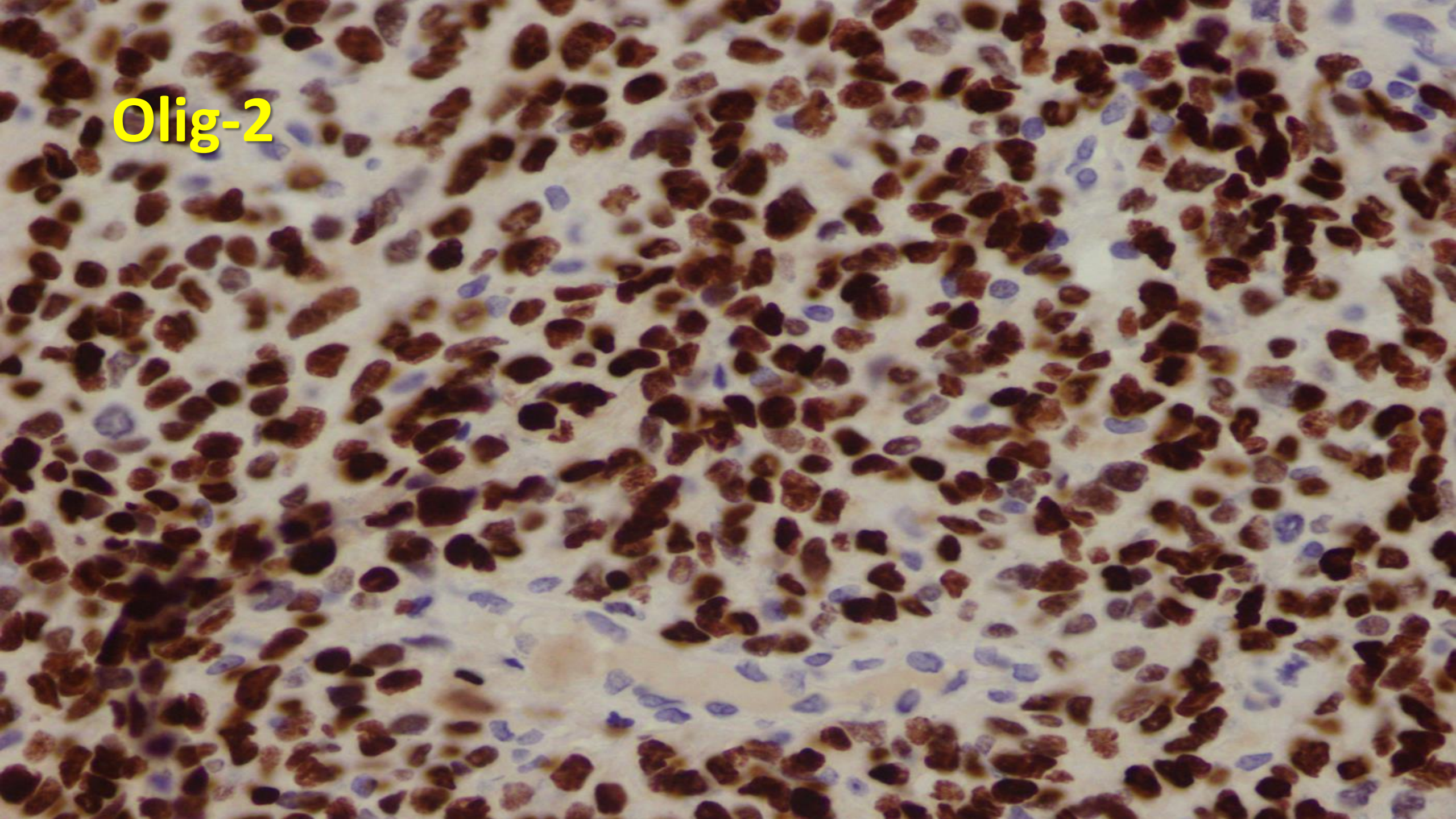


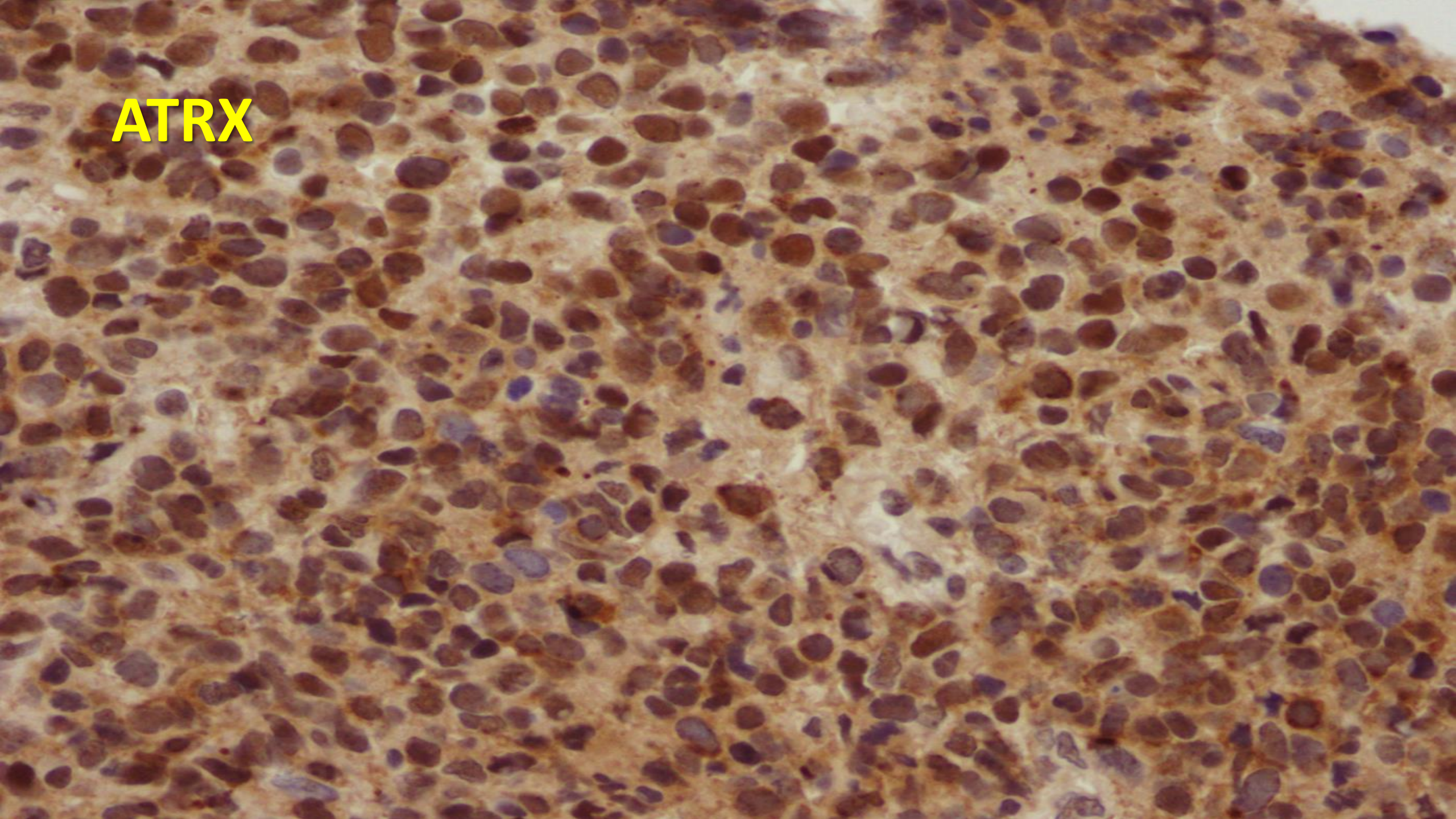


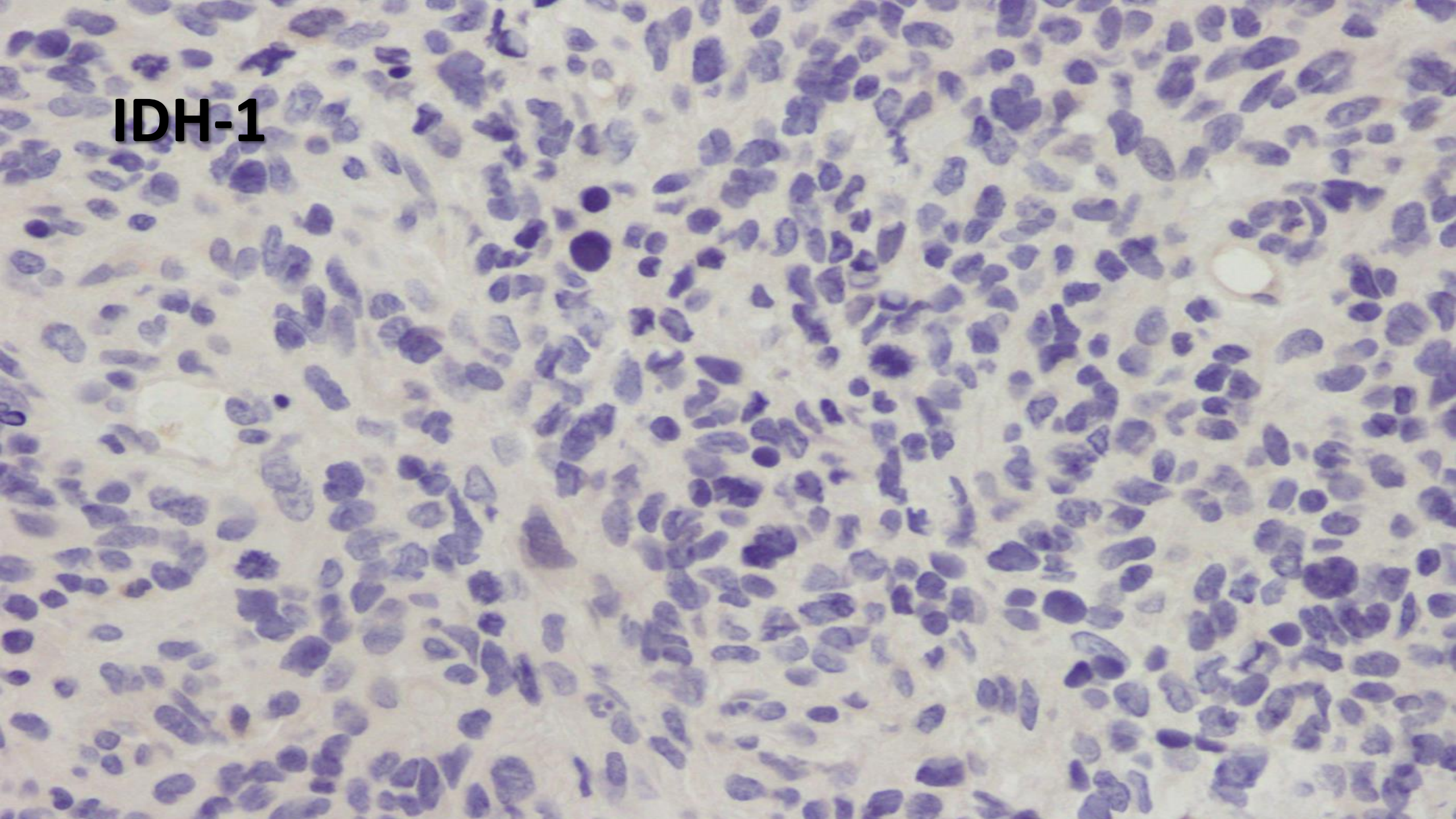


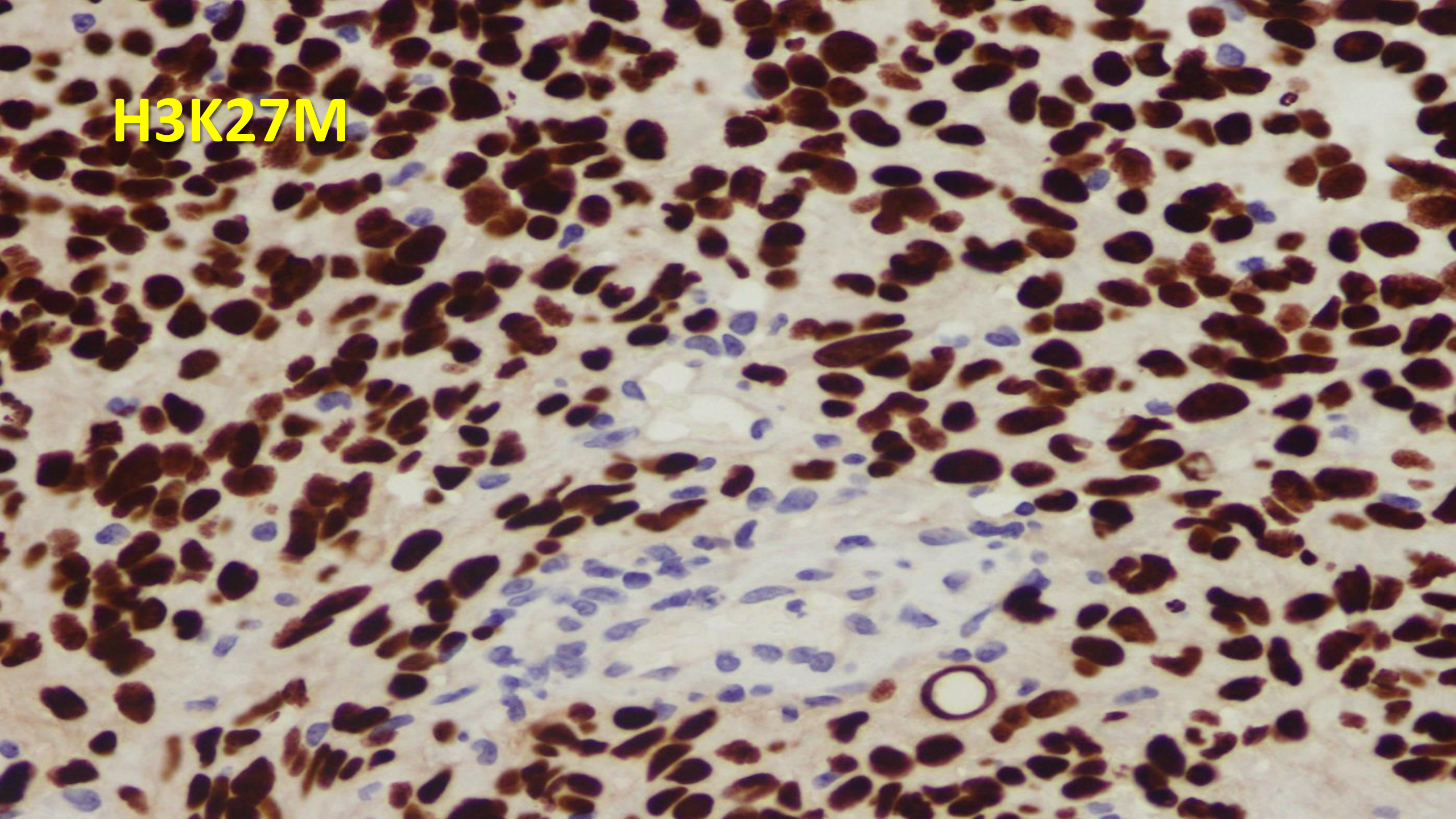


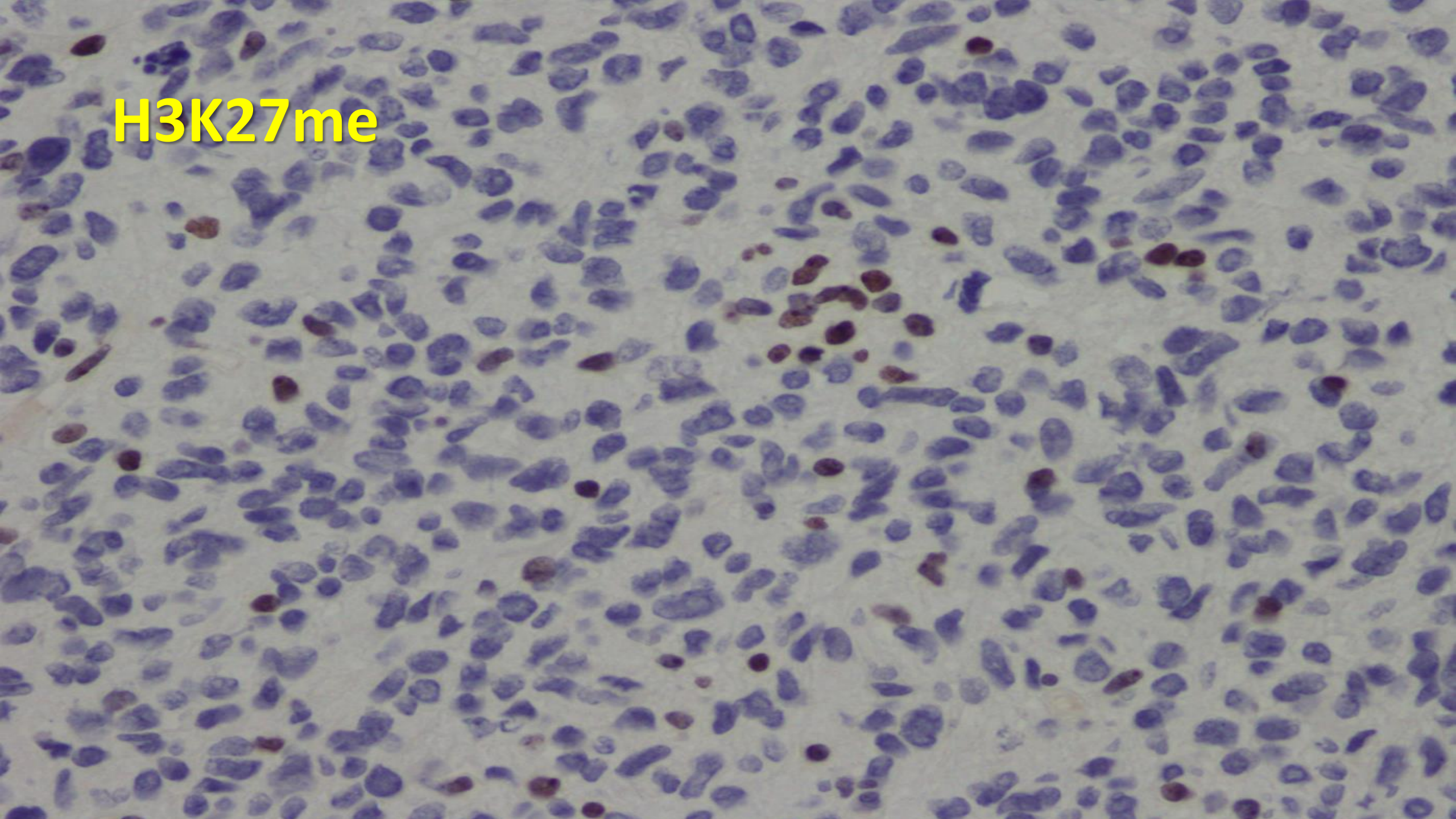

GFAP

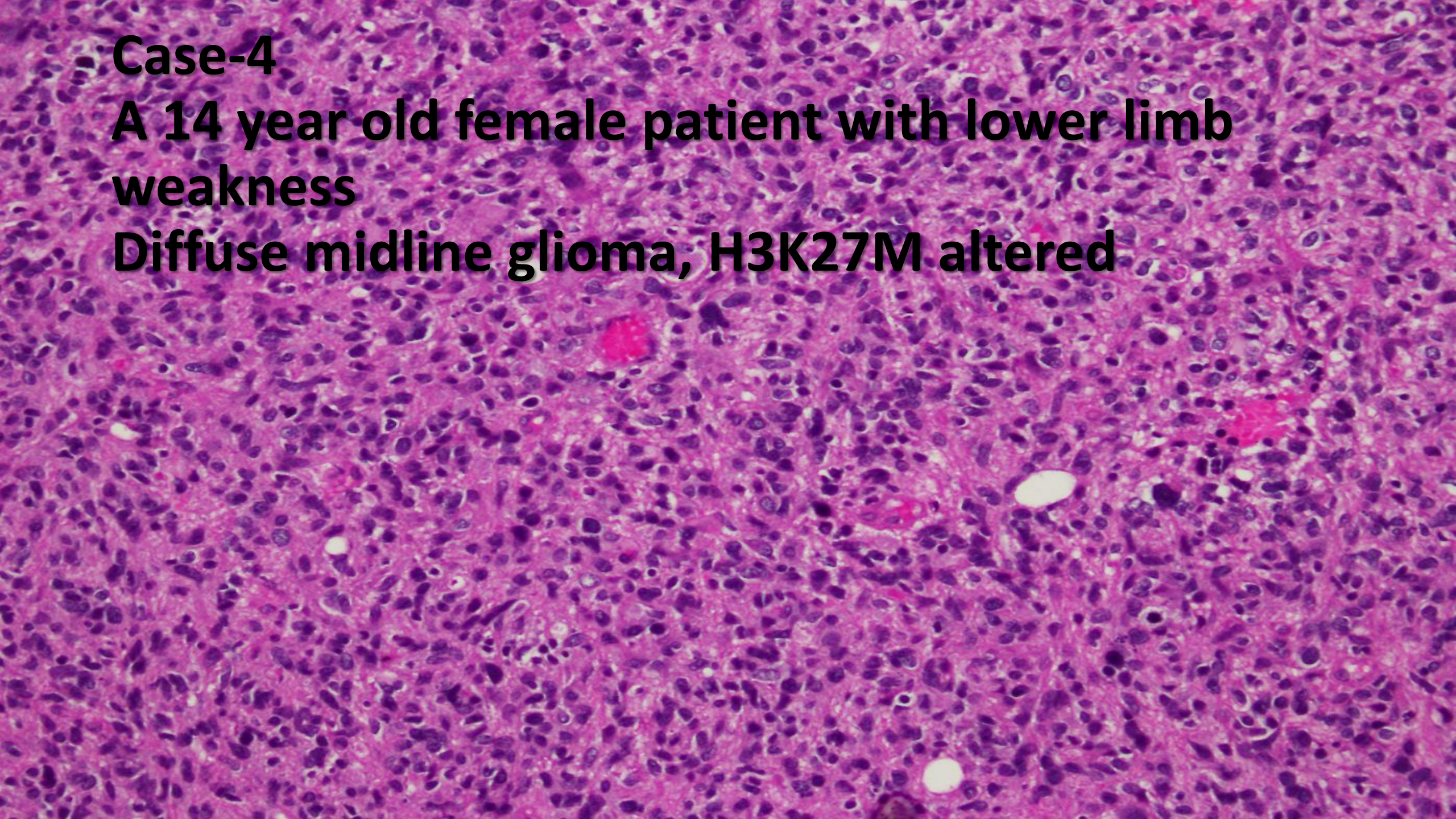

Olig-2


ATRX


IDH-1


H3K27M

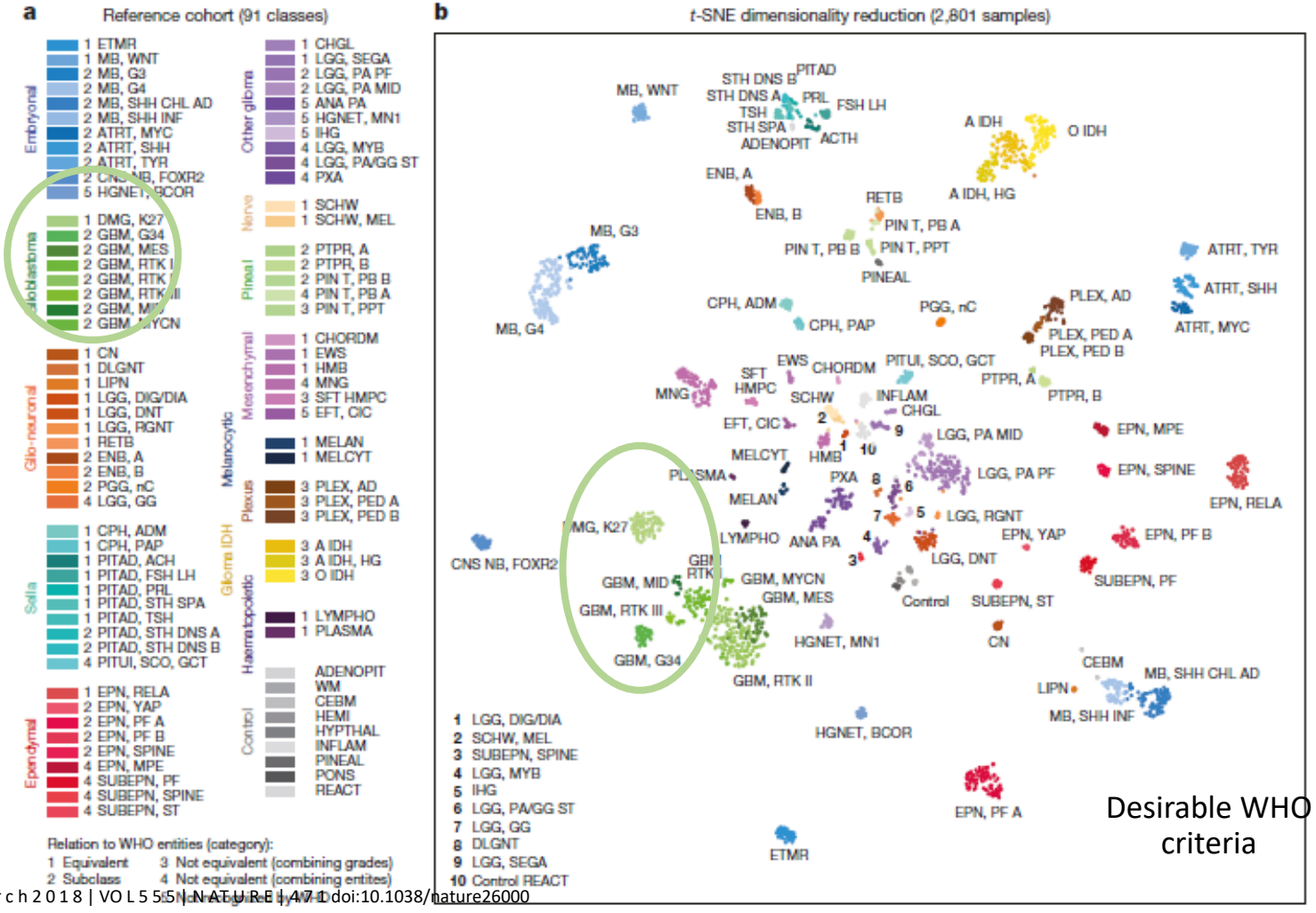

H3K27me


Case-4
A 14 year old female patient with lower limb weakness
Diffuse midline glioma, H3K27M altered

3. All diffuse midline gliomas should be tested for H3 K27 mutations

Methylation Profile

DHG, H3 G34 mutant



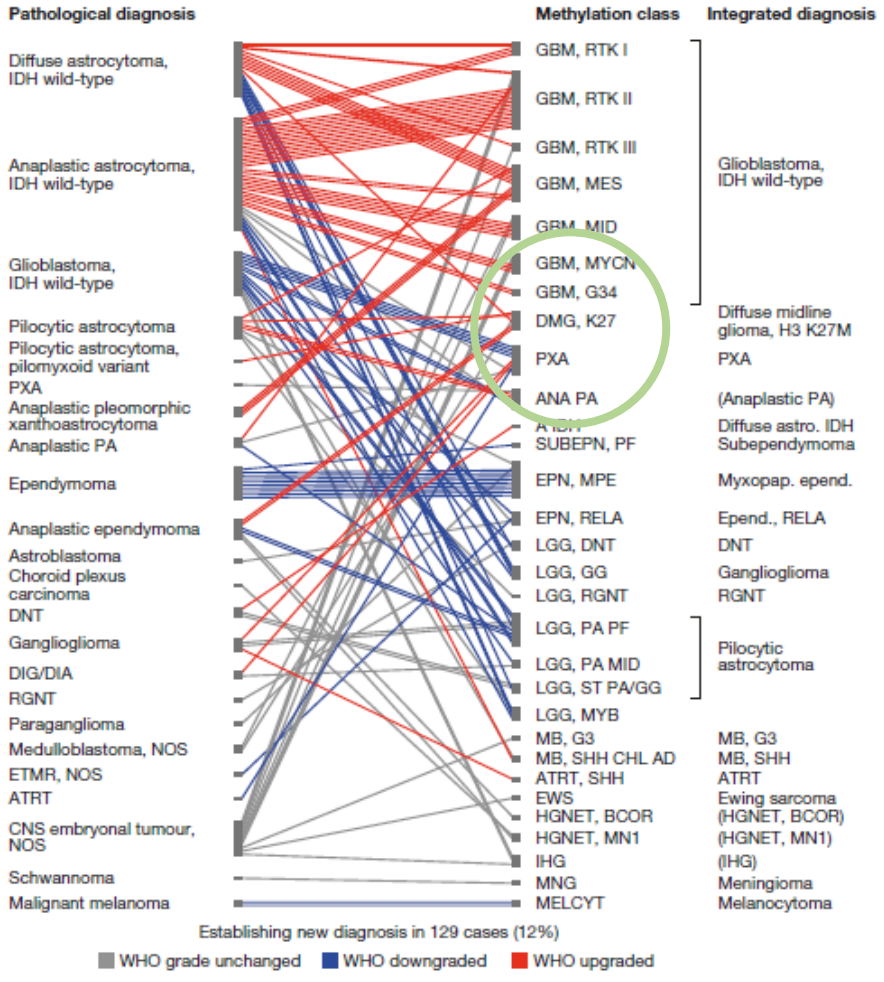
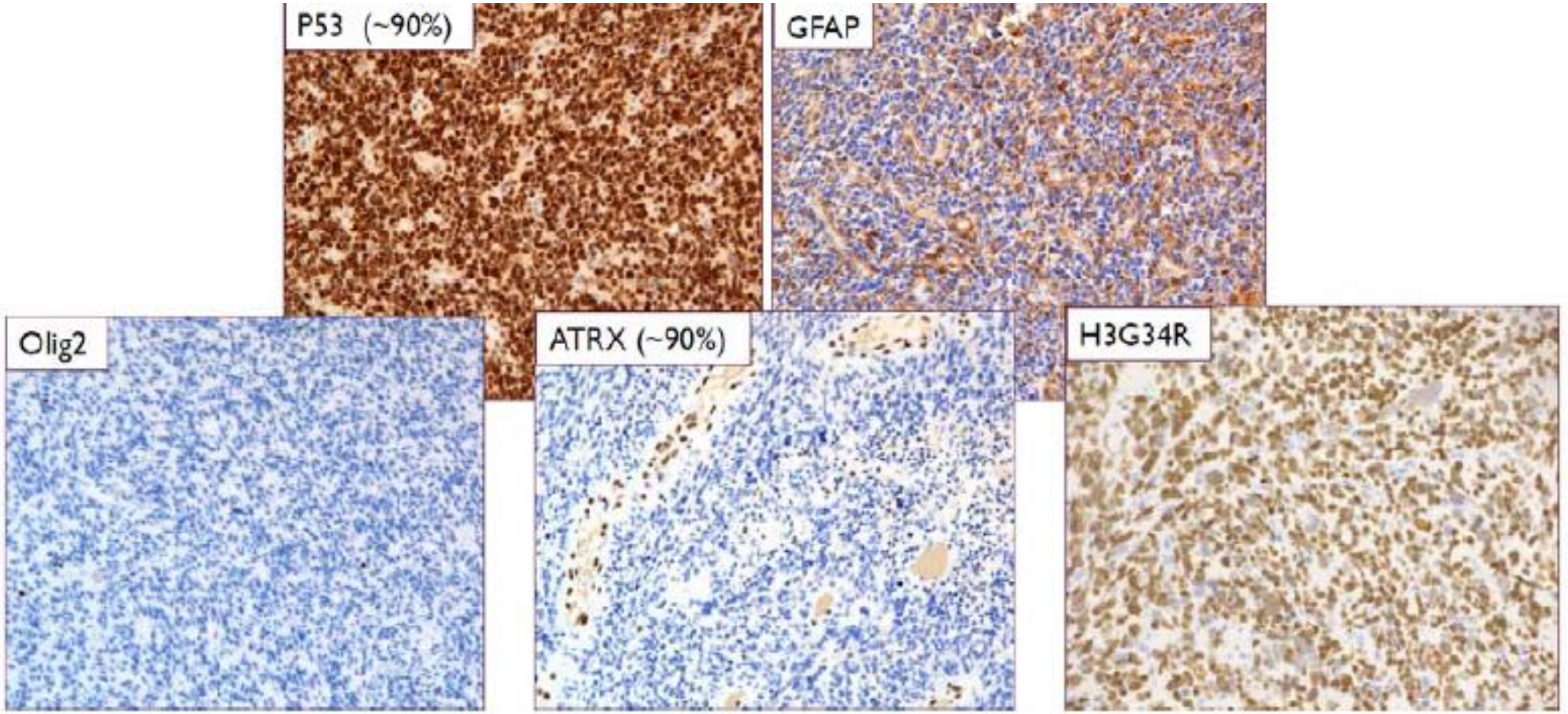
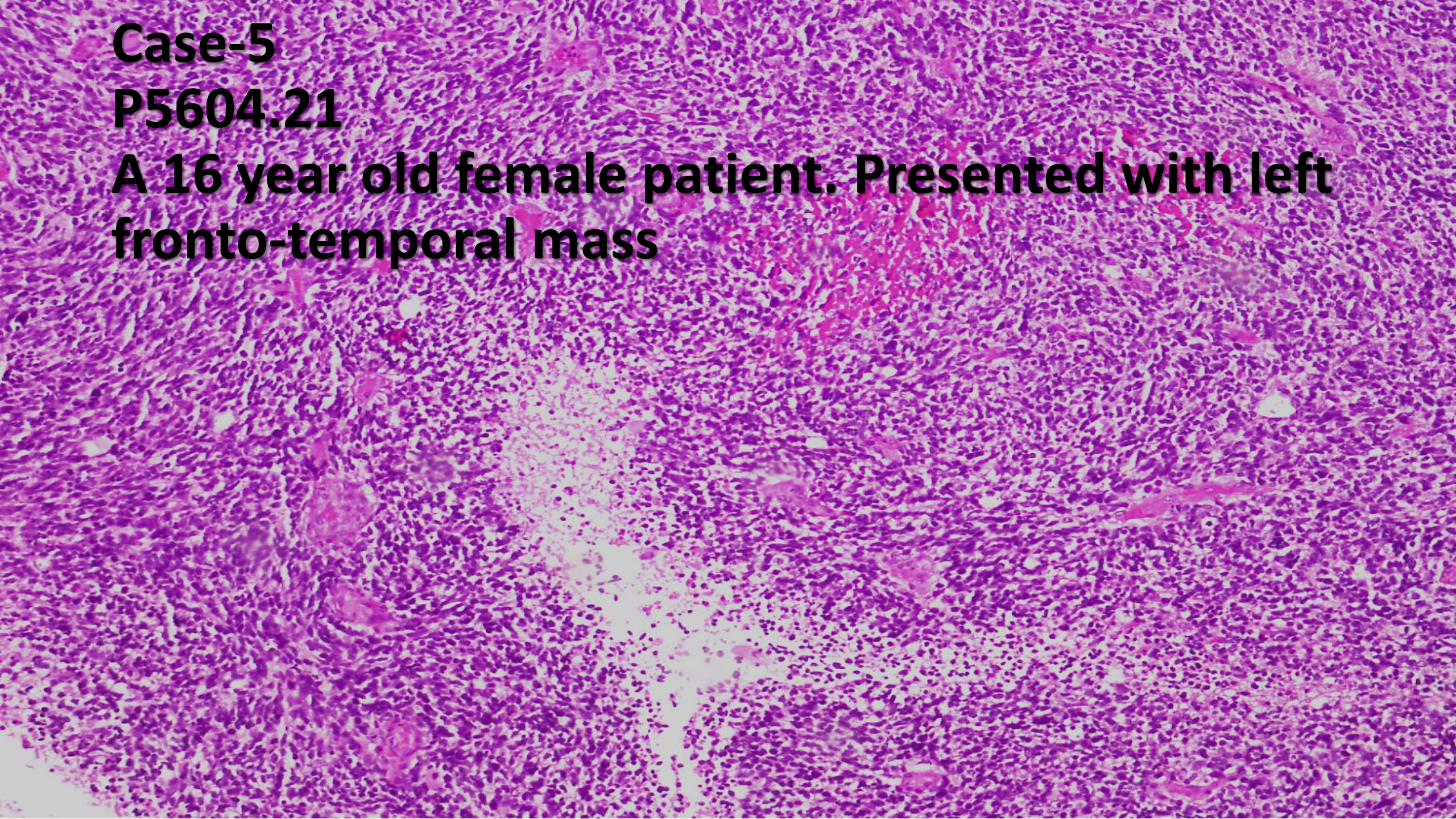
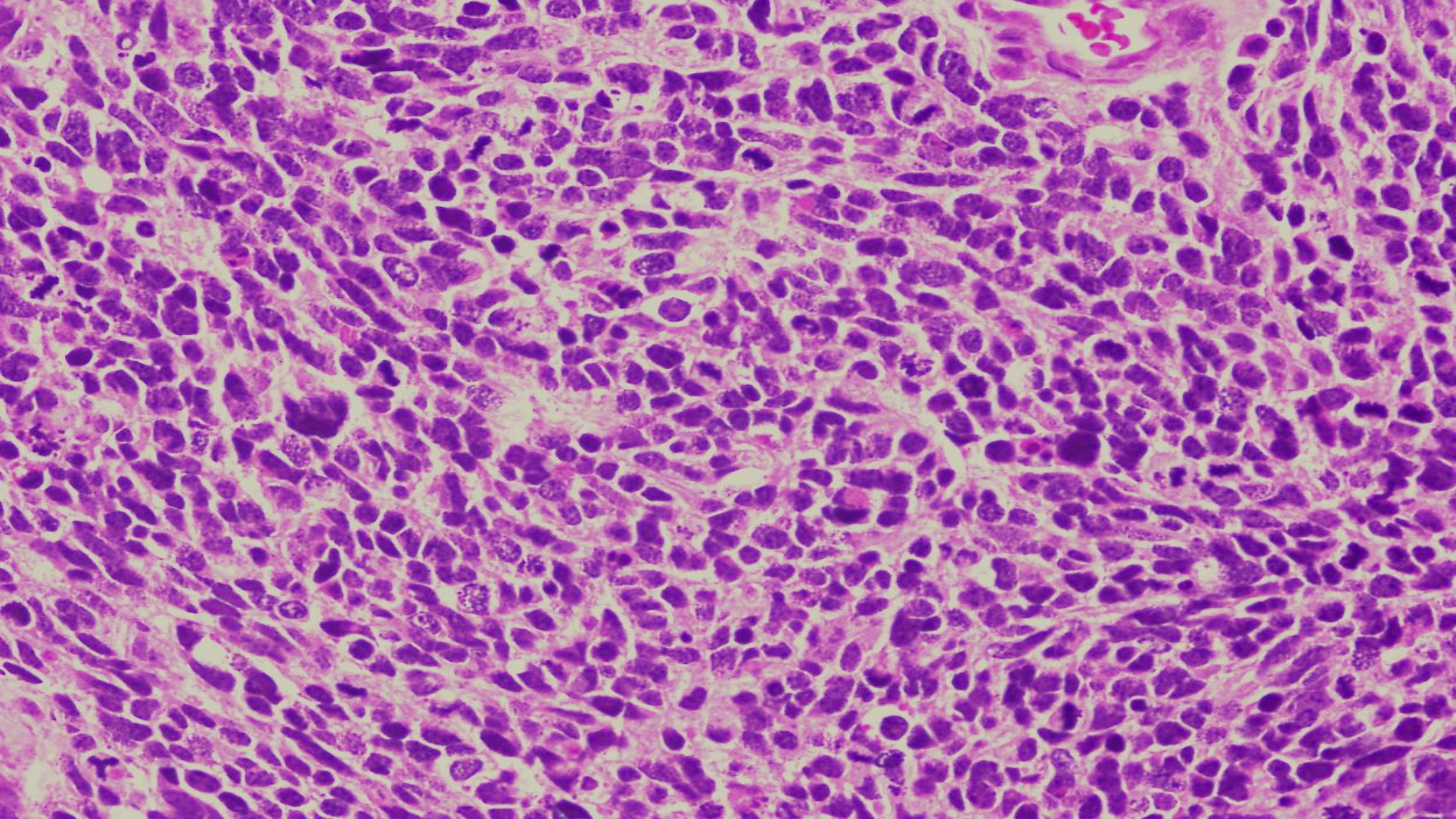


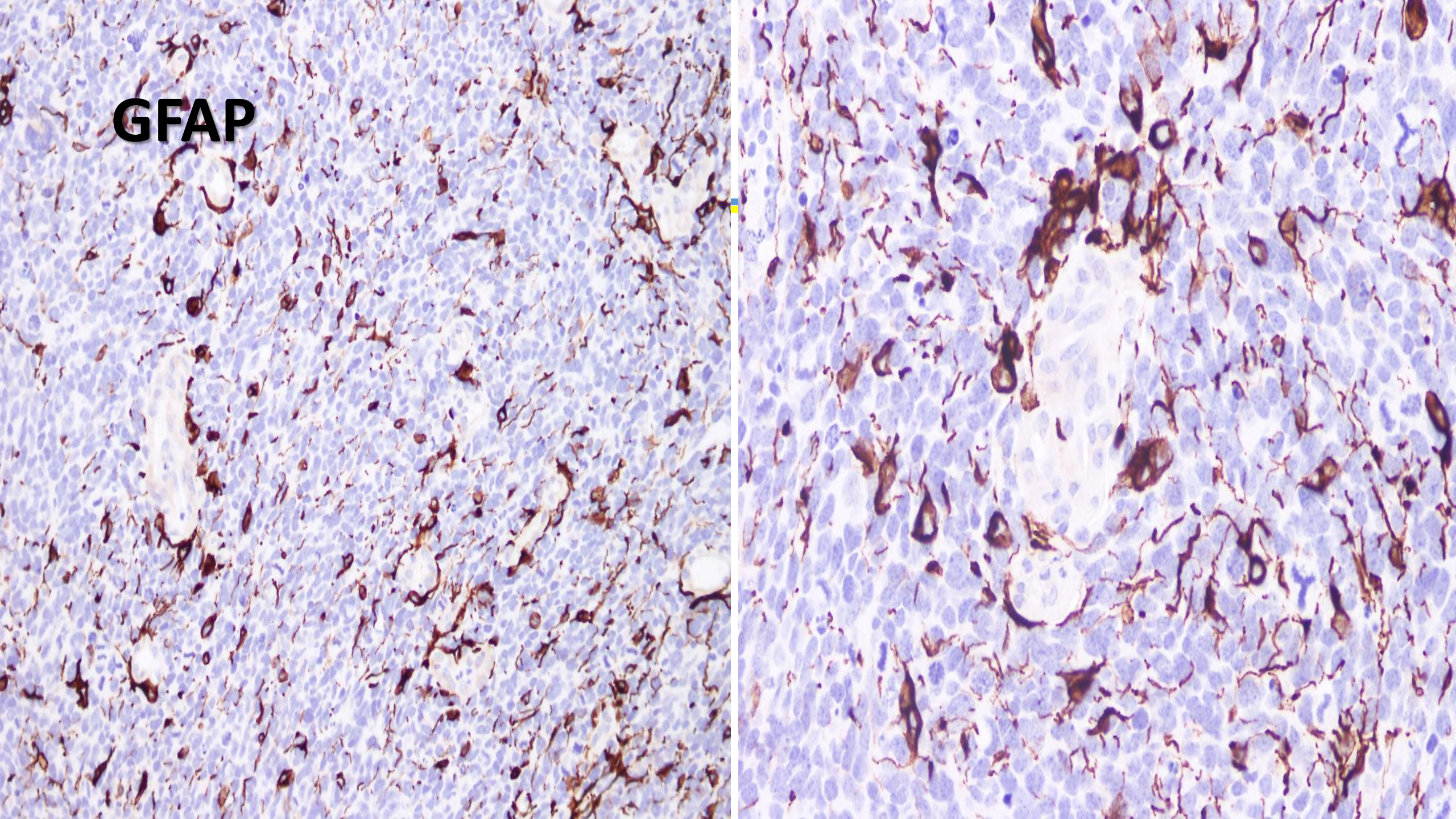
Figure 4 | Reassessment of discrepant cases and establishment of

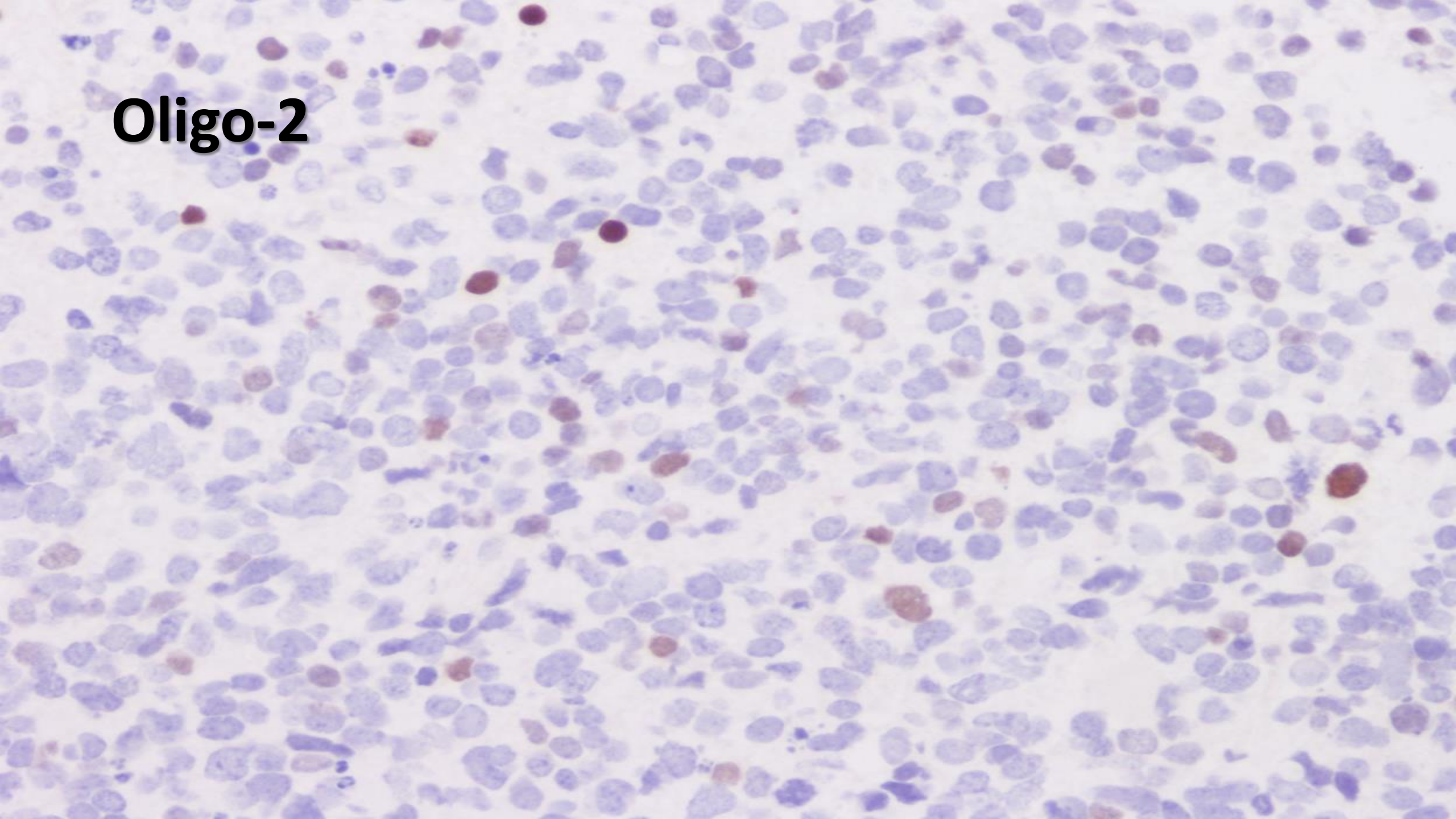
Diffuse hemispheric glioma, H3 G34R-m, grade 4

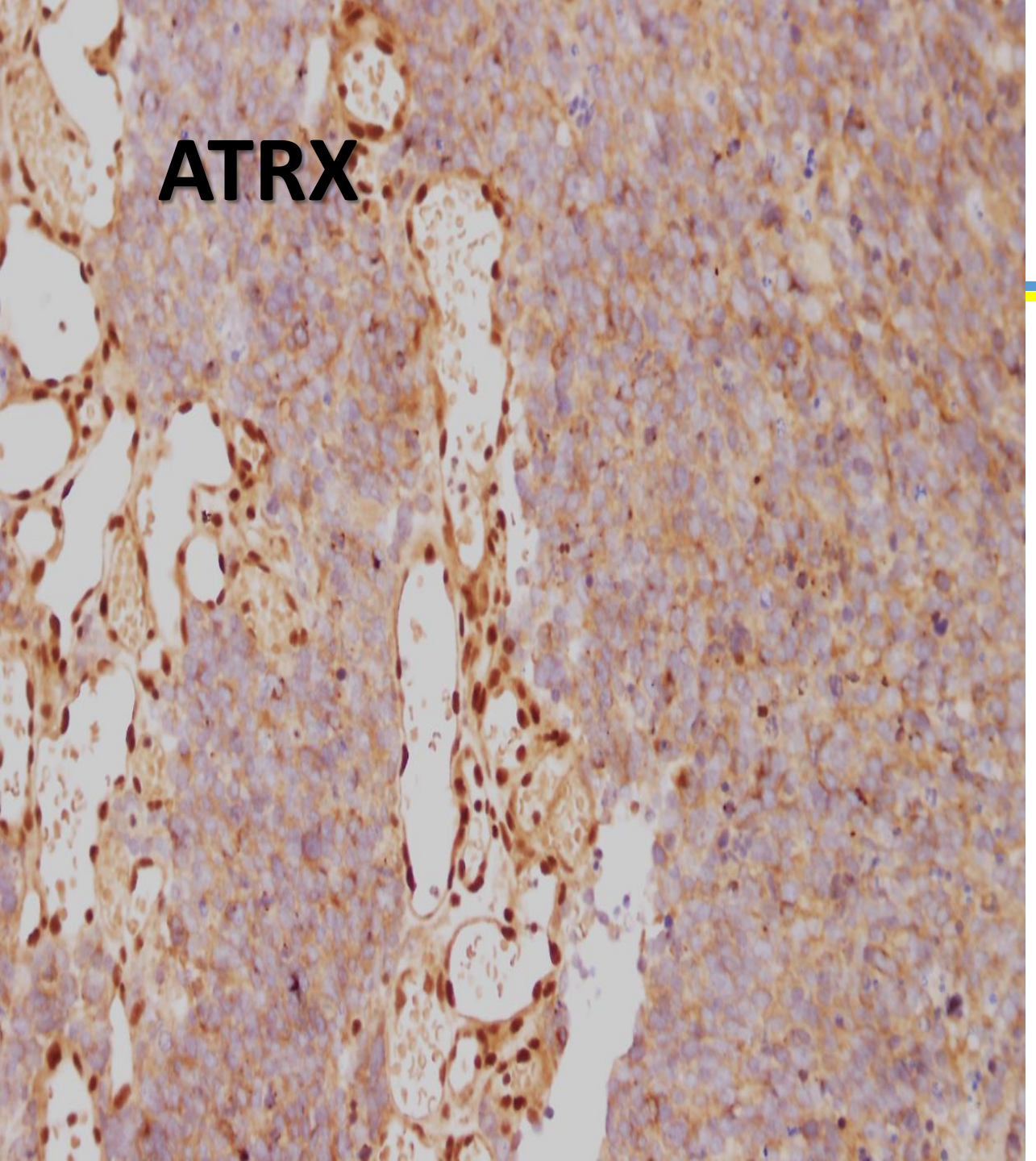


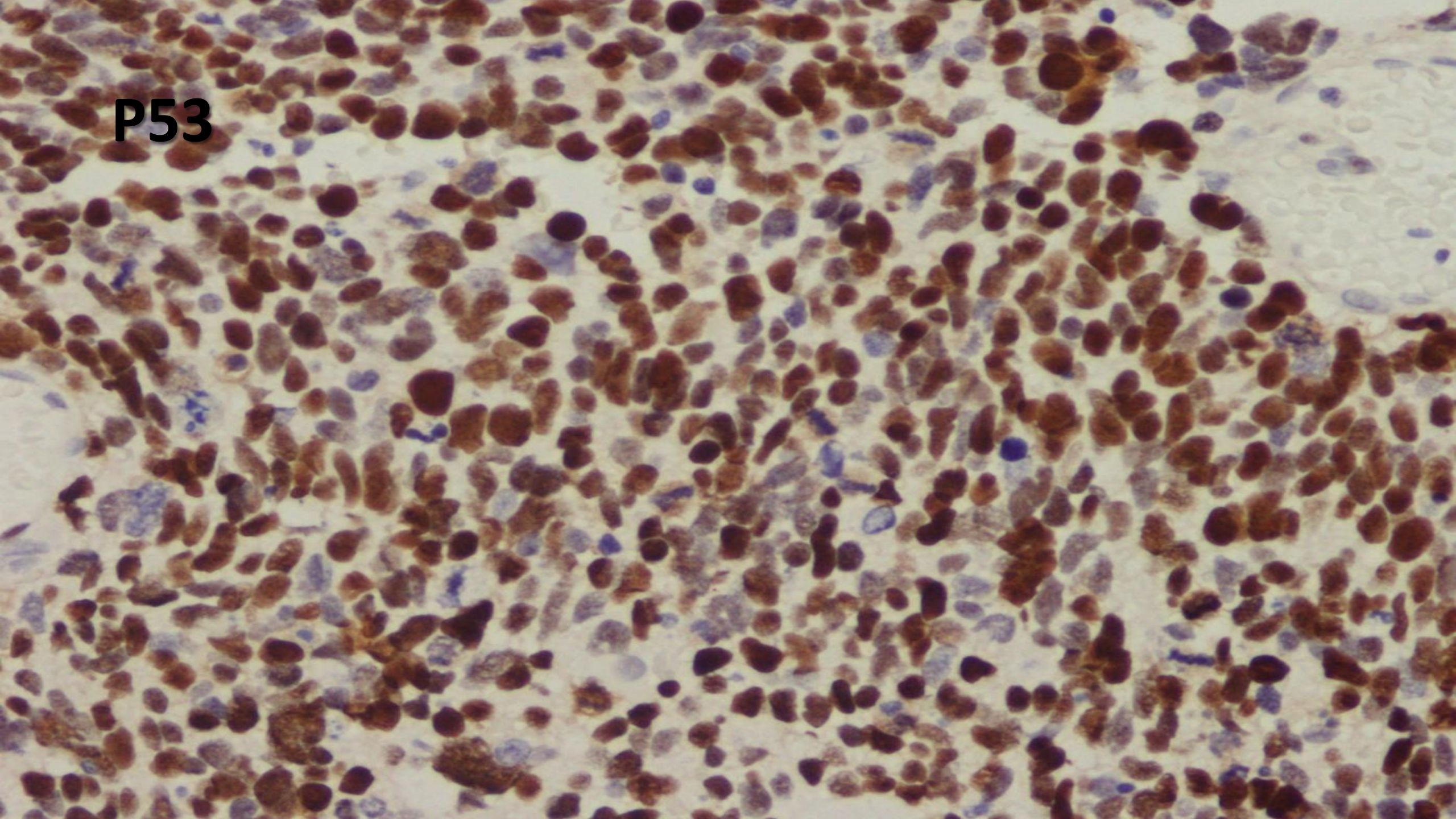

Case-5
P5604.21
A 16 year old female patient. Presented with left fronto-temporal mass

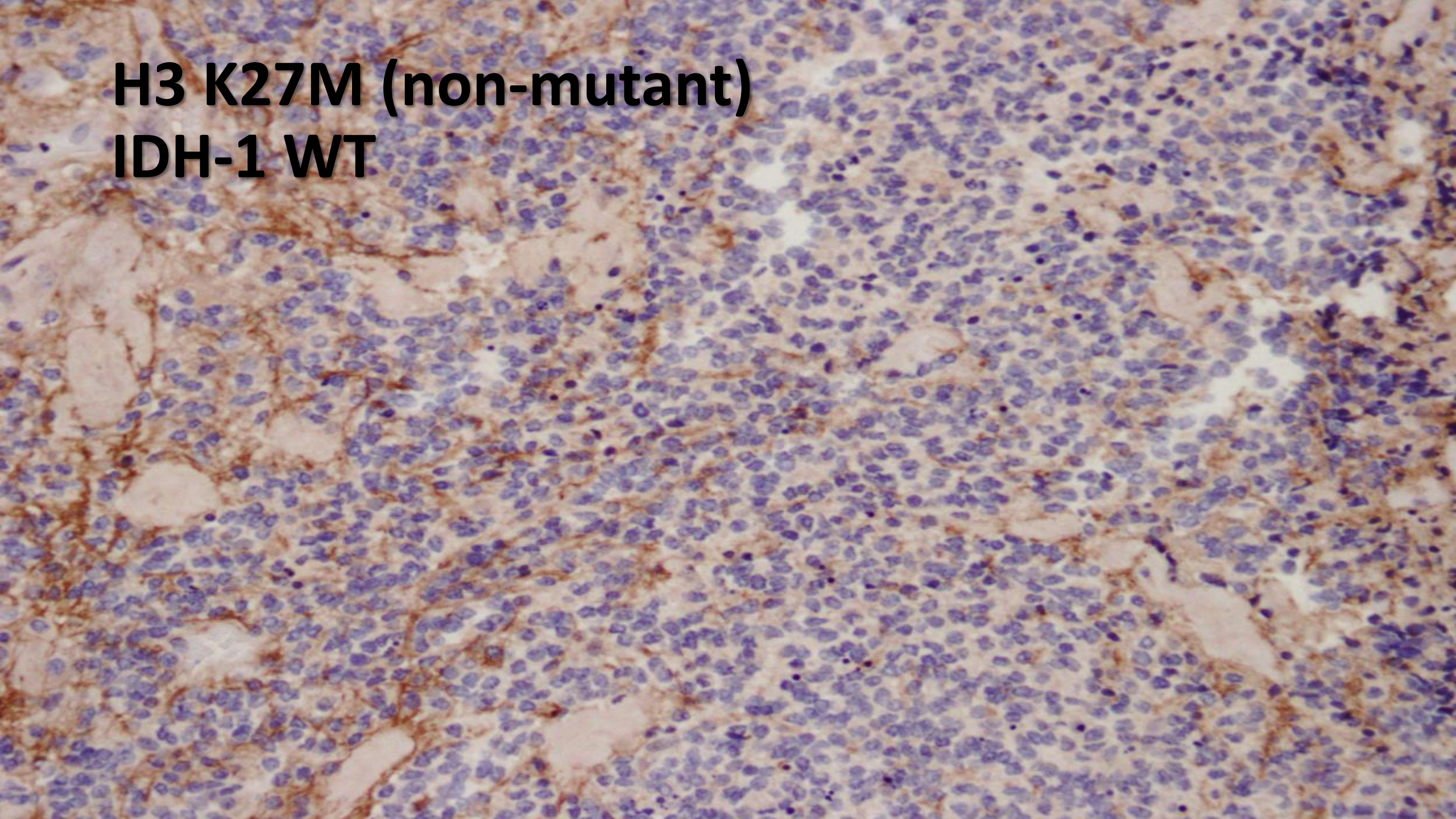


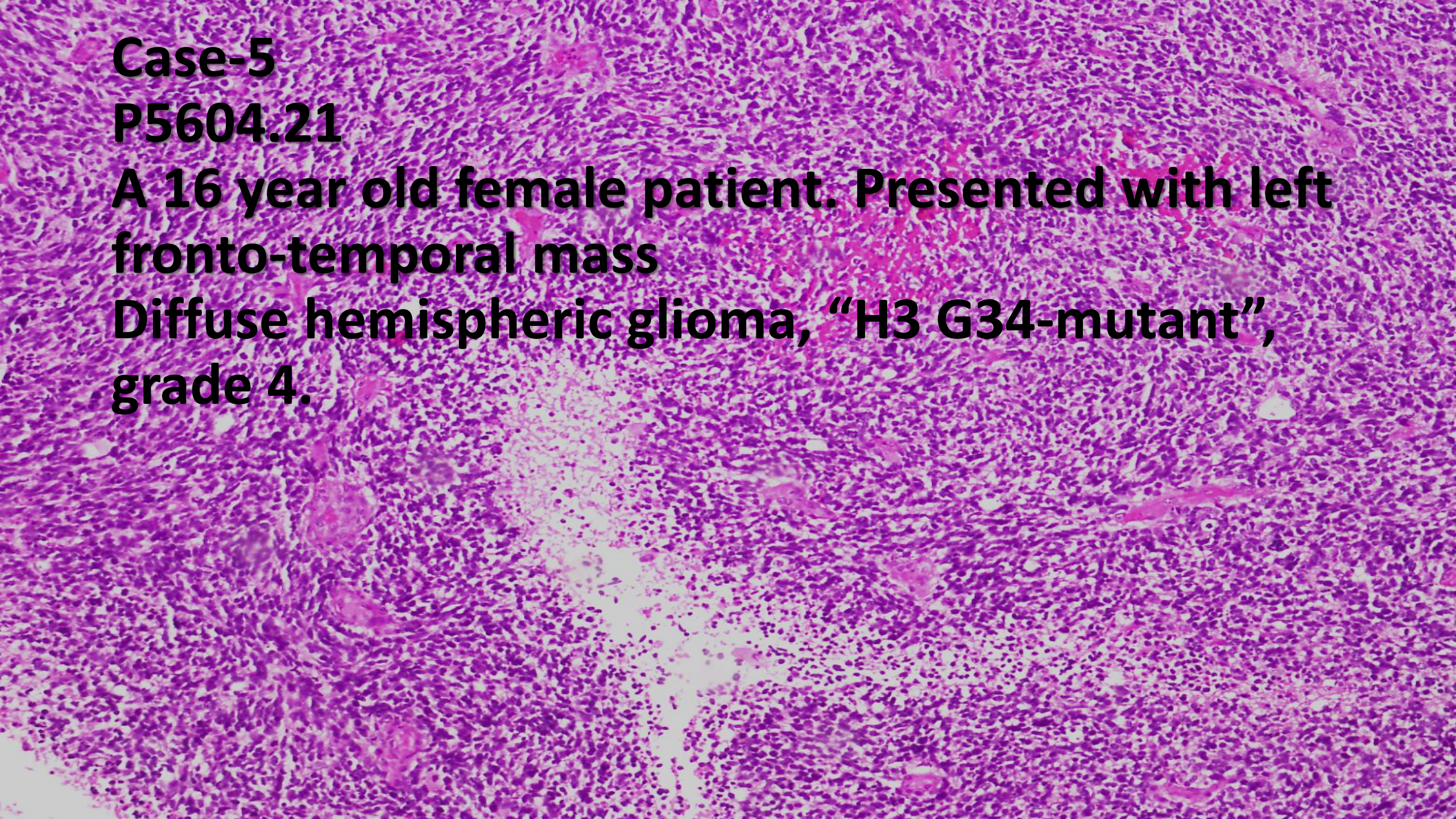

GFAP


Oligo-2


ATRX


P53


H3 K27M (non-mutant)
IDH-1 WT


Case-5
P5604.21
A 16 year old female patient. Presented with left fronto-temporal mass
Diffuse hemispheric glioma, “H3 G34-mutant”, grade 4.

4. Pediatric-type diffuse hemispheric gliomas should be tested for H3 G34 mutation

2.1.2: Pediatric-type diffuse low-grade gliomas

- 2.1.2.1: Diffuse astrocytoma, MYB- or MYBL1-altered
- 2.1.2.2: Angiocentric glioma
- 2.1.2.3: Diffuse low-grade glioma, MAPK-altered
- 2.1.2.4: Polymorphous low-grade neuroepithelial tumour of the young

2.1.3: Pediatric-type diffuse high-grade gliomas

- 2.1.3.1: Diffuse midline glioma, H3 K27M-mutant
- 2.1.3.2: Diffuse hemispheric glioma, H3 G34-mutant
- 2.1.3.3: Diffuse paediatric-type high-grade glioma, H3-wildtype and IDH-wildtype
- 2.1.3.4: Diffuse midline glioma, EGFR-mutant
- 2.1.3.5: Infant-type hemispheric glioma, H3-wildtype

2.1.4: Circumscribed astrocytic gliomas

- 2.1.4.1: Pilocytic astrocytoma
- 2.1.4.2: High-grade astrocytoma with piloid features
- 2.1.4.3: Pleomorphic xanthoastrocytoma
- 2.1.4.6: Subependymal giant cell astrocytoma
- 2.1.4.7: Chordoid glioma
- 2.1.4.8: Astroblastoma-MN1

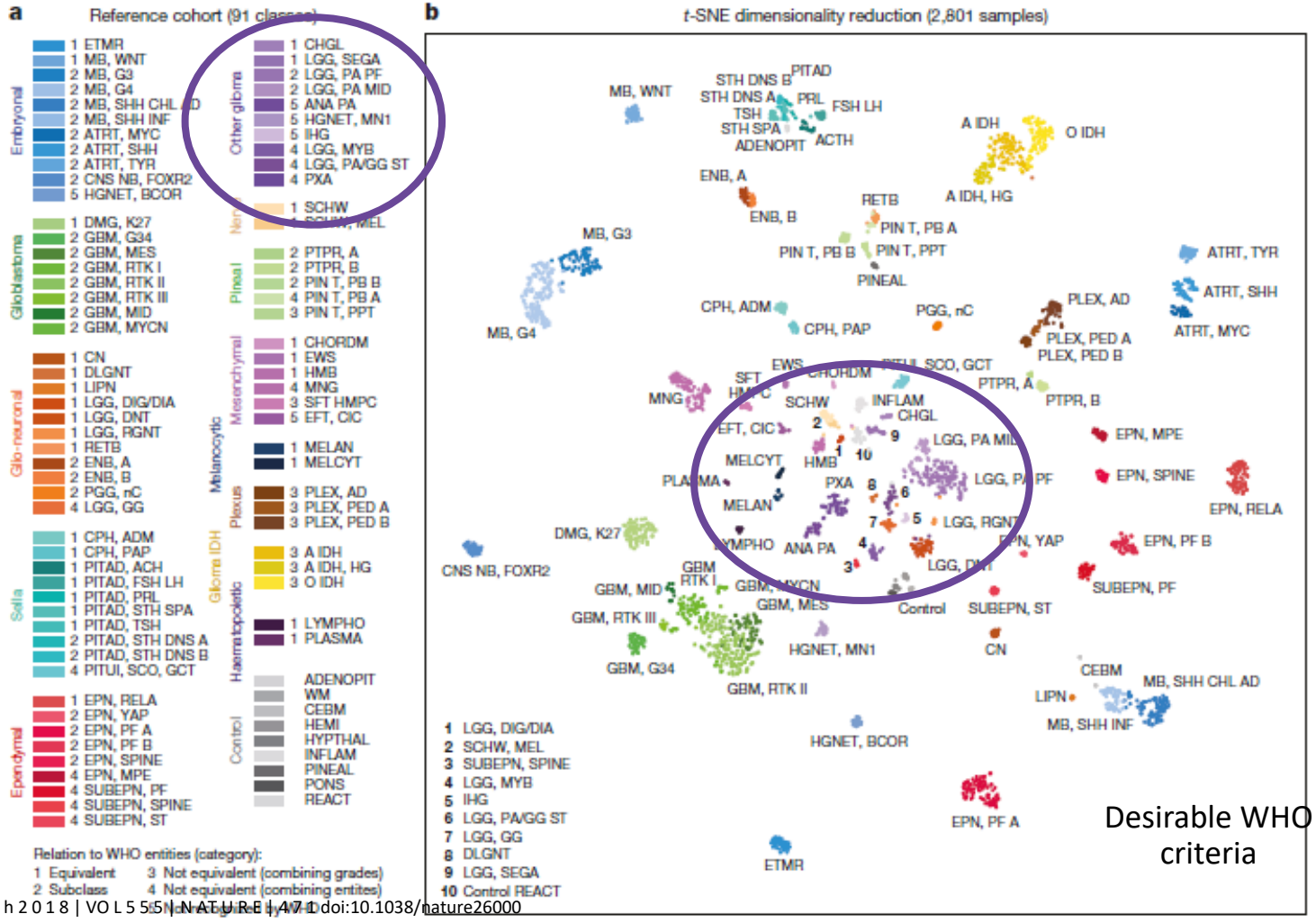
2.1.5: Glioneuronal and neuronal tumours

- 2.1.5.1: Gangliioglioma
- 2.1.5.2: Desmoplastic infantile astrocytoma / gangliioglioma
- 2.1.5.3: Dysembryoplastic neuroepithelial tumour
- 2.1.5.4: Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters
- 2.1.5.5: Papillary glioneuronal tumour
- 2.1.3.13 Diffuse leptomeningeal glioneuronal tumor

Many others.....

Methylation Profile

Circumscribed Astrocytic gliomas



Desirable WHO criteria

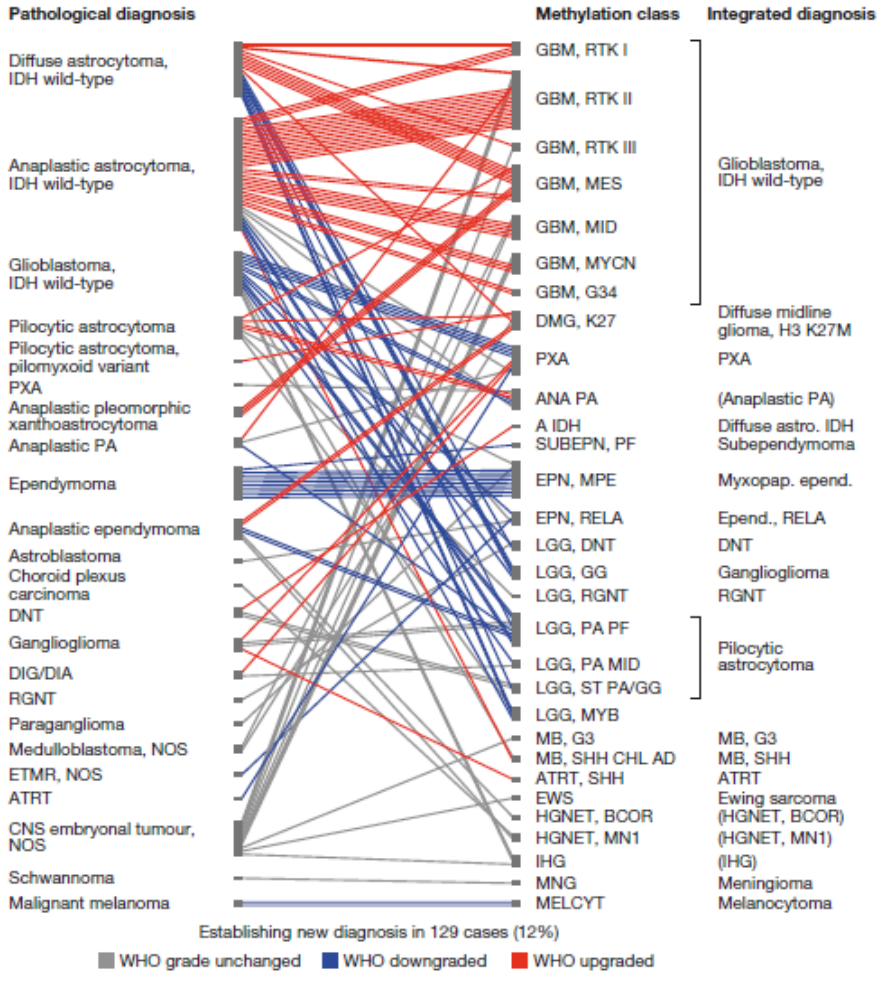


Figure 4 | Reassessment of discrepant cases and establishment of

Major Changes Relevant to Glioma in 2016

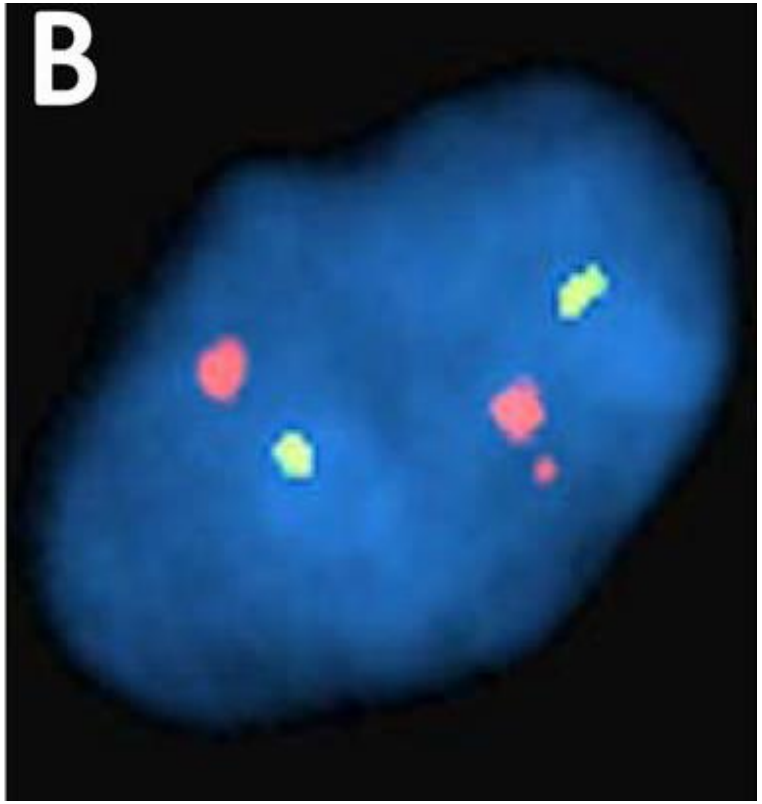
Rebuilding of glioma family tree

Pathogenetic, prognostic and probably therapeutic similarities

Separation of diffuse gliomas from circumscribed astrocytic tumors

Major restructuring of **diffuse gliomas,** with incorporation of **genetically defined** entities

Depending on the success of current clinical trials, “low grade glioma with BRAF fusion” or “low-grade glioma with BRAF V600E” could become success story for the pediatric neurooncology world



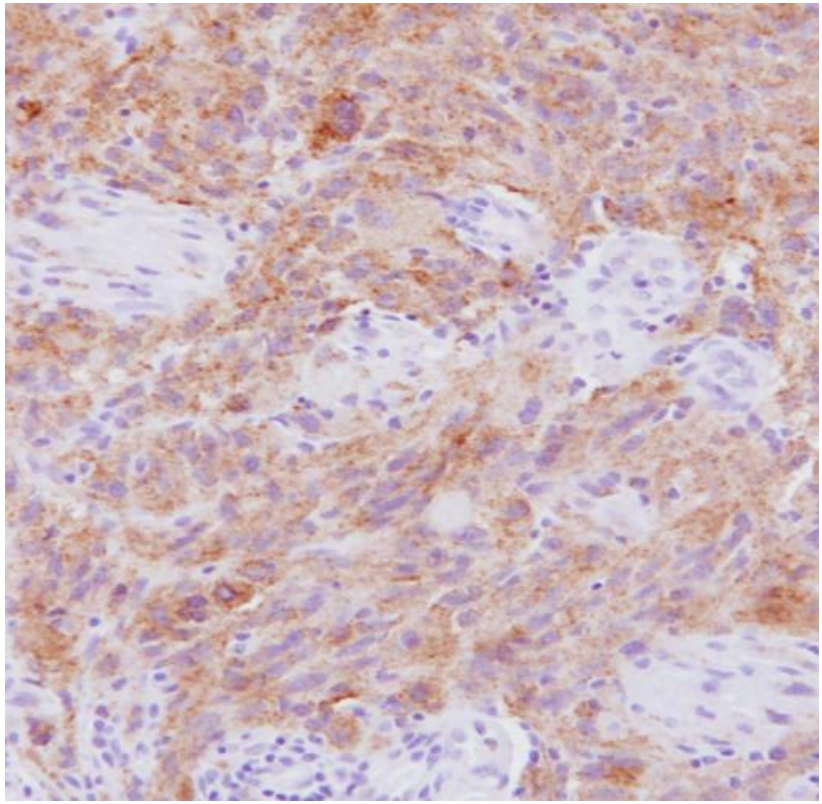
low-grade glioma on light microscopy

BRAF fusion

BRAF V600E

PA or PMA most likely

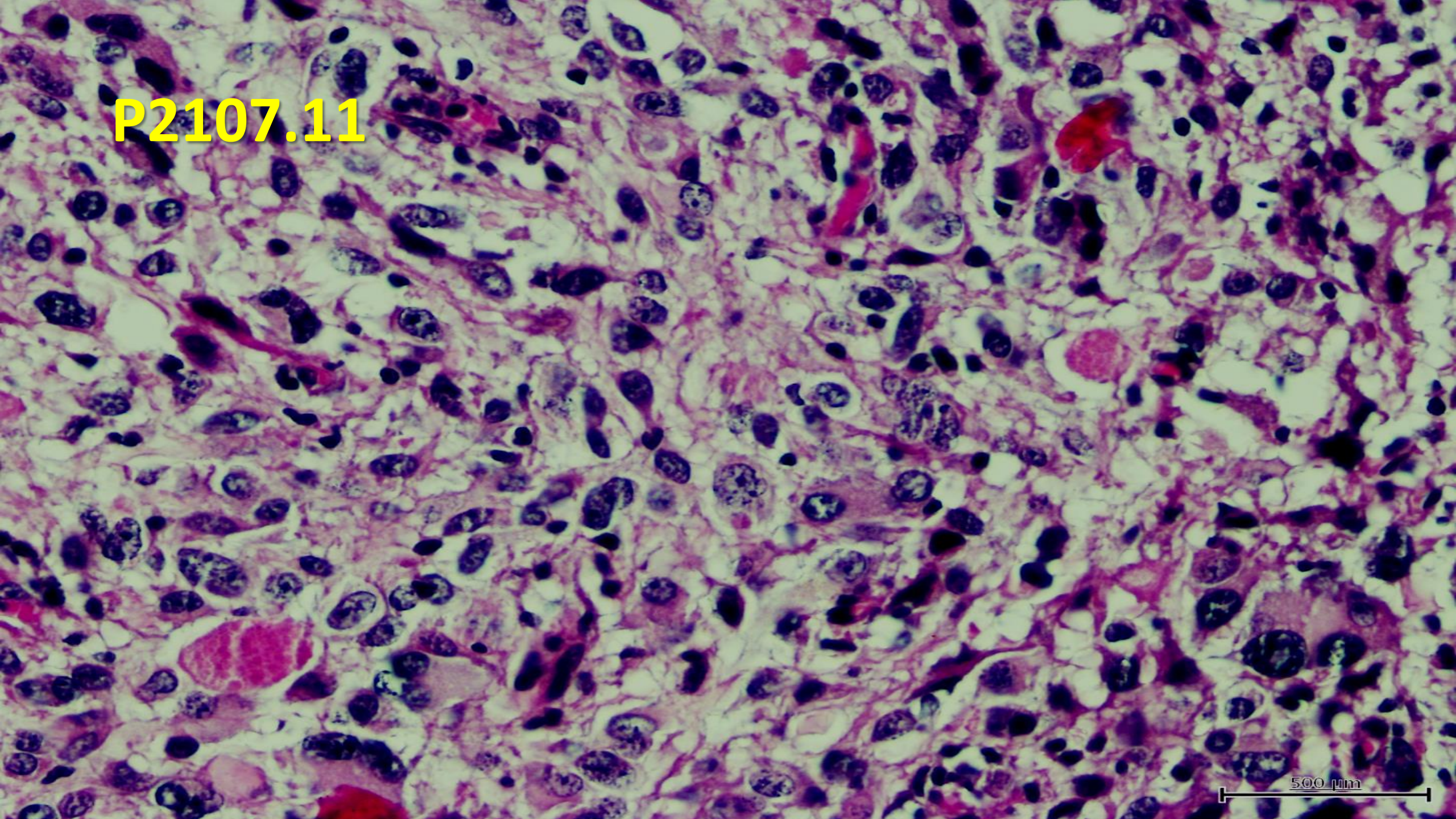
favor PXA, GG, or DA

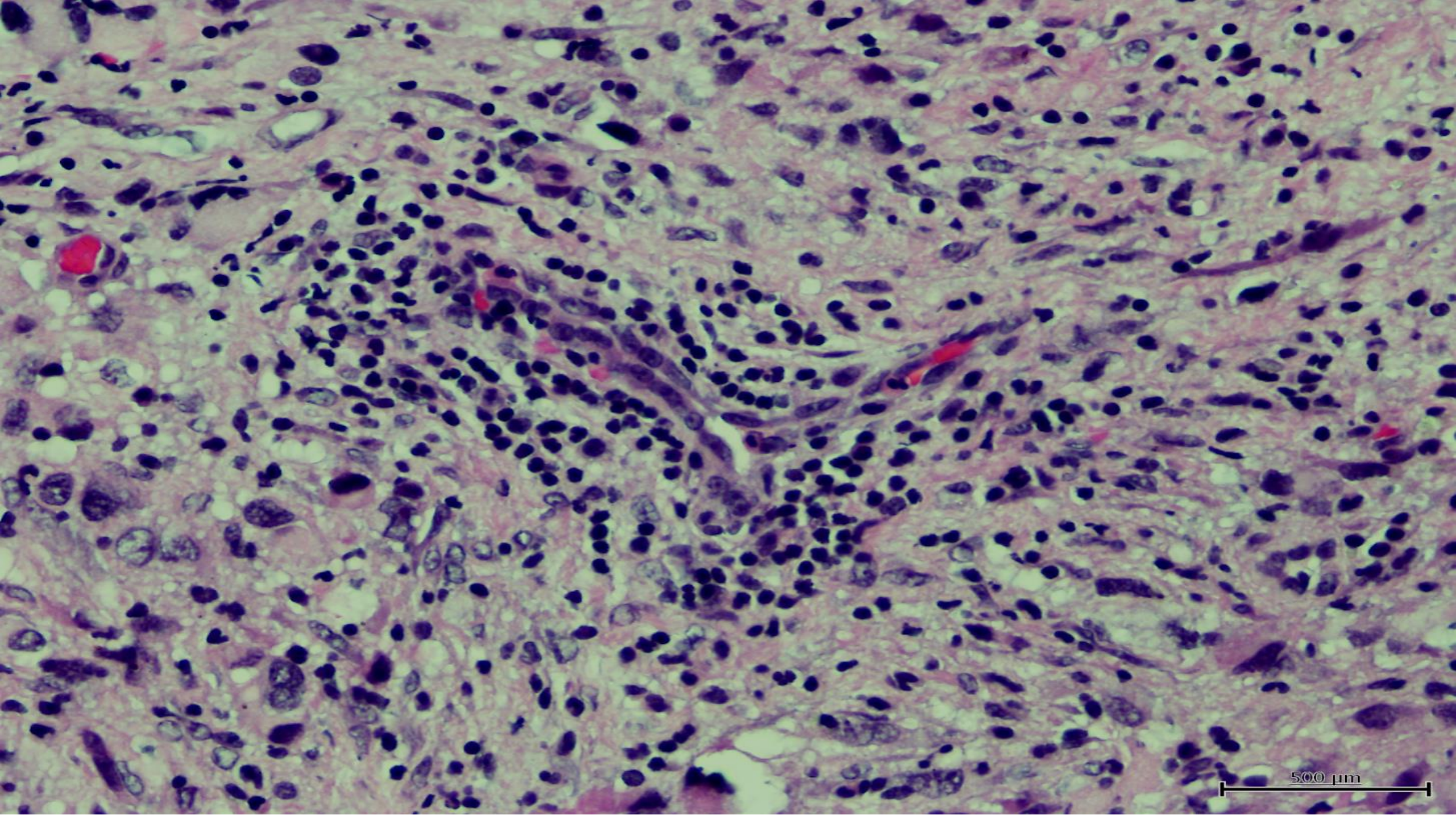


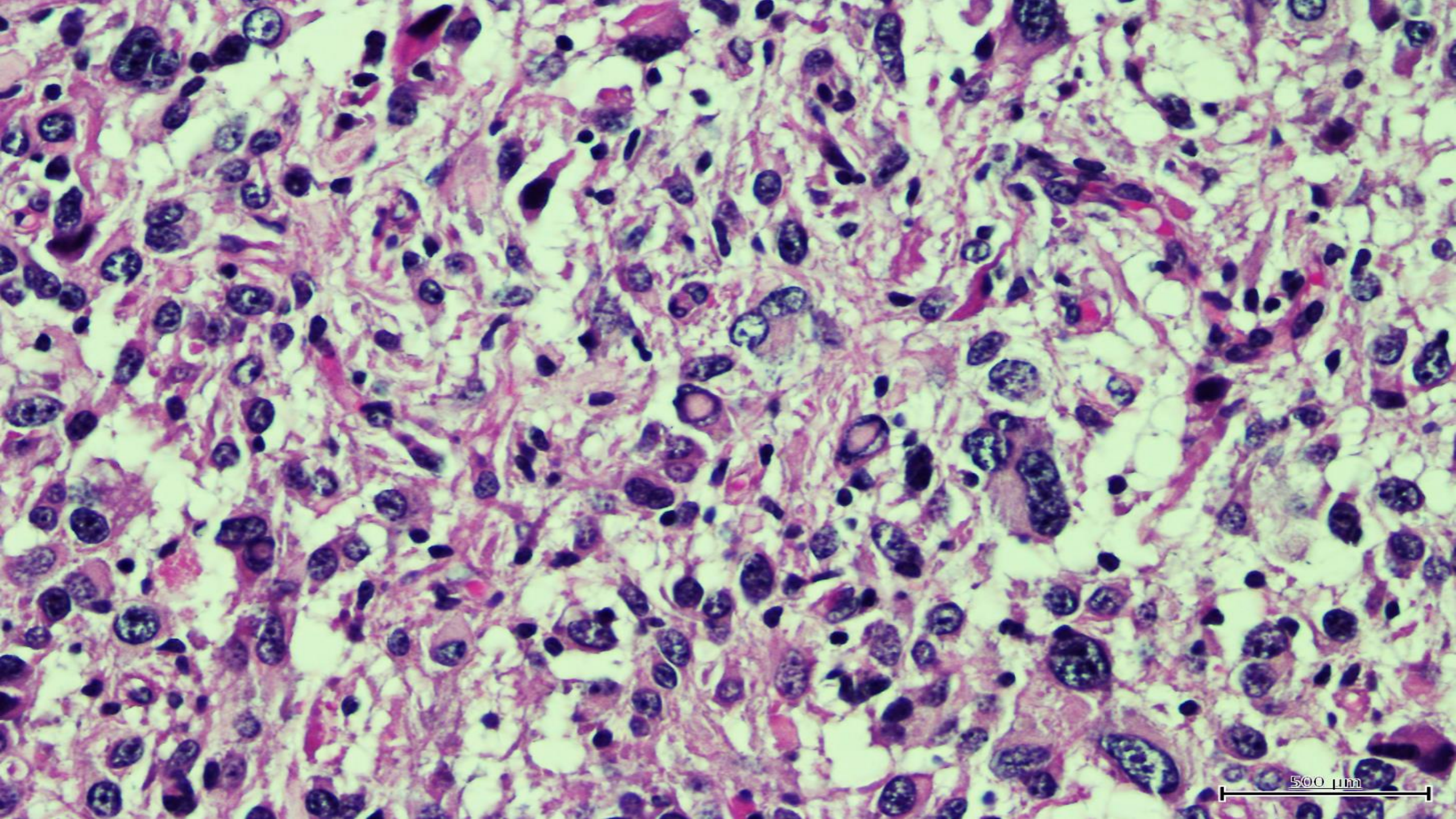
Case-06

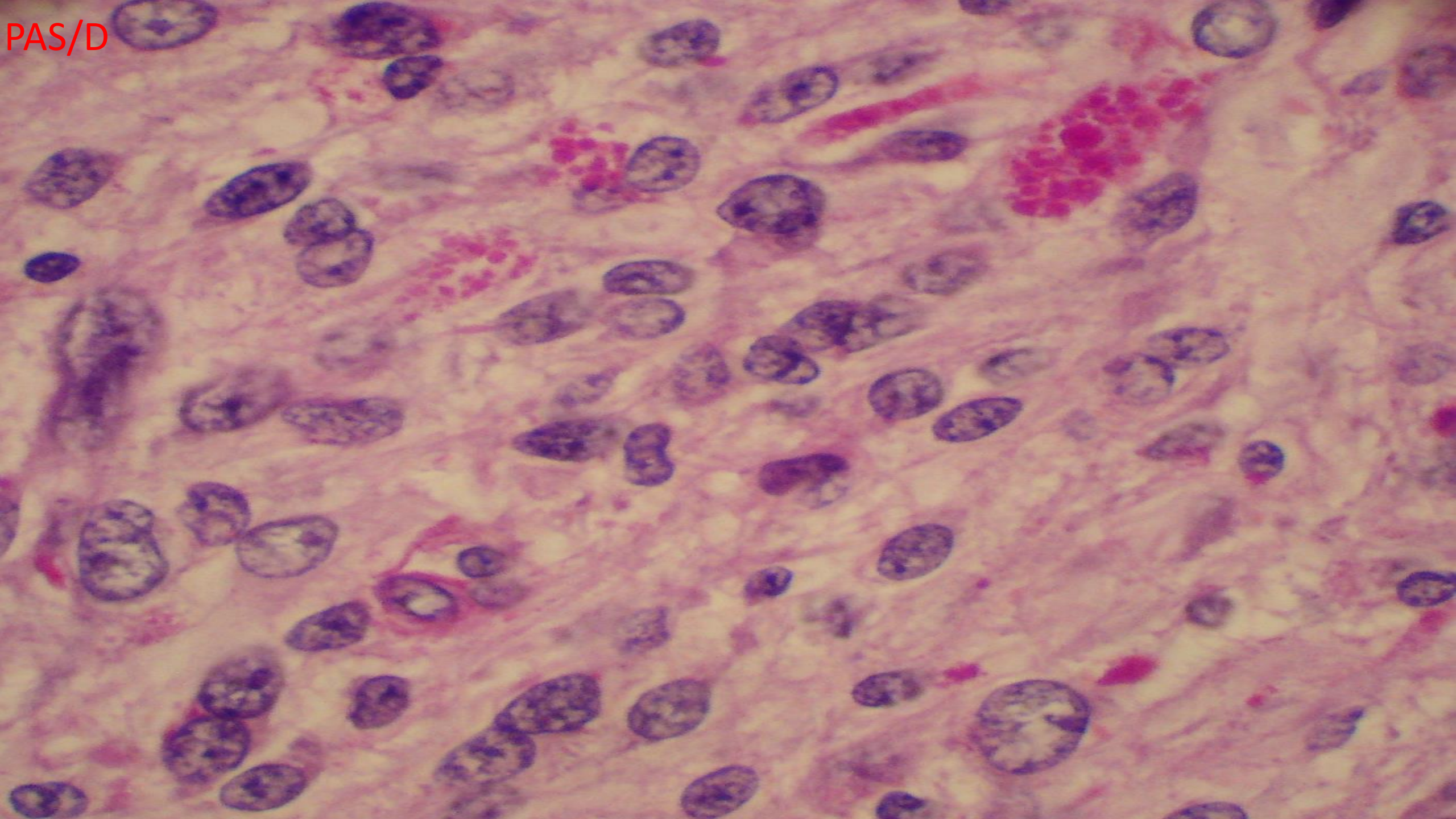
- 2011
  - A 16-year-old girl, presented with tonic-clonic convulsions
  - Brain MRI; Non-metastatic large complex solid/cystic mass at left parietal lobe at initial presentation.
  - STR

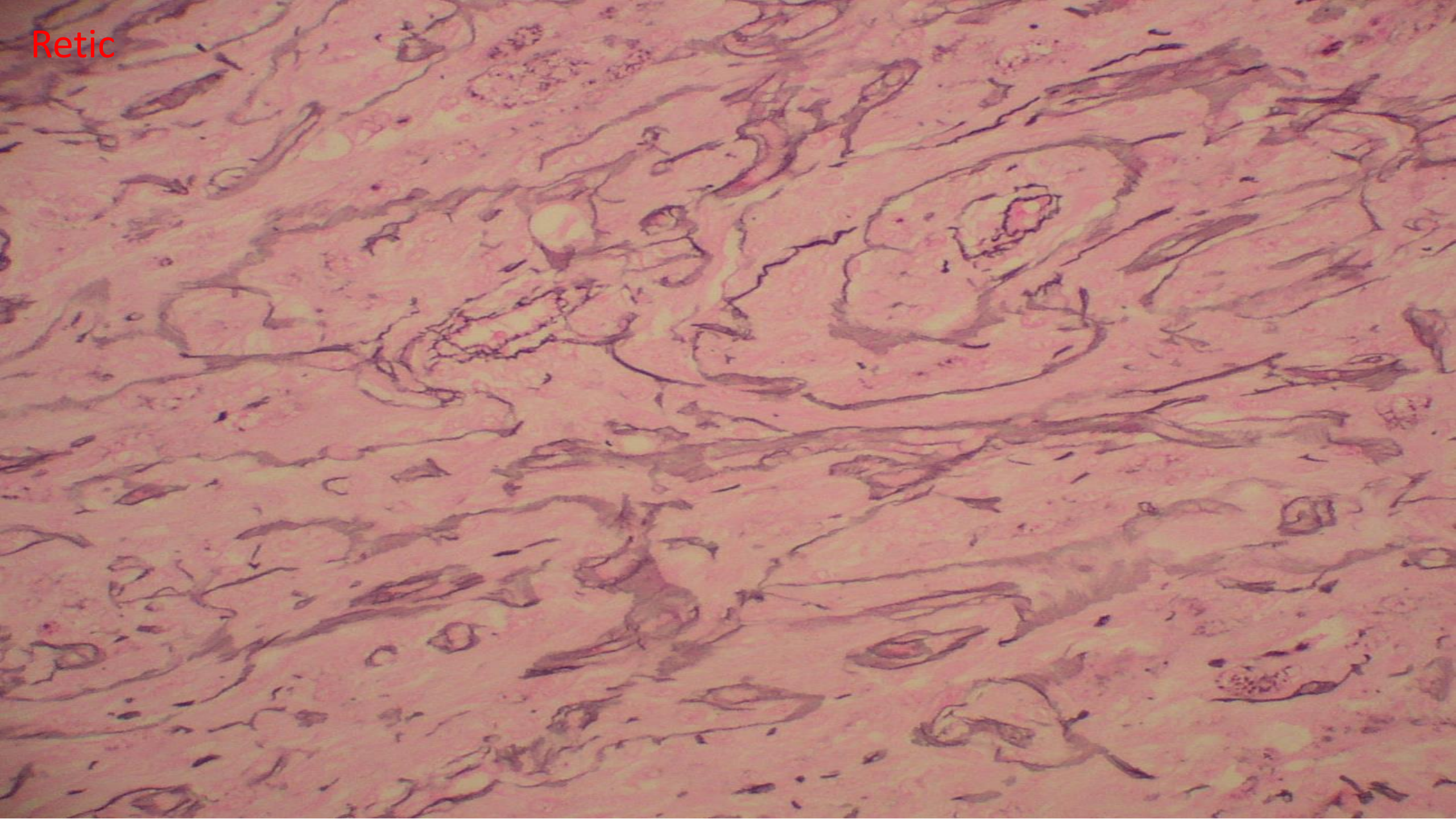


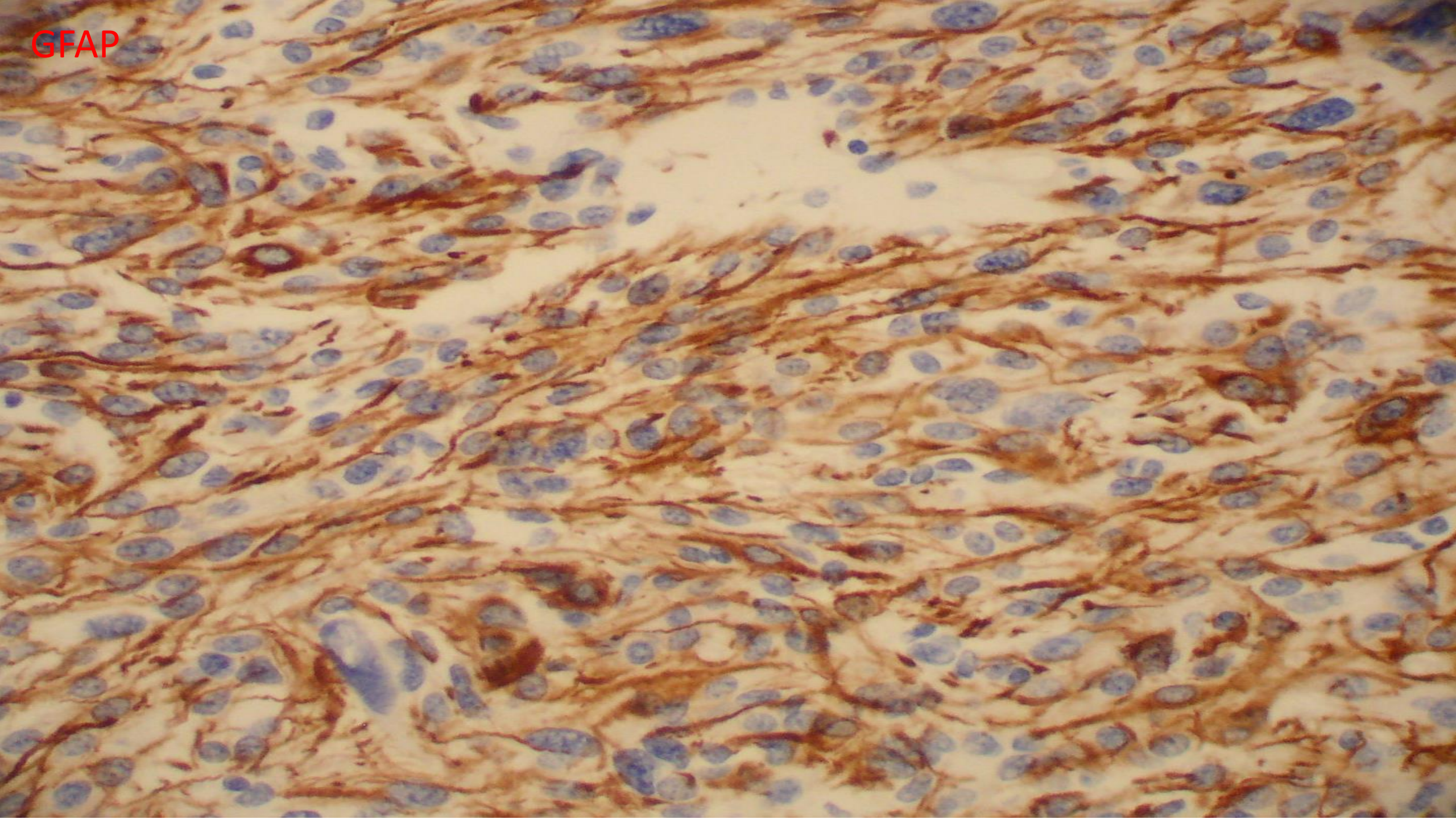

P2107.11
500 µm

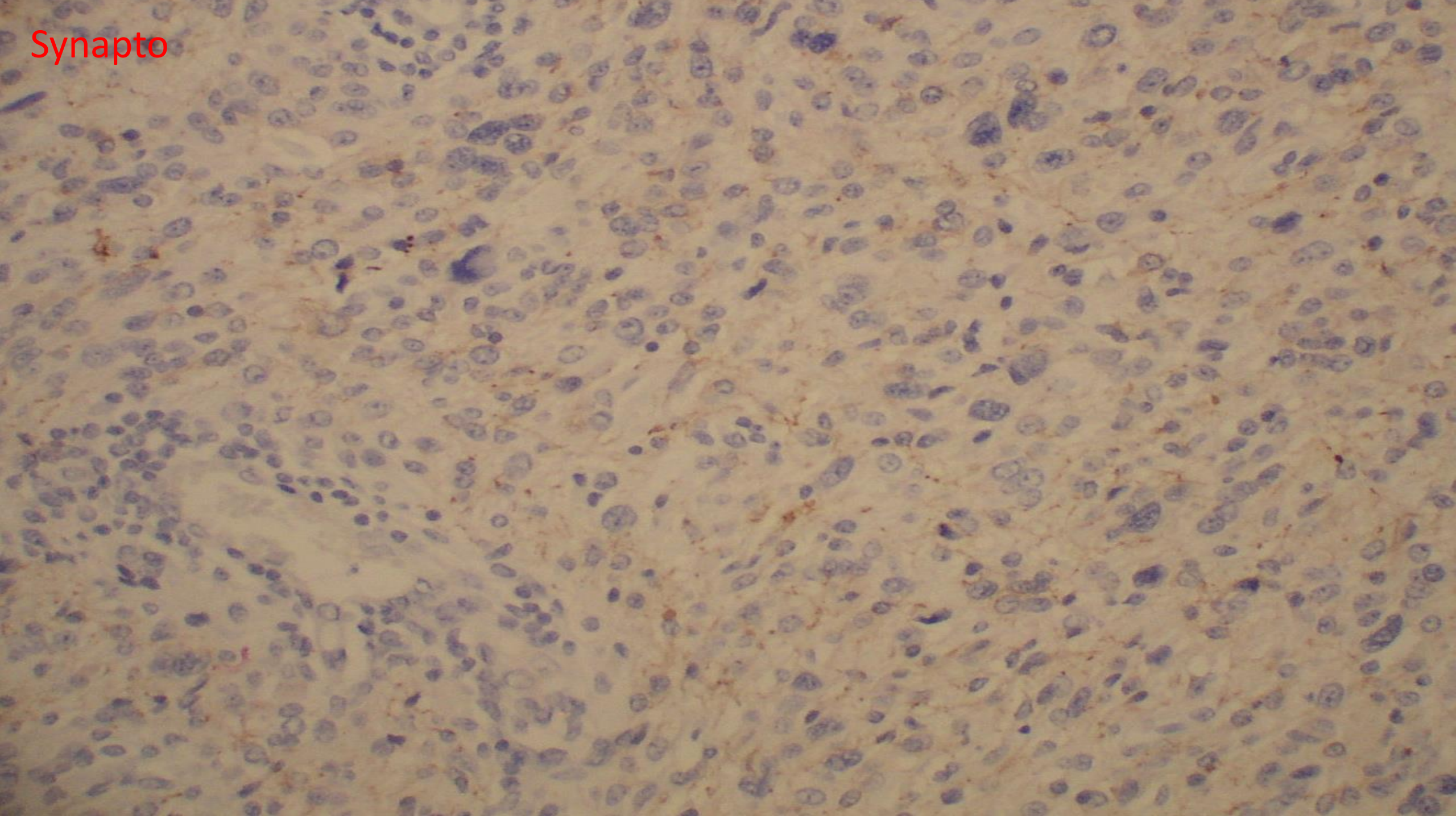

500 µm

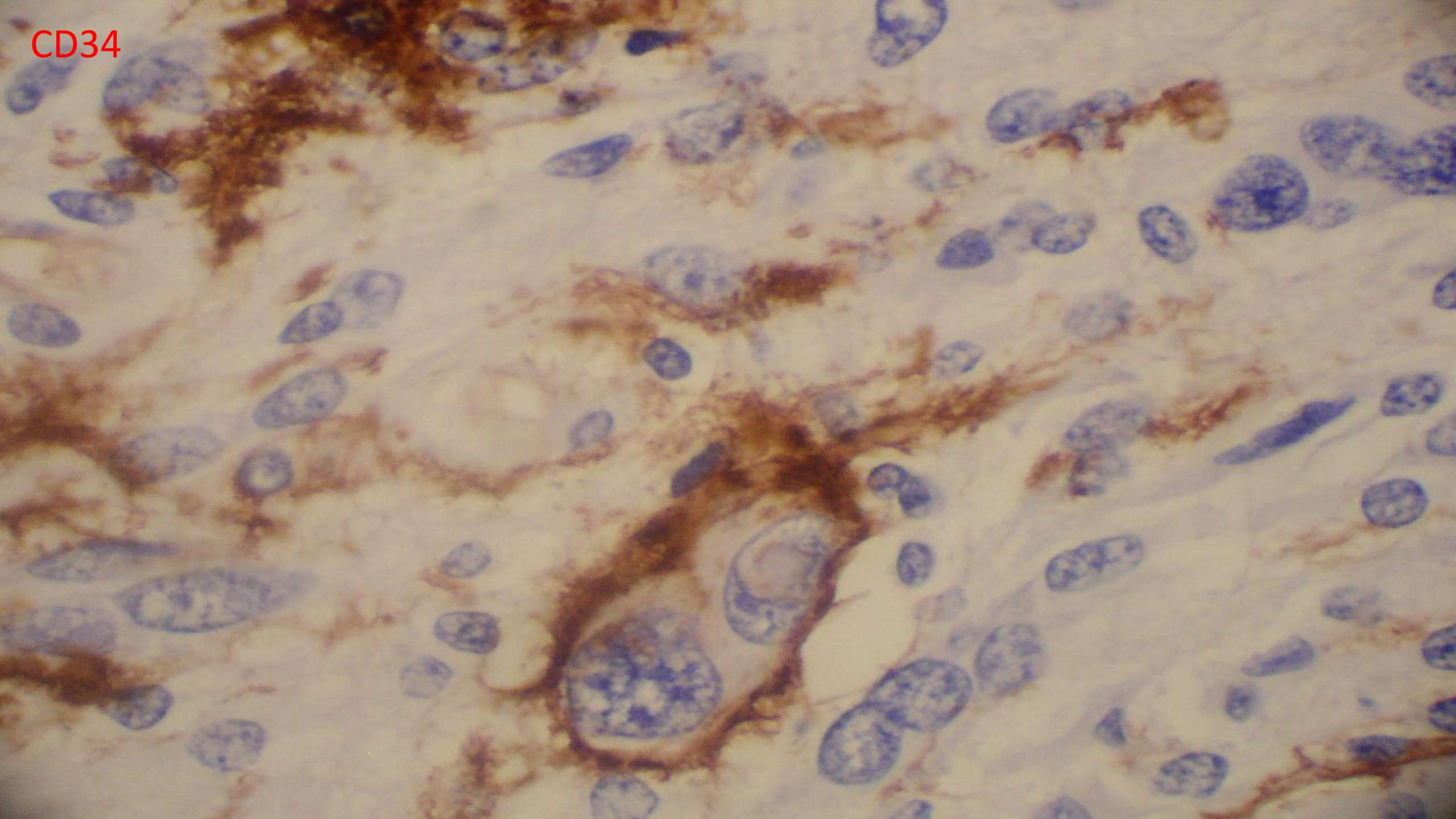

500 µm

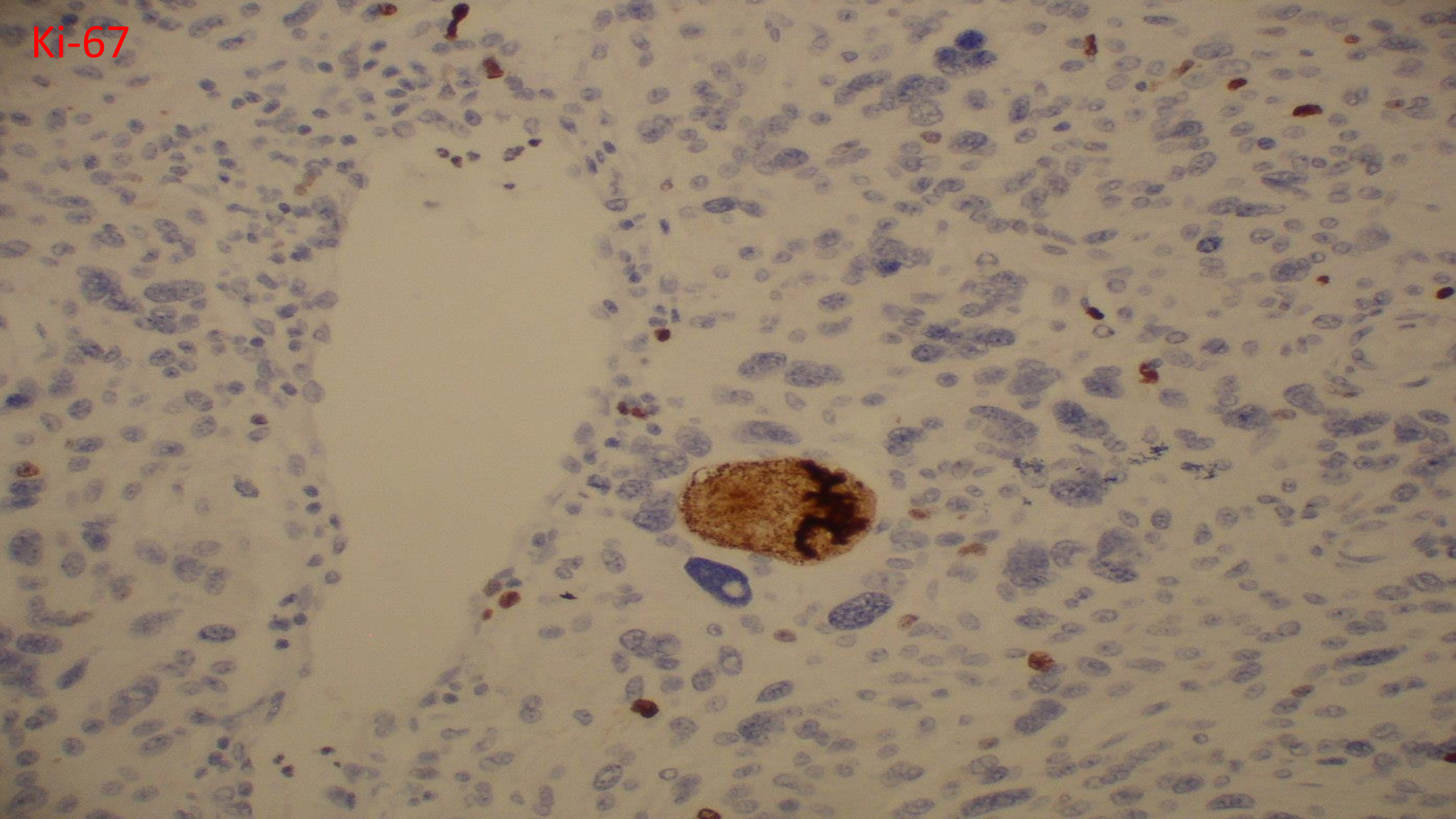

PAS/D


Retic


GFAP


Synapto


CD34


Ki-67

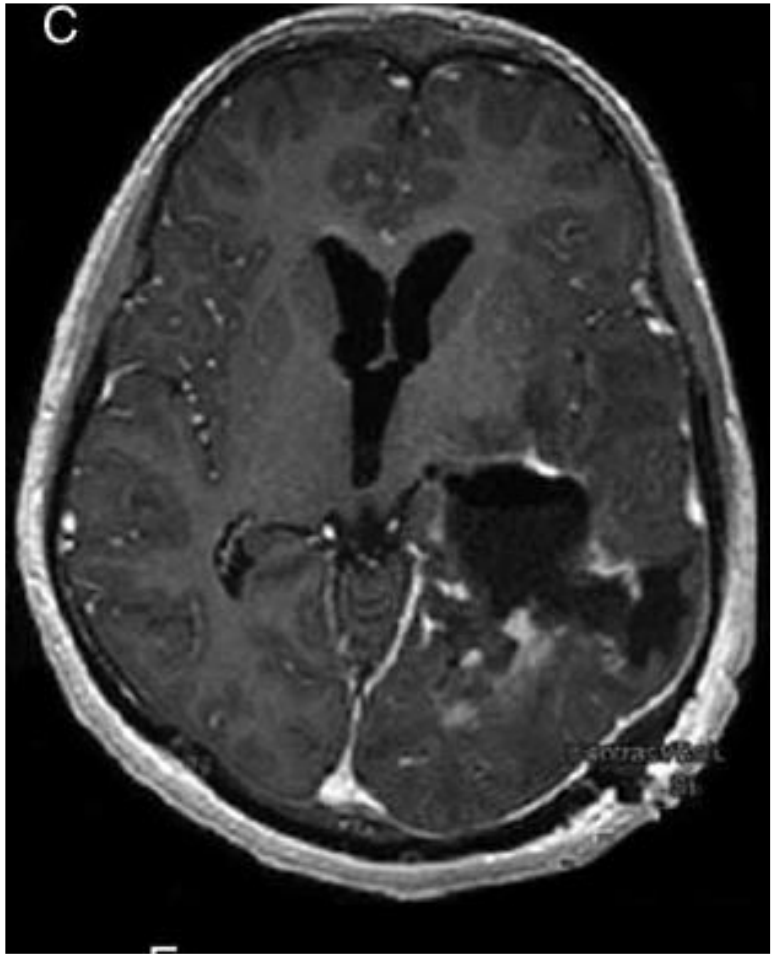
Diagnosis
PXA with anaplasia

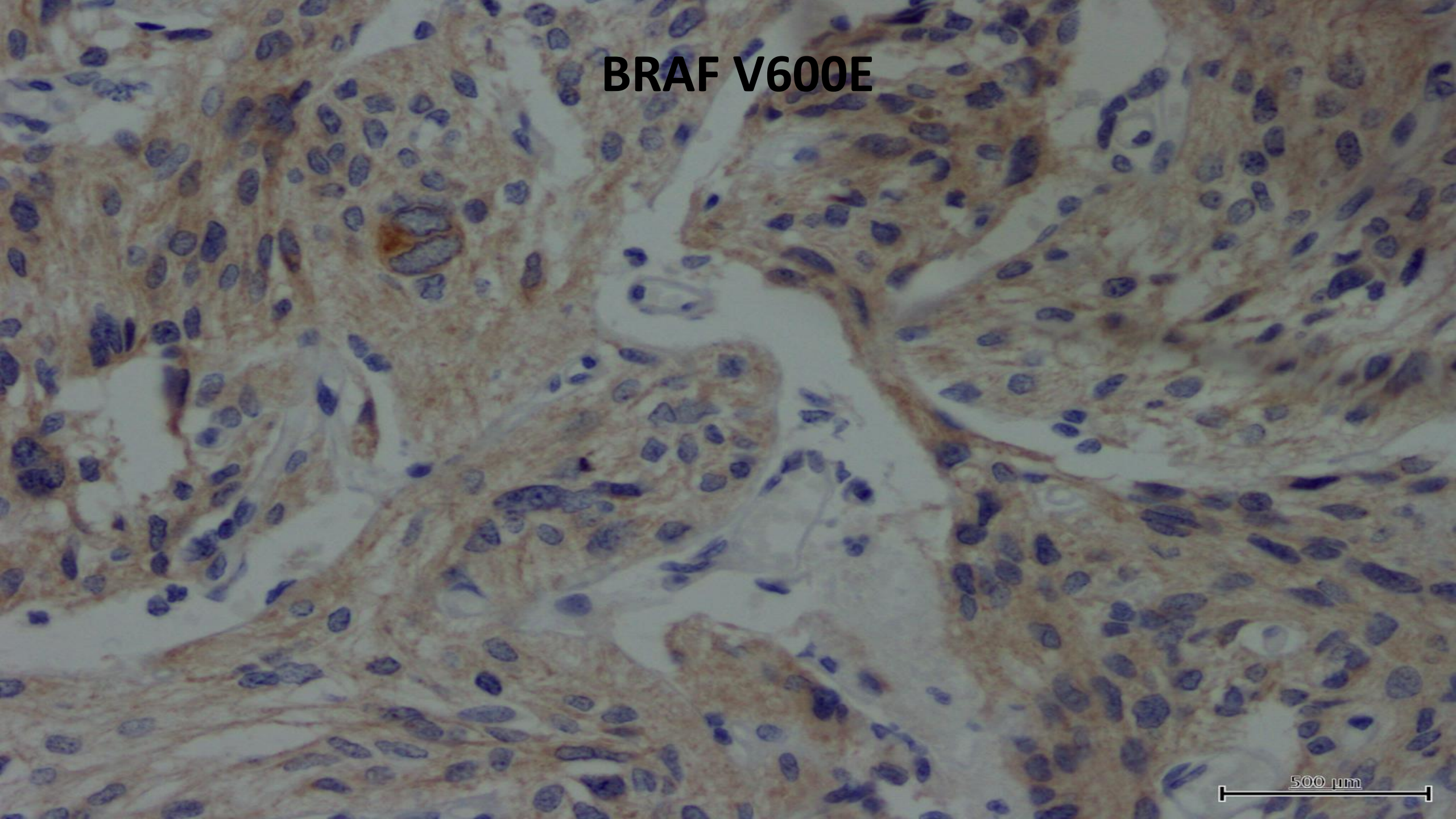
- Scattered mitotic figures
- No necrosis or MVP
- Reticulin stain is focal/negative
- Immunostains
  - GFFAP positive
  - S-100 positive
  - CD34 positive
  - Synaptophysin occasional positive
  - NFP; absence of infiltration
  - Ki-67 (5%)

Three Years Later (2013)



- Local progression
- Re-discussed at videoconference
- Underwent near total surgical resection
- Same pathology
- Tested for BRAF V600E




BRAF V600E
500 µm

2.1.2: Pediatric-type diffuse low-grade gliomas

- 2.1.2.1: Diffuse astrocytoma, MYB- or MYBL1-altered
- 2.1.2.2: Angiocentric glioma
- 2.1.2.3: Diffuse low-grade glioma, MAPK-altered
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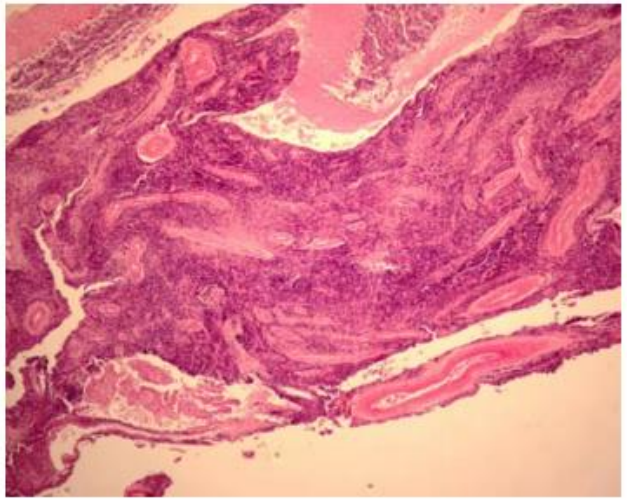
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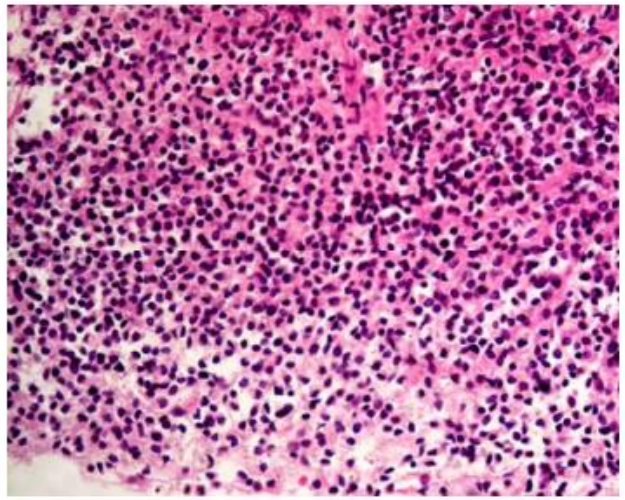
- 2.1.5.1: Ganglioglioma
- 2.1.5.2: Desmoplastic infantile astrocytoma / ganglioglioma
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- 2.1.5.4: Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters
- 2.1.5.5: Papillary glioneuronal tumour
- 2.1.3.13 Diffuse leptomeningeal glioneuronal tumor

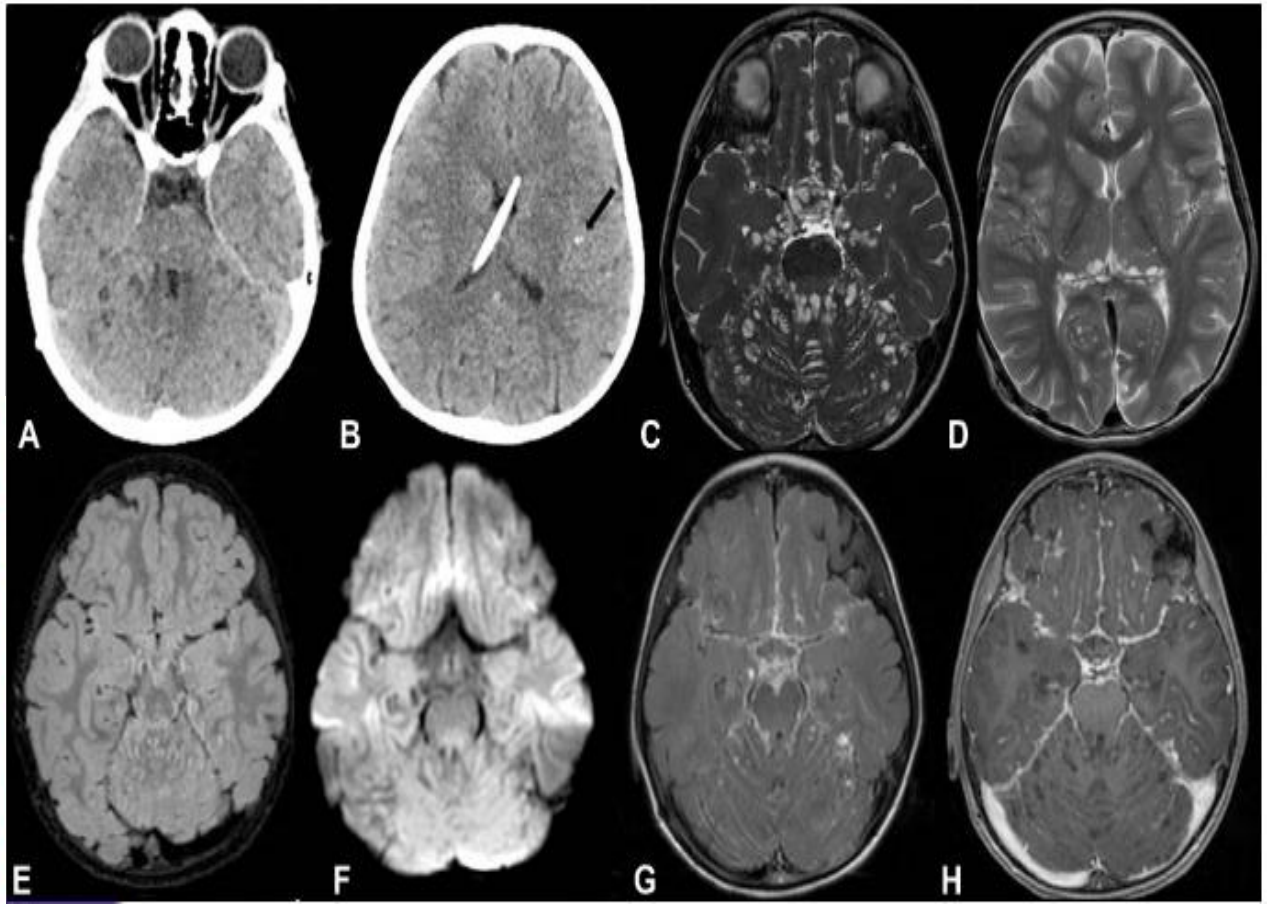
Many others.....

Diffuse glioneuronal tumor with oligodendroglial features and nuclear clusters (DGONC)

- Diffuse glioneuronal tumor with oligodendroglial features and nuclear clusters (DGONC)

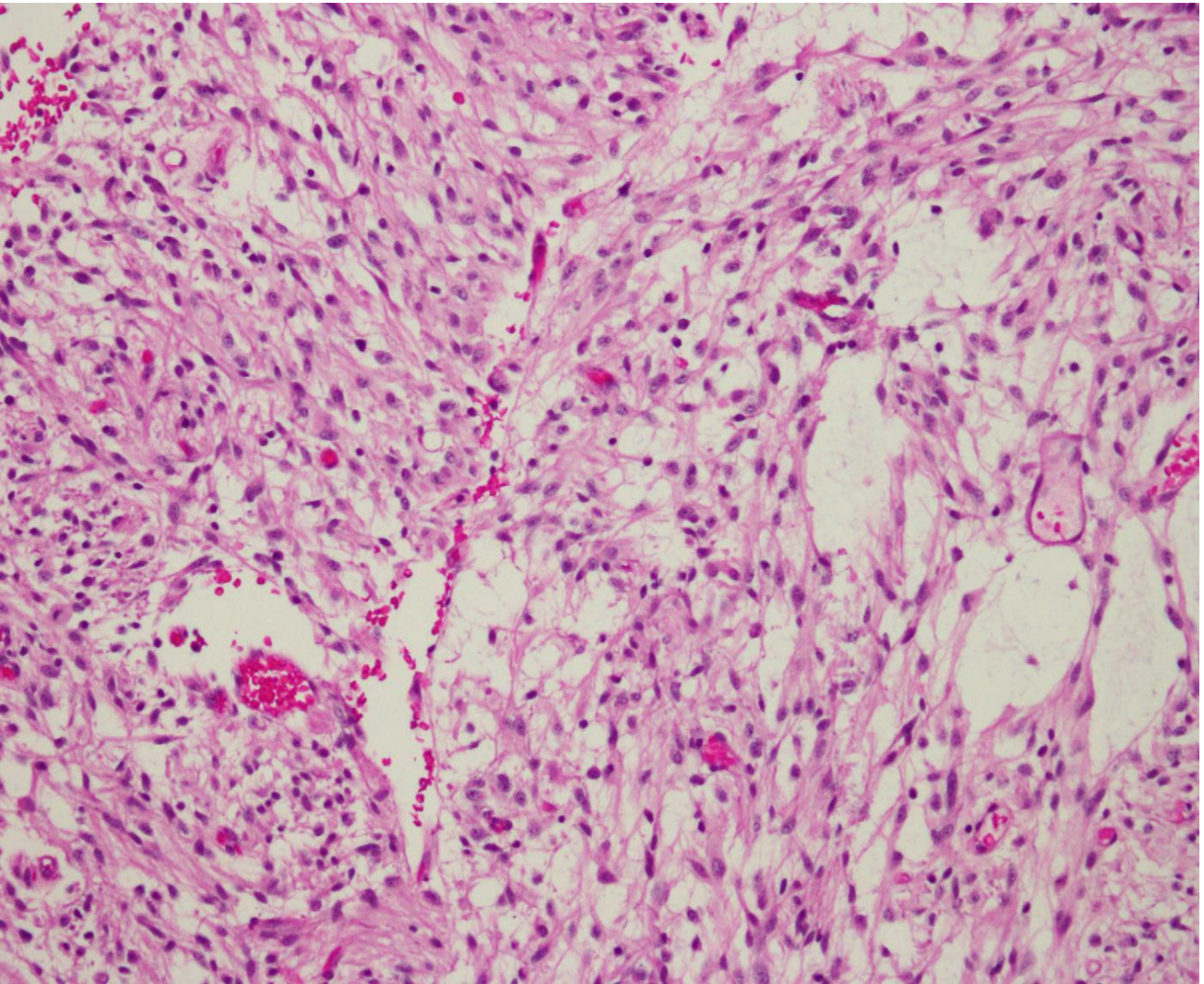


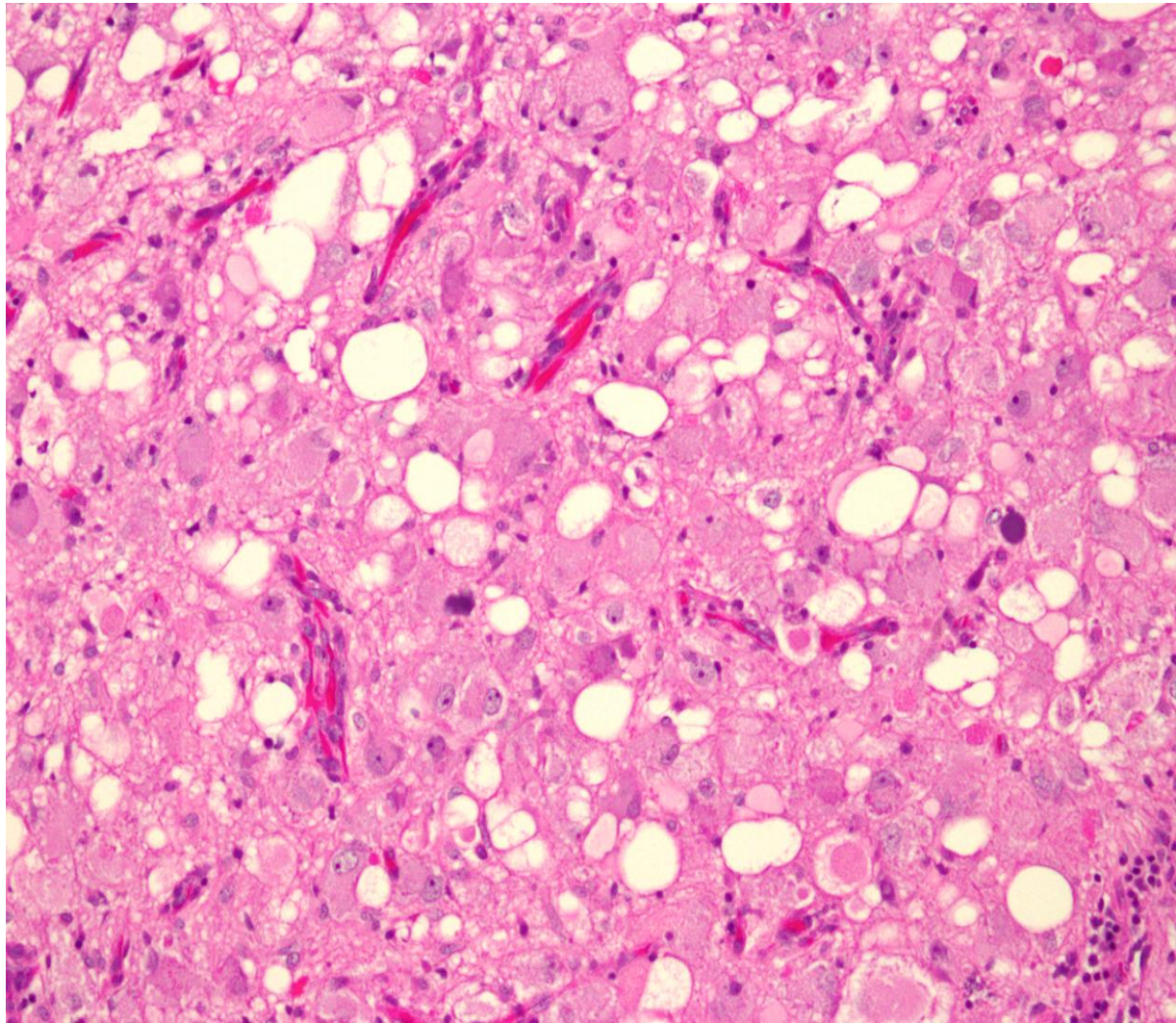


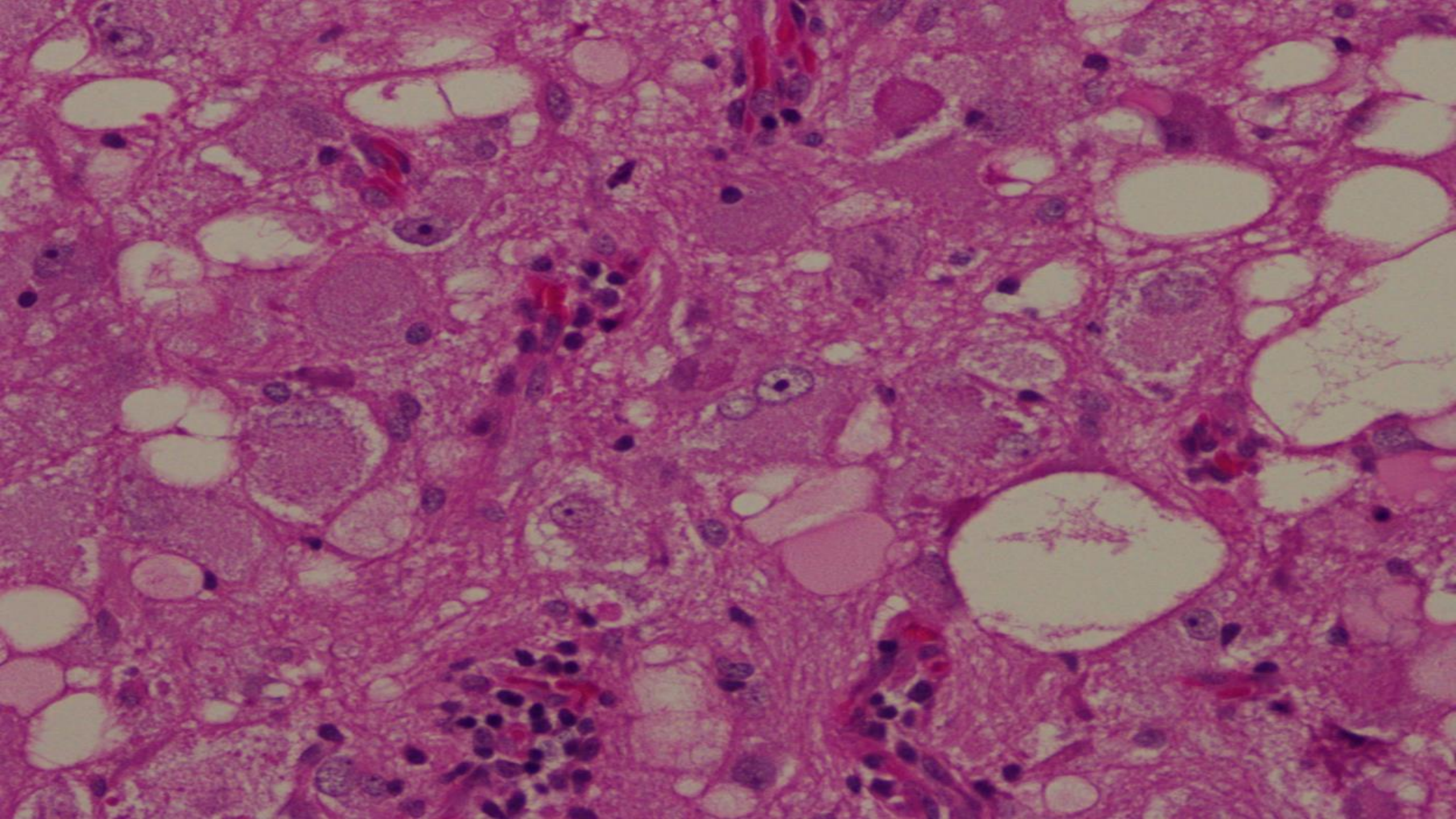


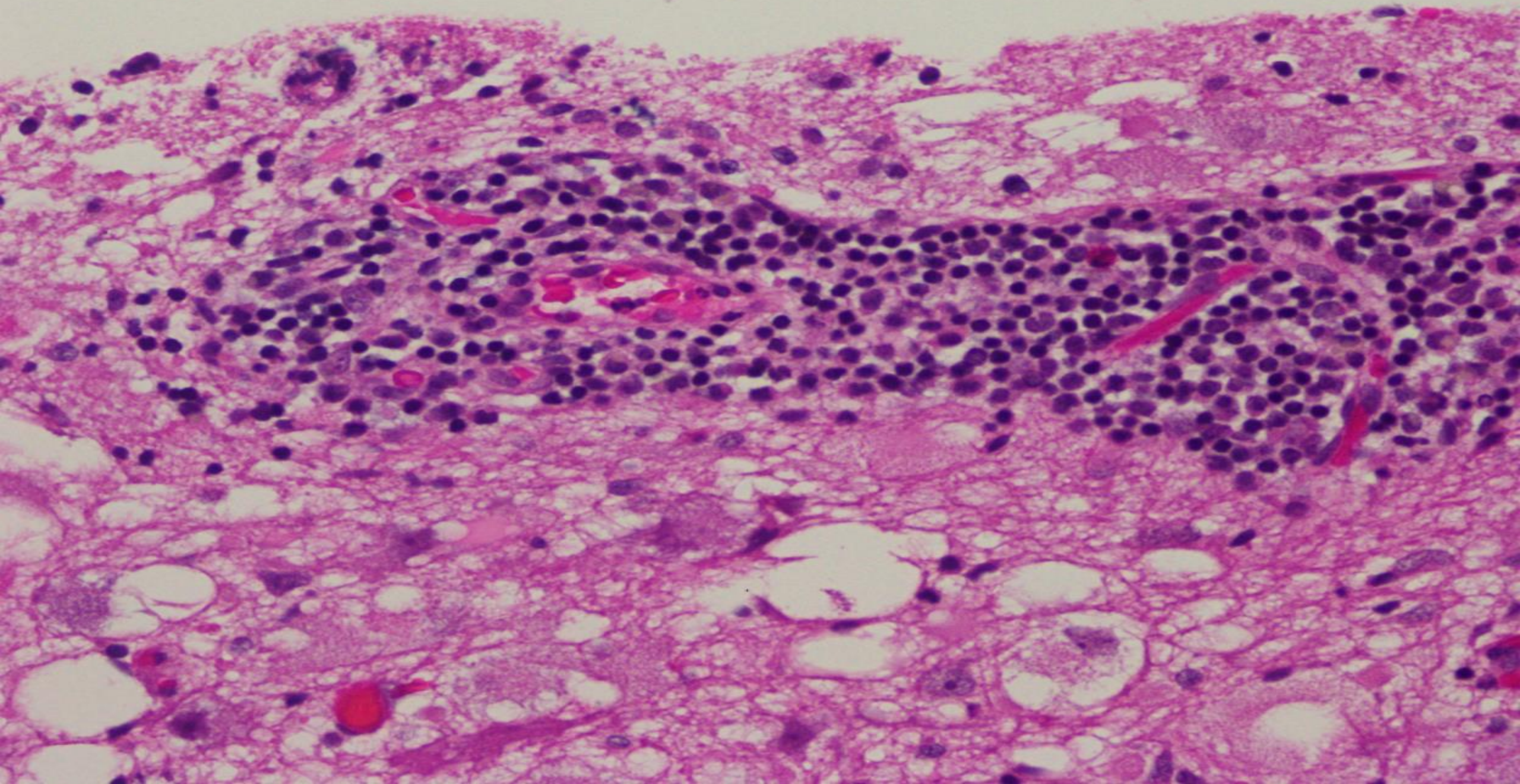
E. J. Rushing. MEMO. 2 February 2021. https://doi.org/10.1007/s12254-021-00680-x

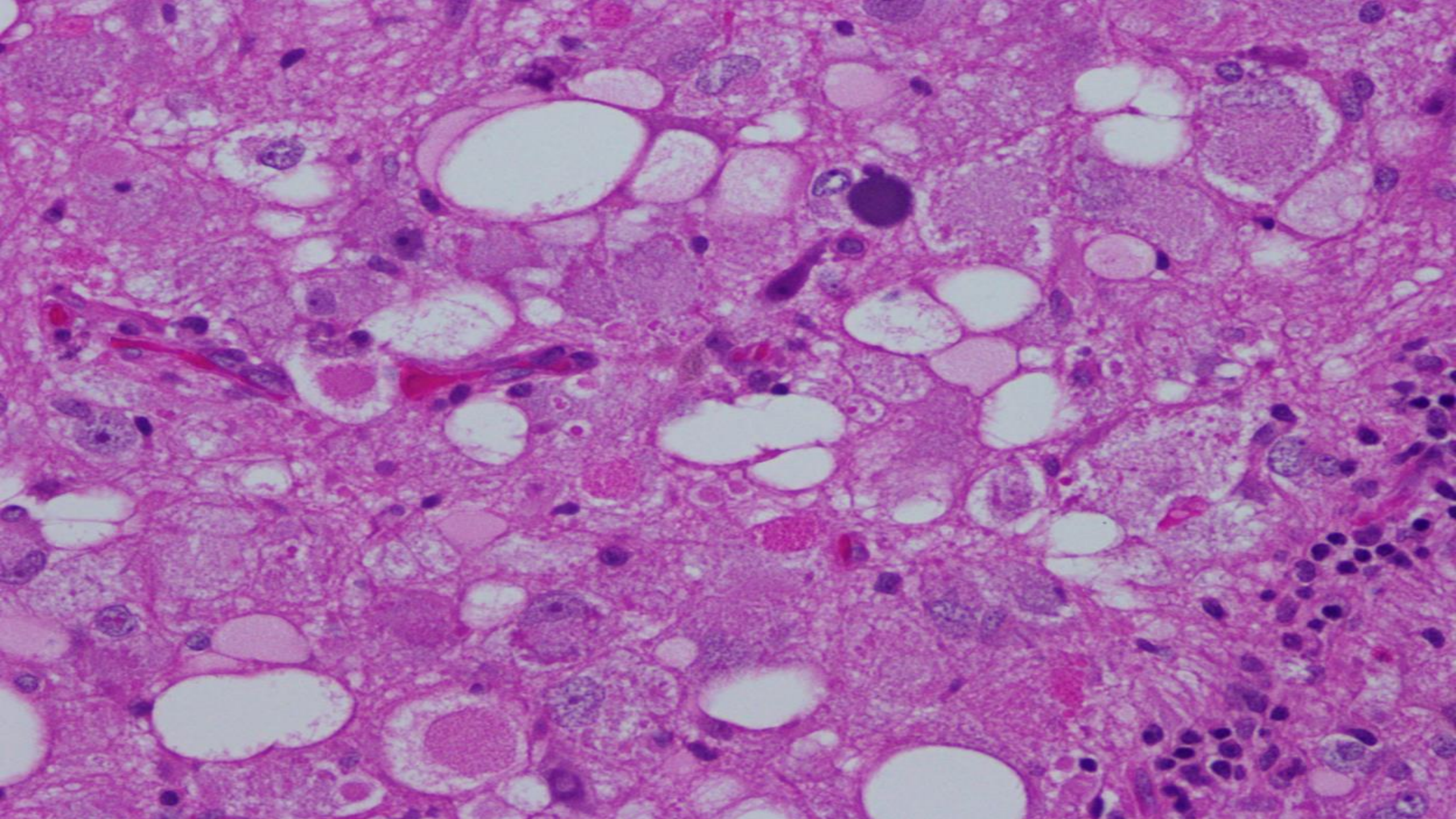
Case-7
P7135.21. A 25 year old male patient with left temporal mass

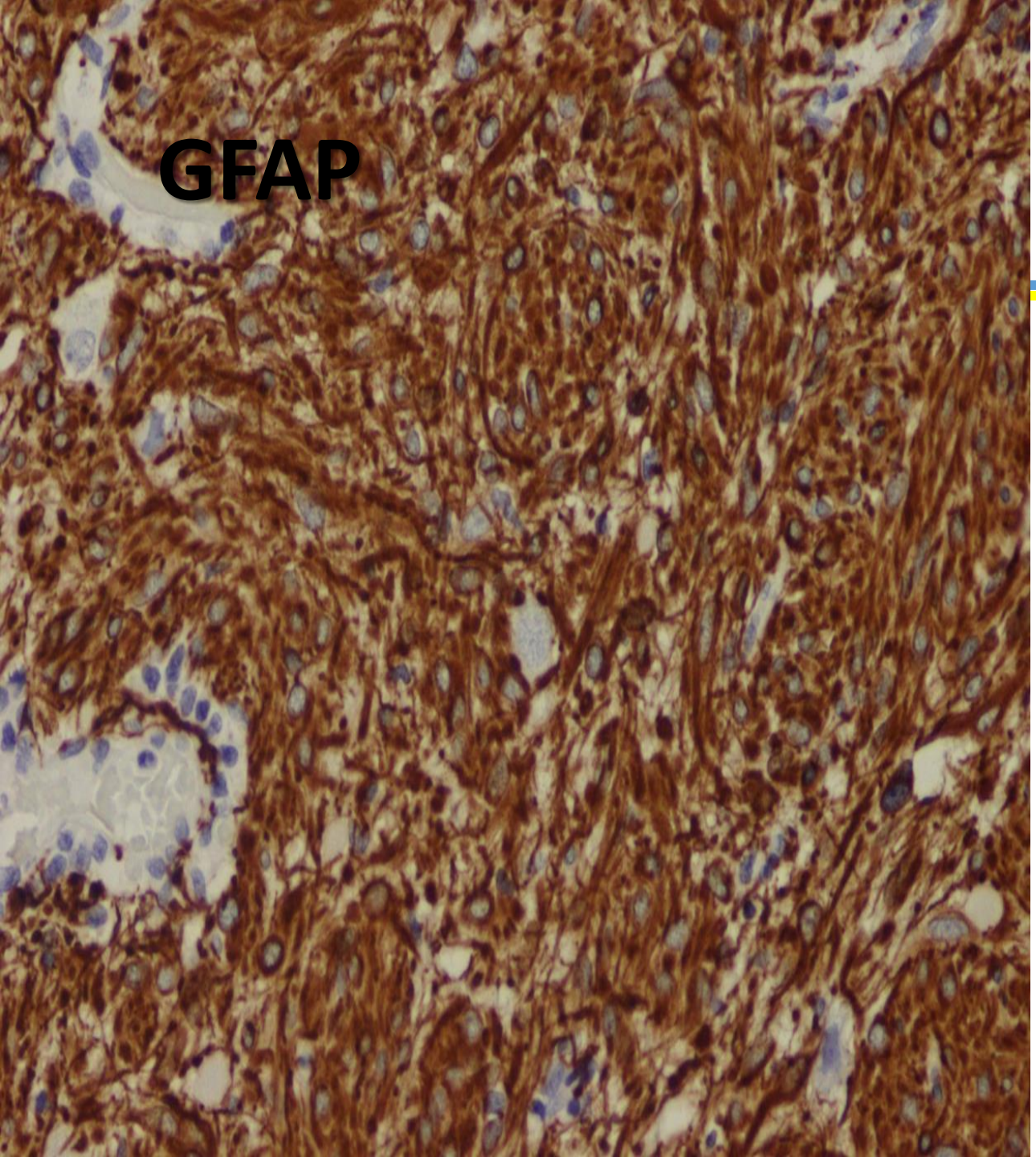


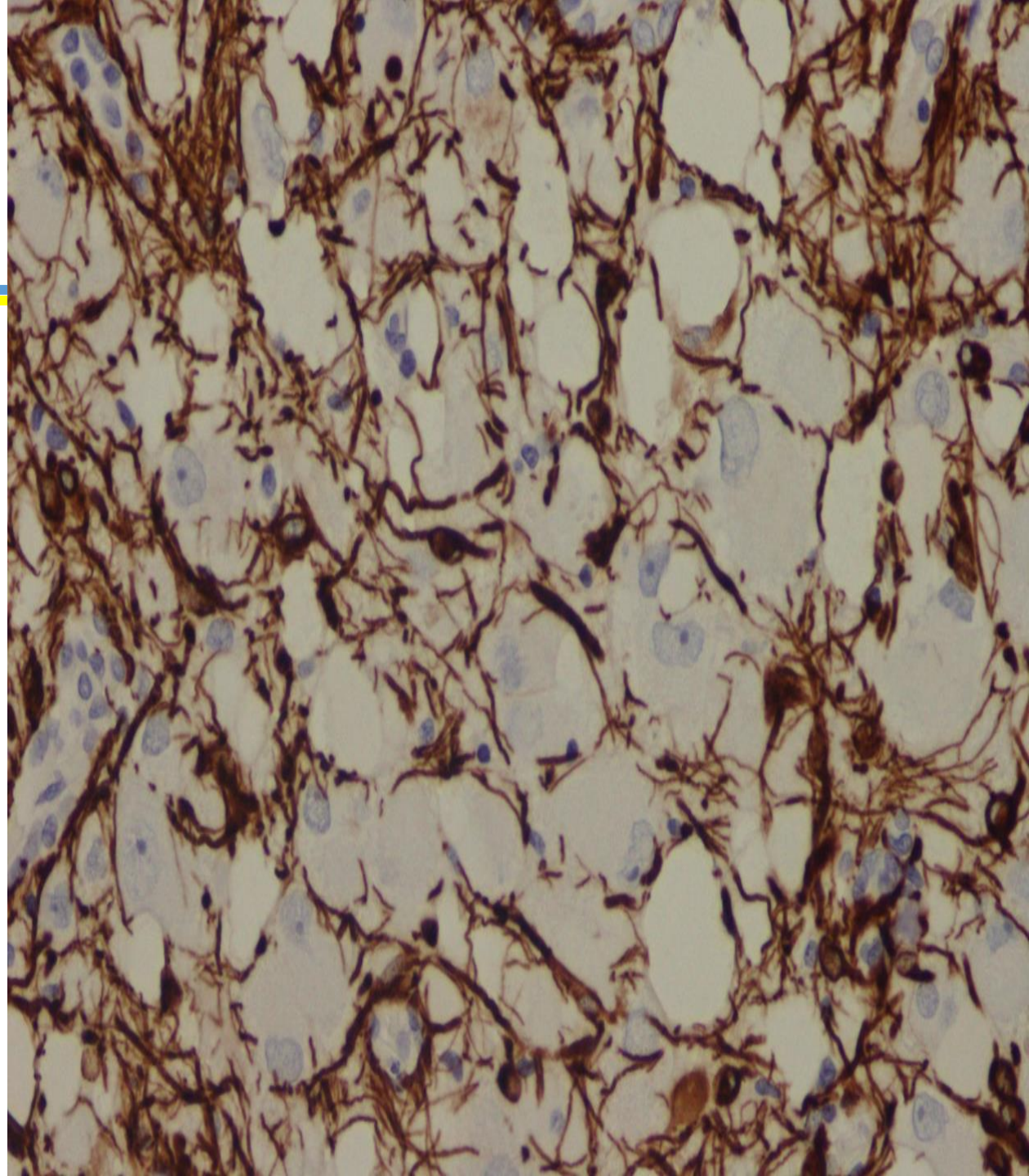


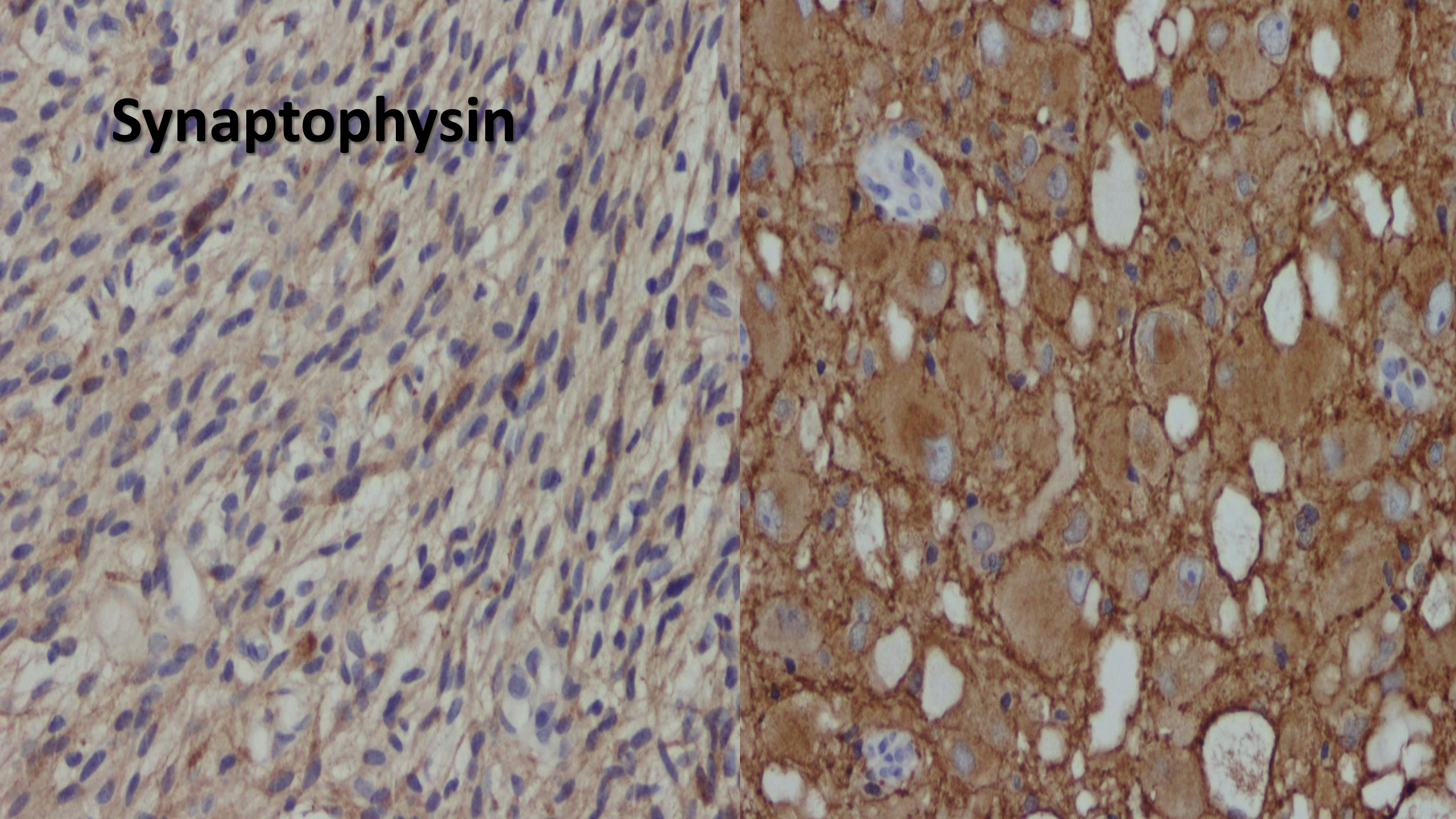




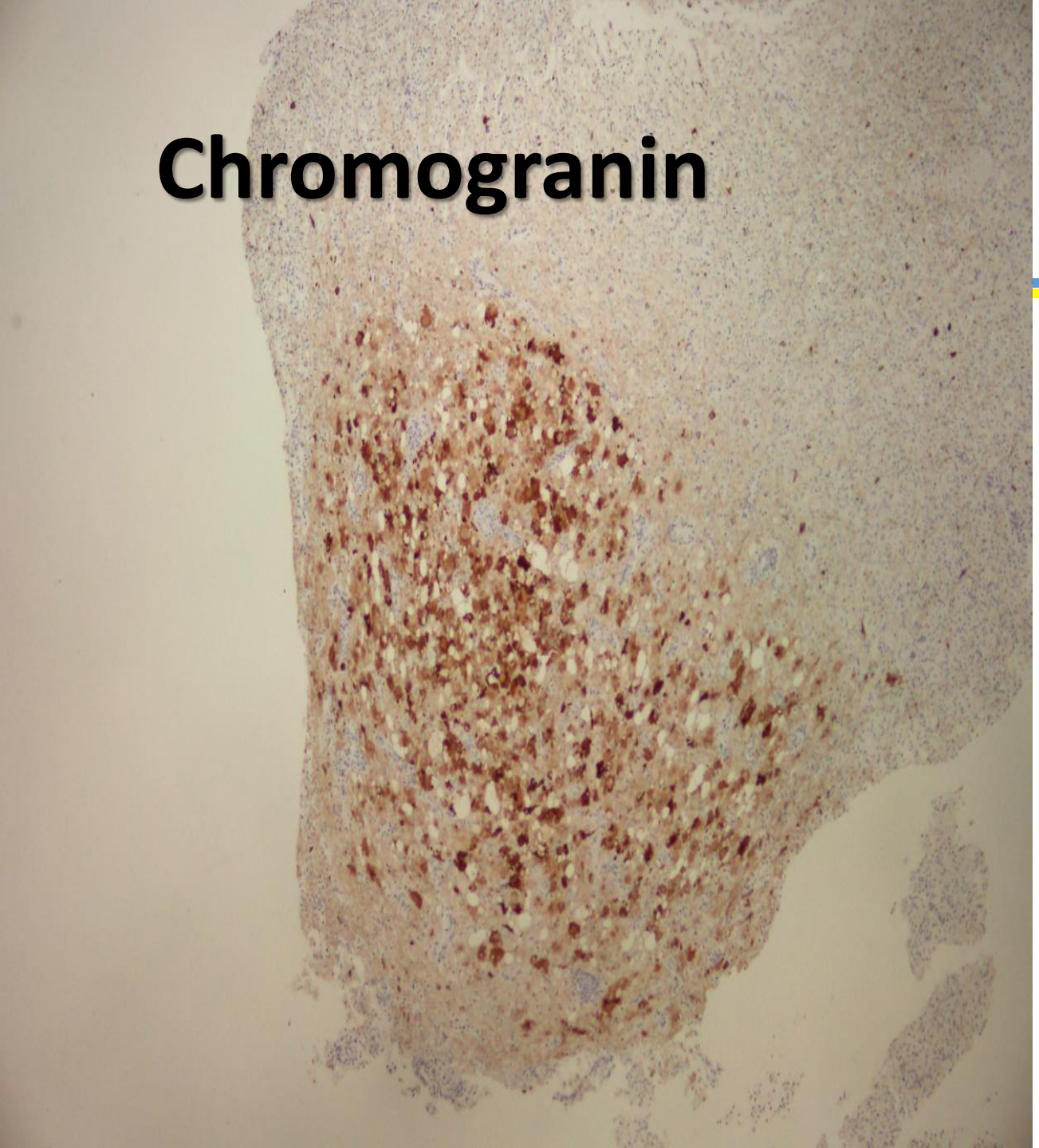


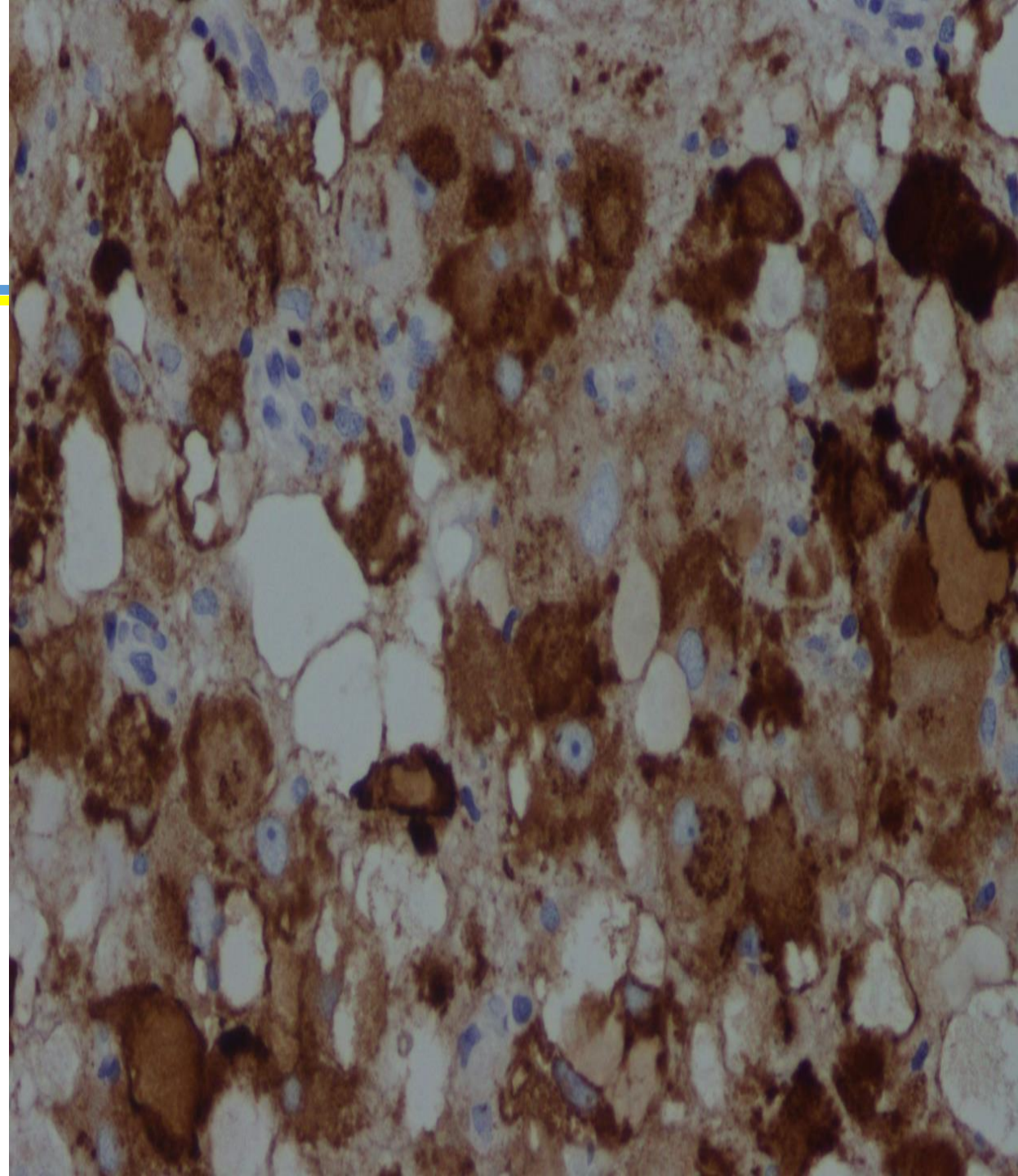

GFAP

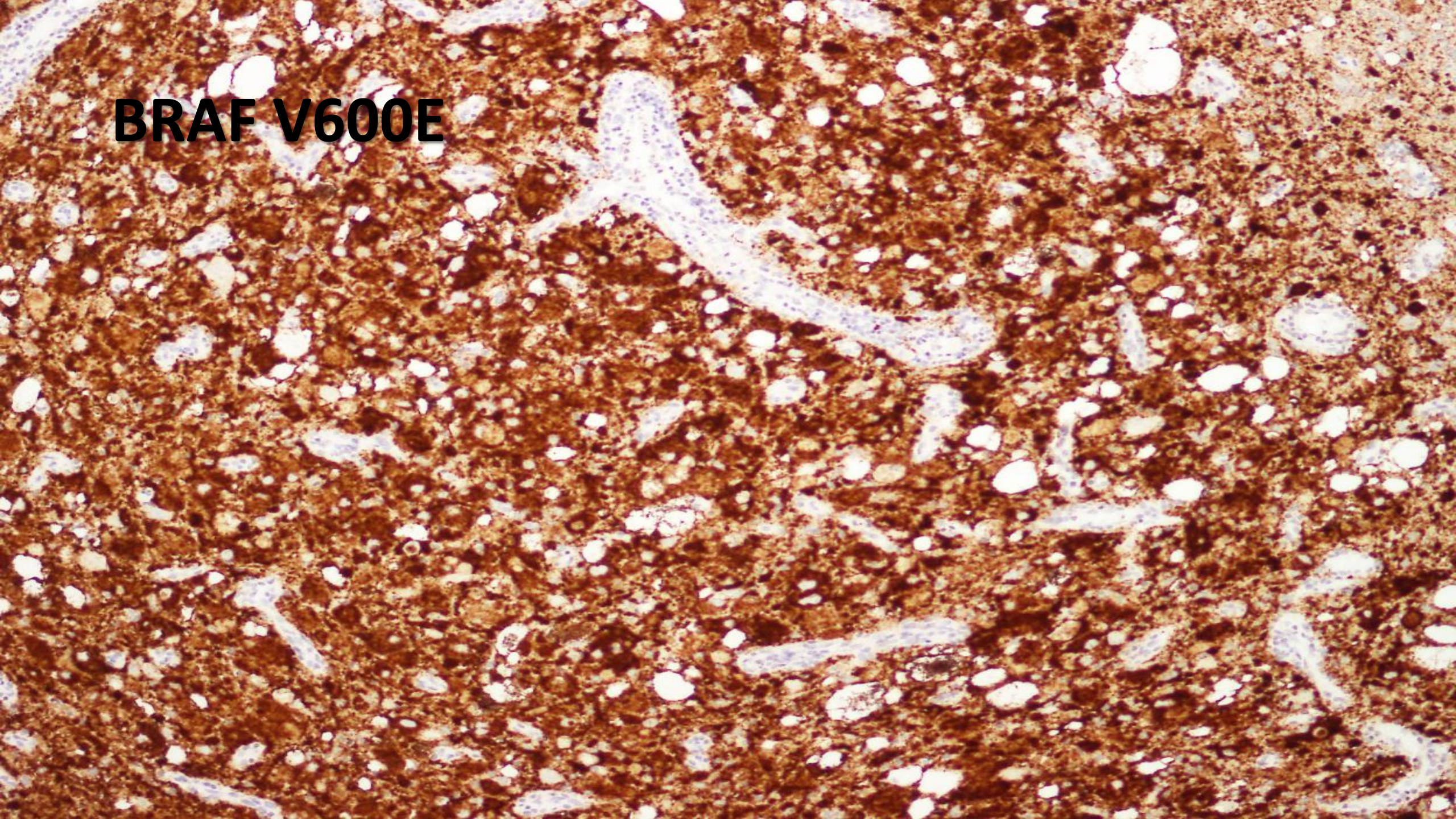


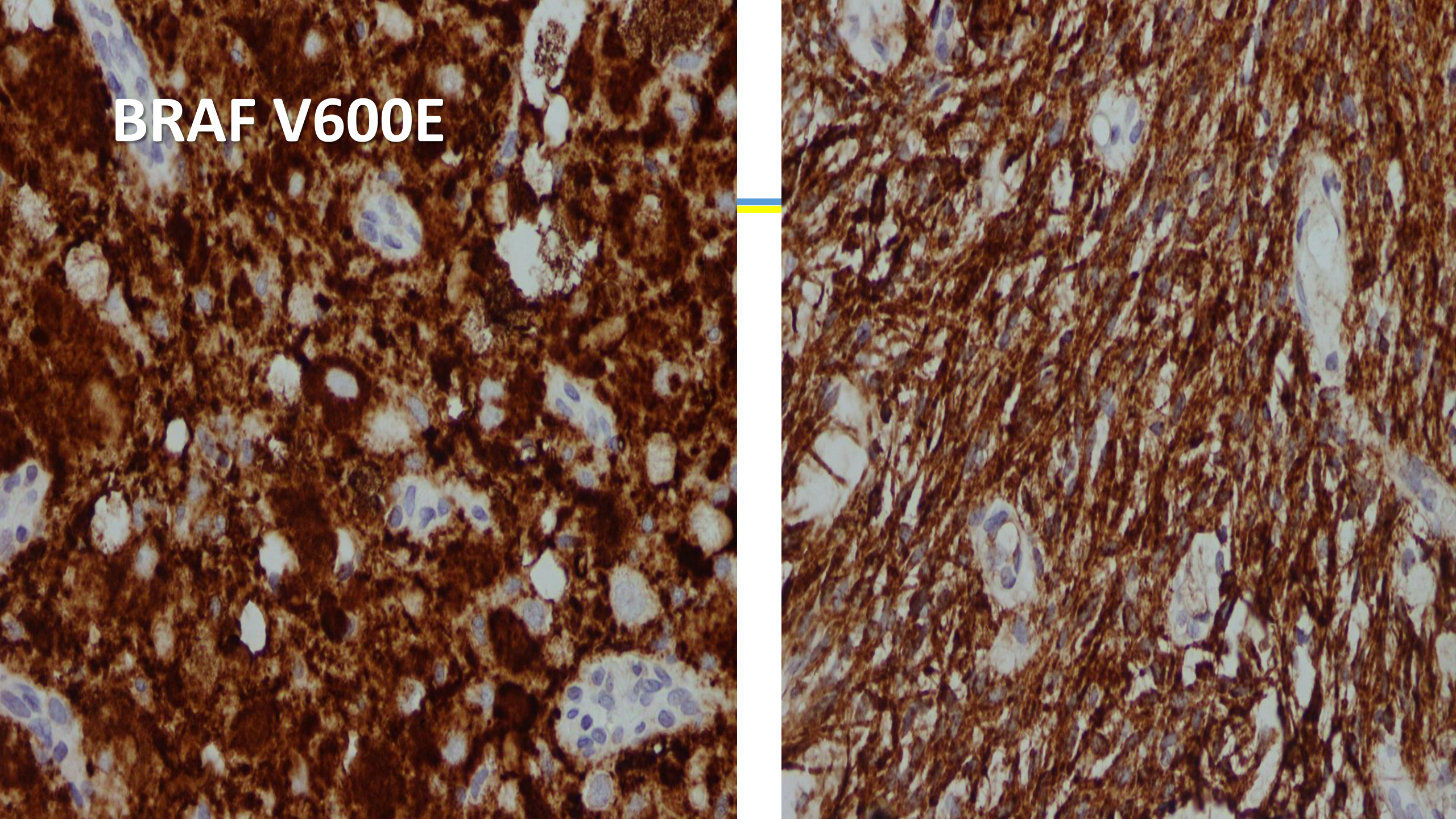

Synaptophysin

Chromogranin

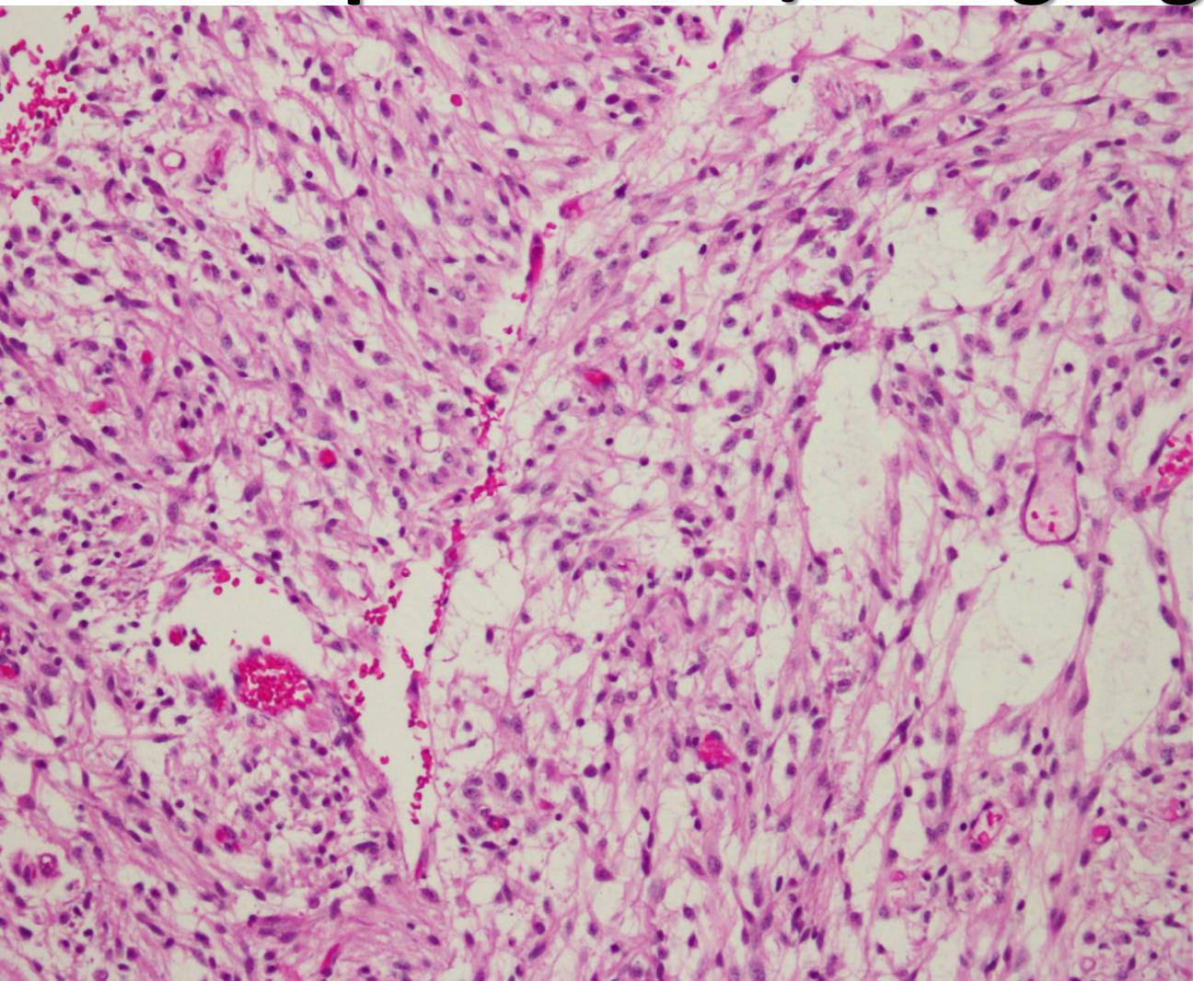


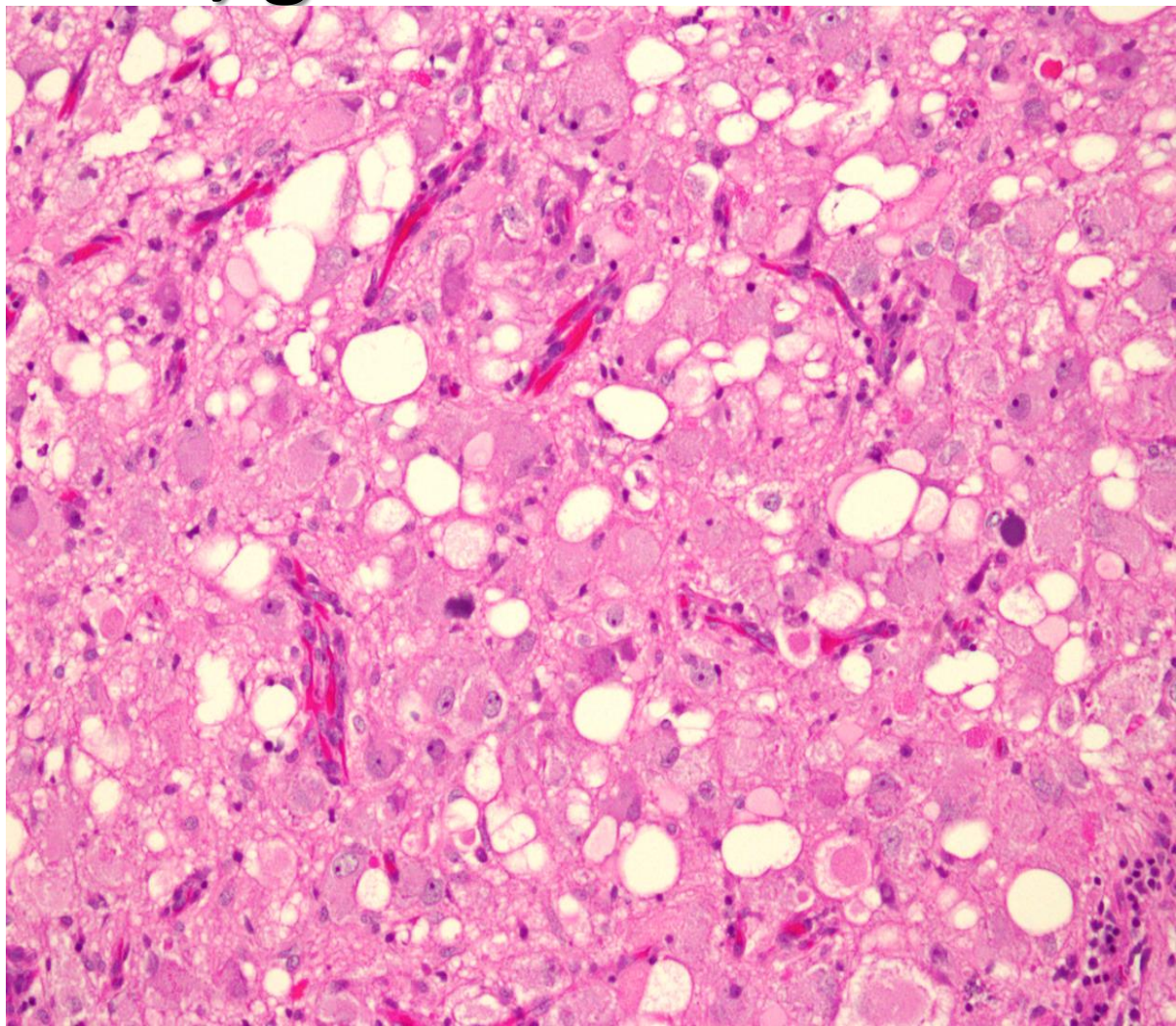



BRAF V600E


BRAF V600E

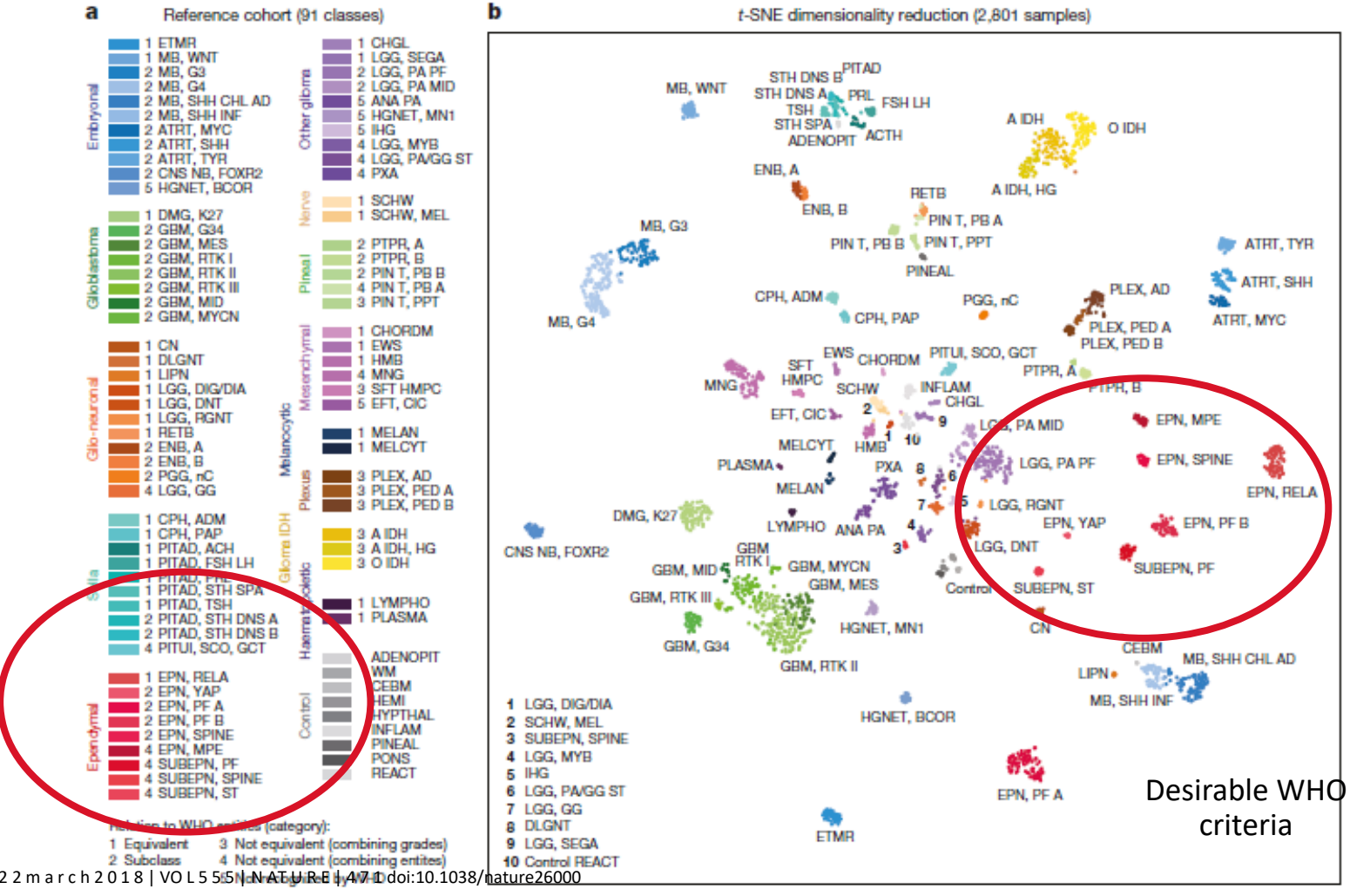
Case-7
P7135.21. A 25 year old male patient with left temporal mass/ Ganglioglioma, grade 1





5. Circumscribed gliomas/ glioneuronal tumors should be tested for BRAF alterations

Methylation Profile
Ependymoma



Desirable WHO criteria

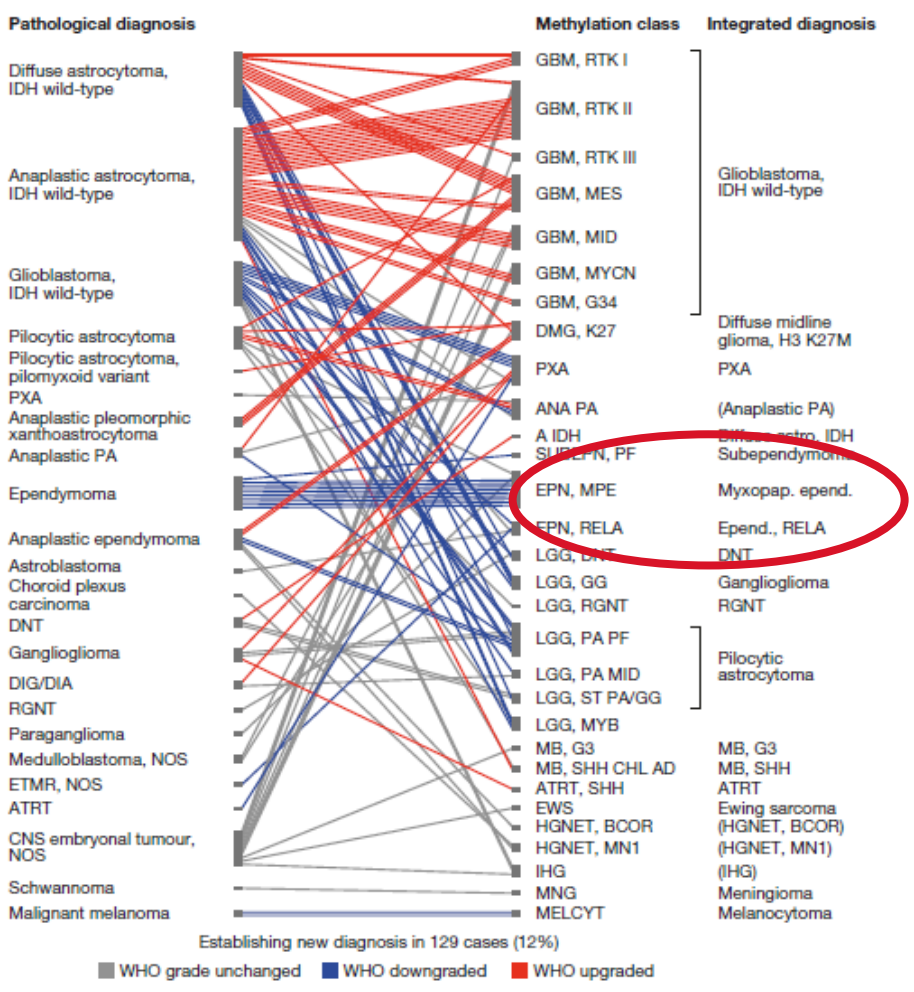
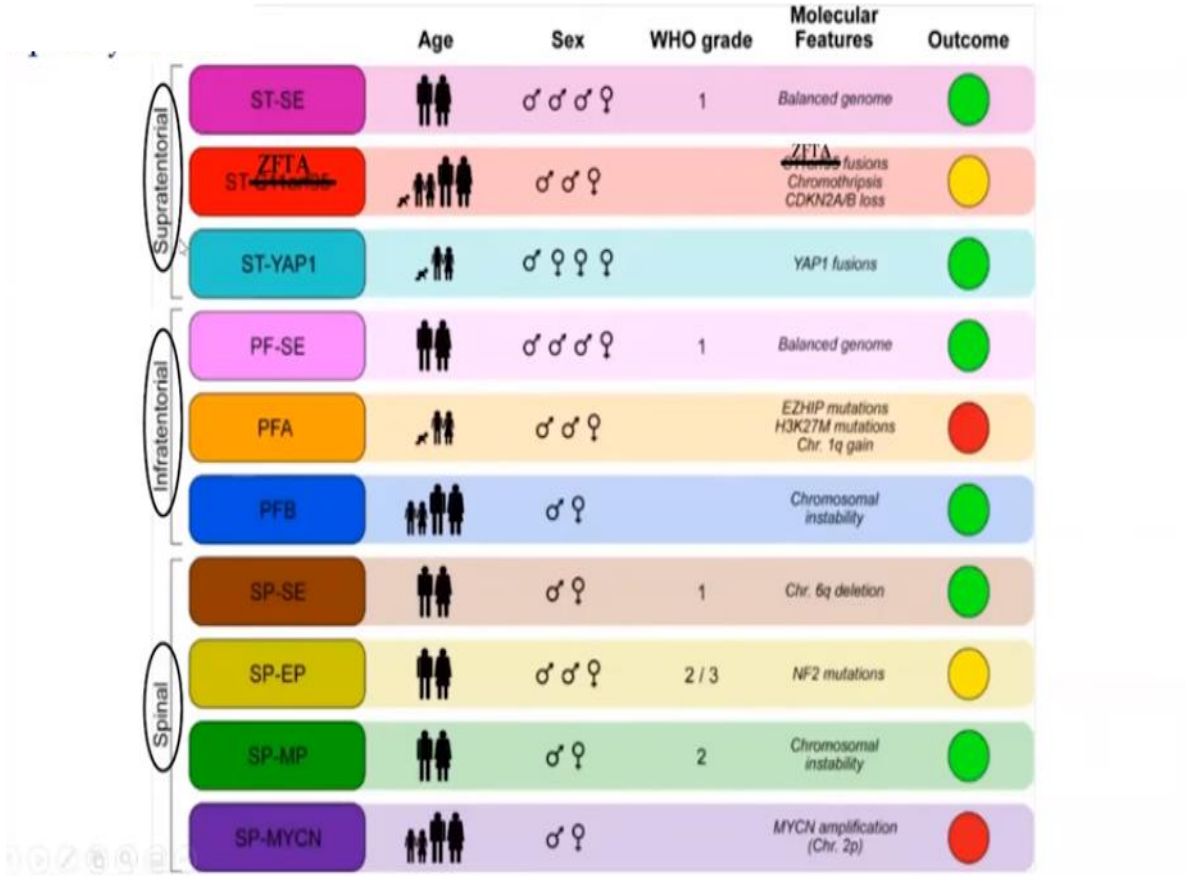
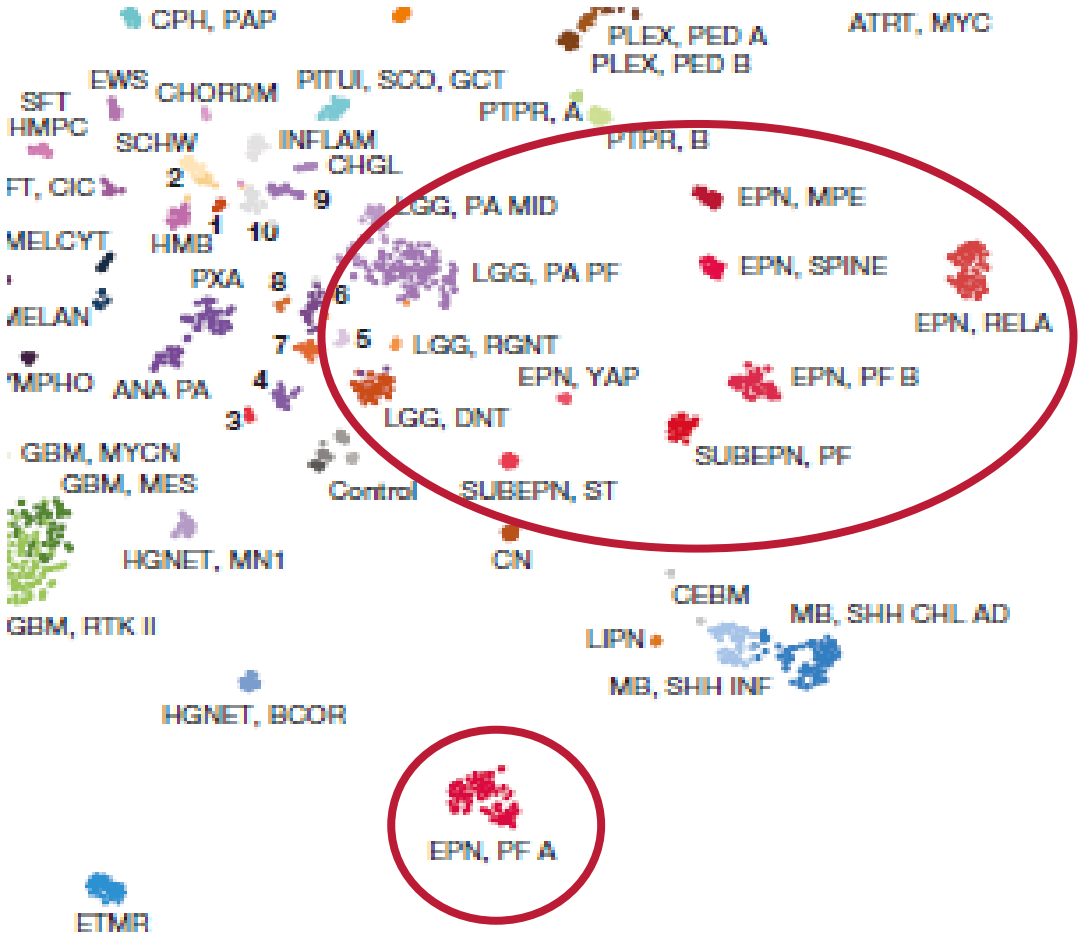


Figure 4 | Reassessment of discrepant cases and establishment of

22 march 2018 | VOL 555 | NATURE | 471 doi:10.1038/nature26000

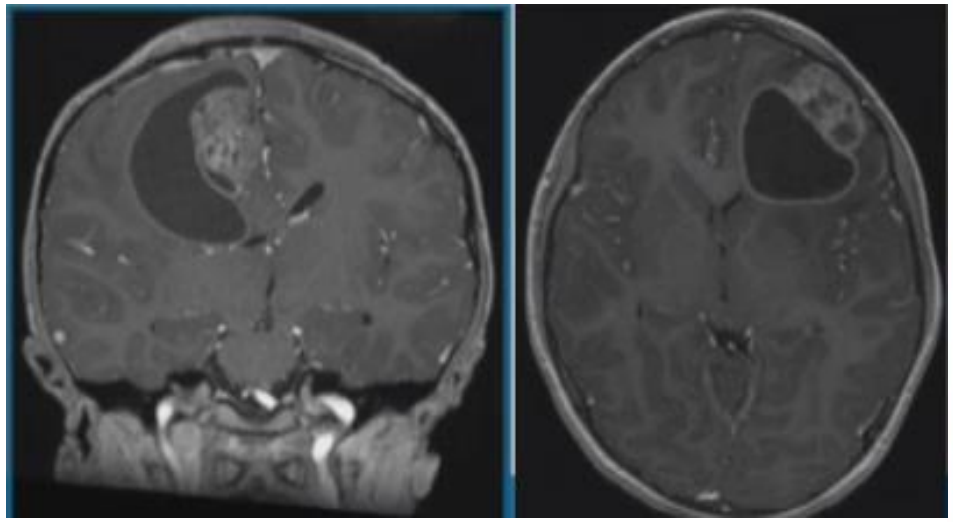
Ependymoma

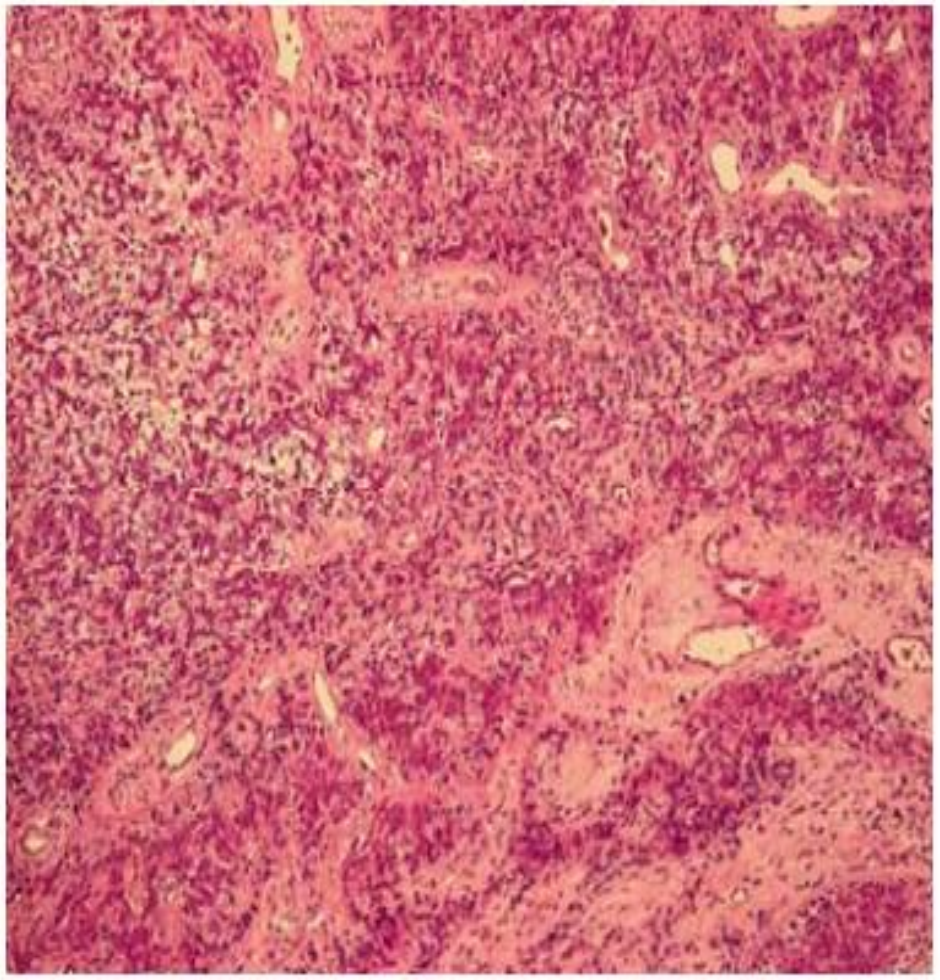


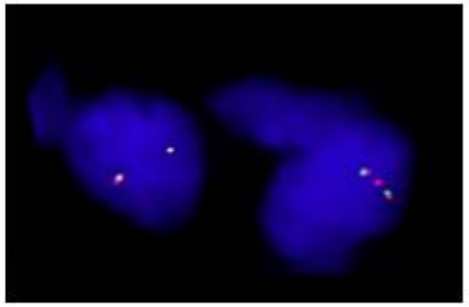


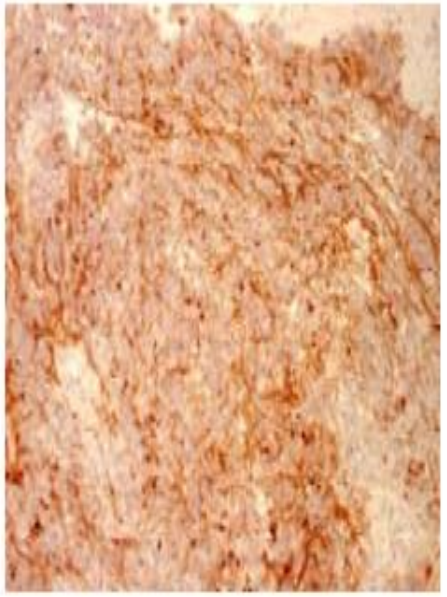
E. J. Rushing. MEMO. 2 February 2021. https://doi.org/10.1007/s12254-021-00680-x

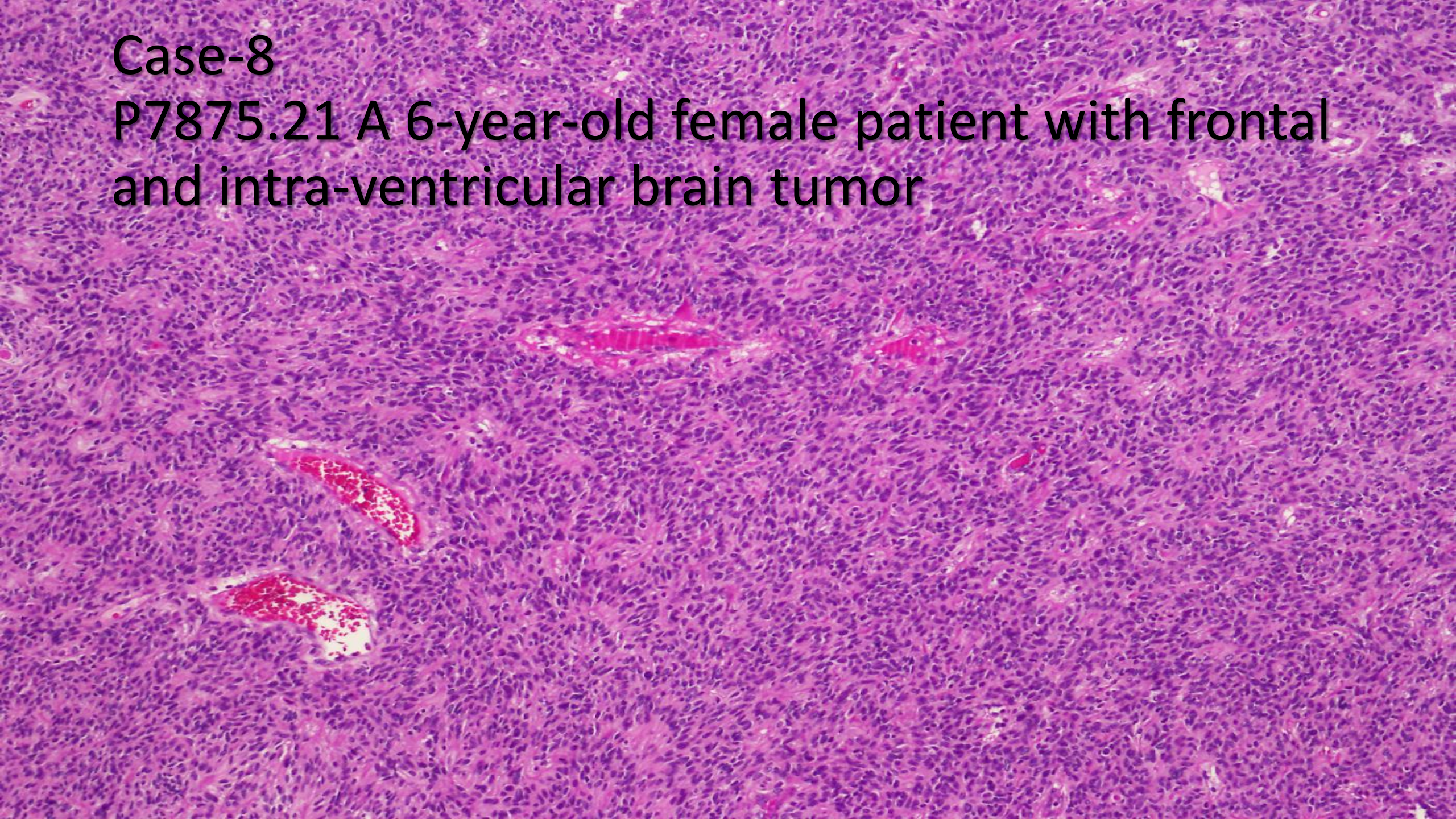
Supratentorial Ependymoma

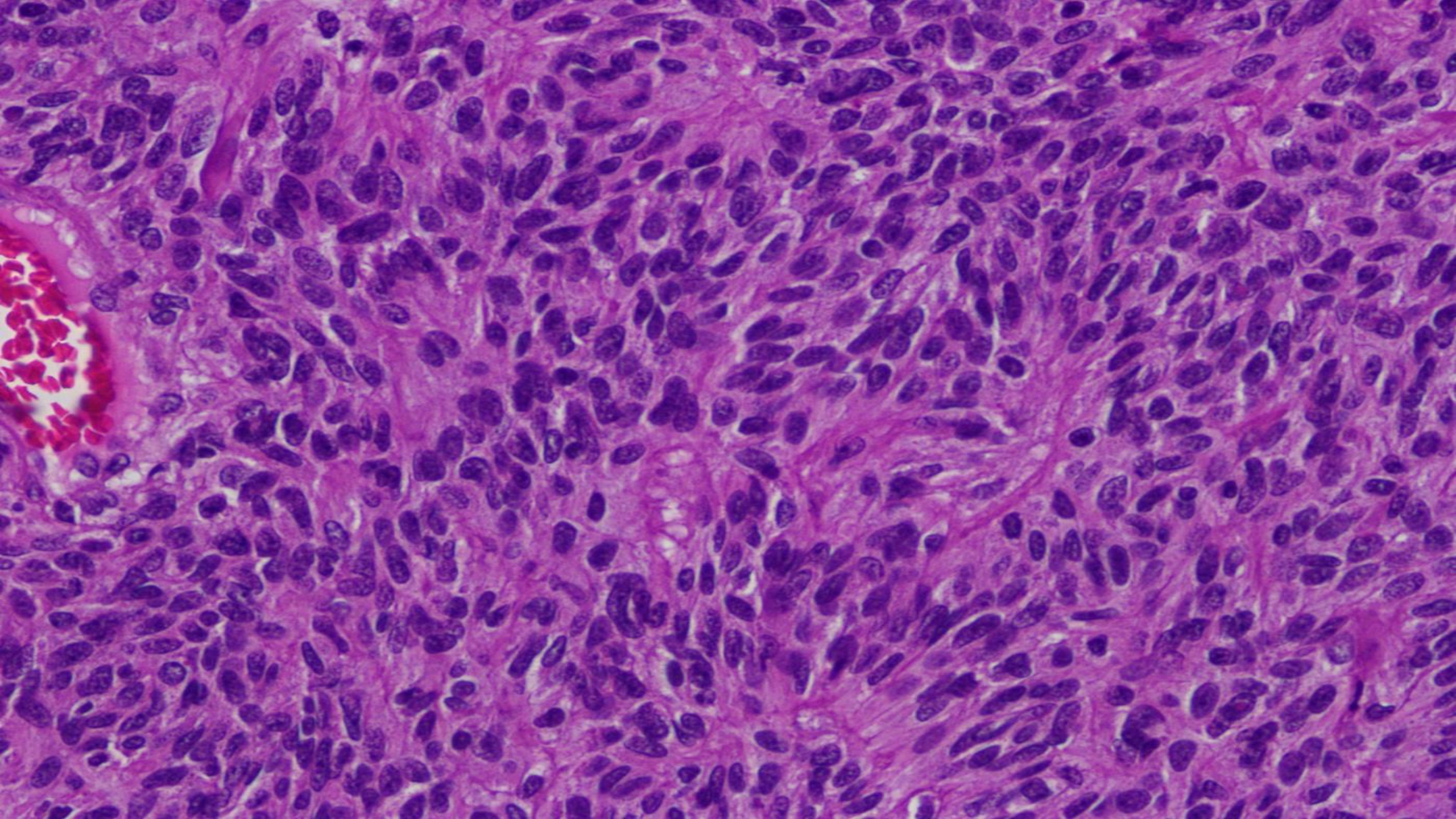


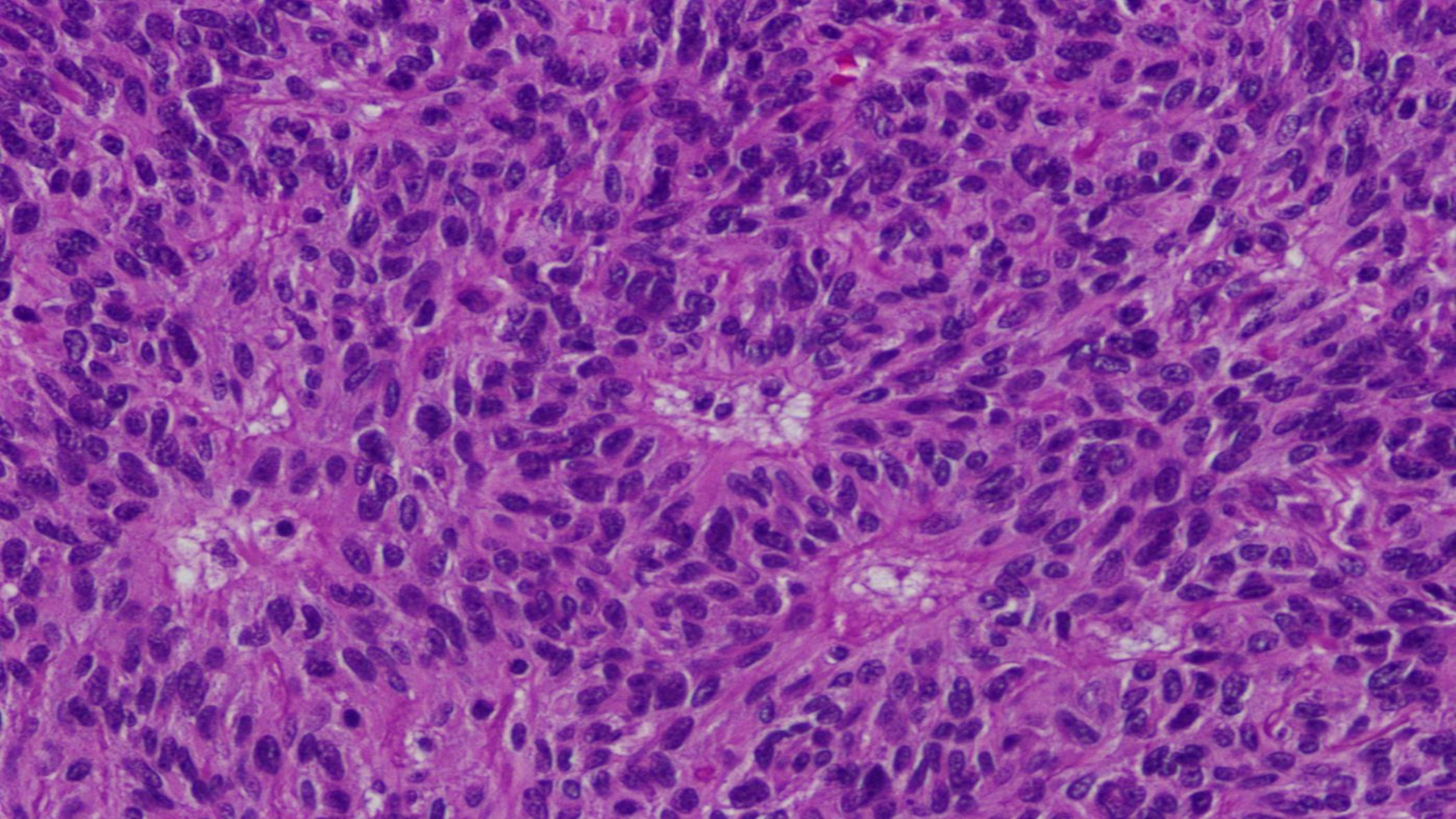


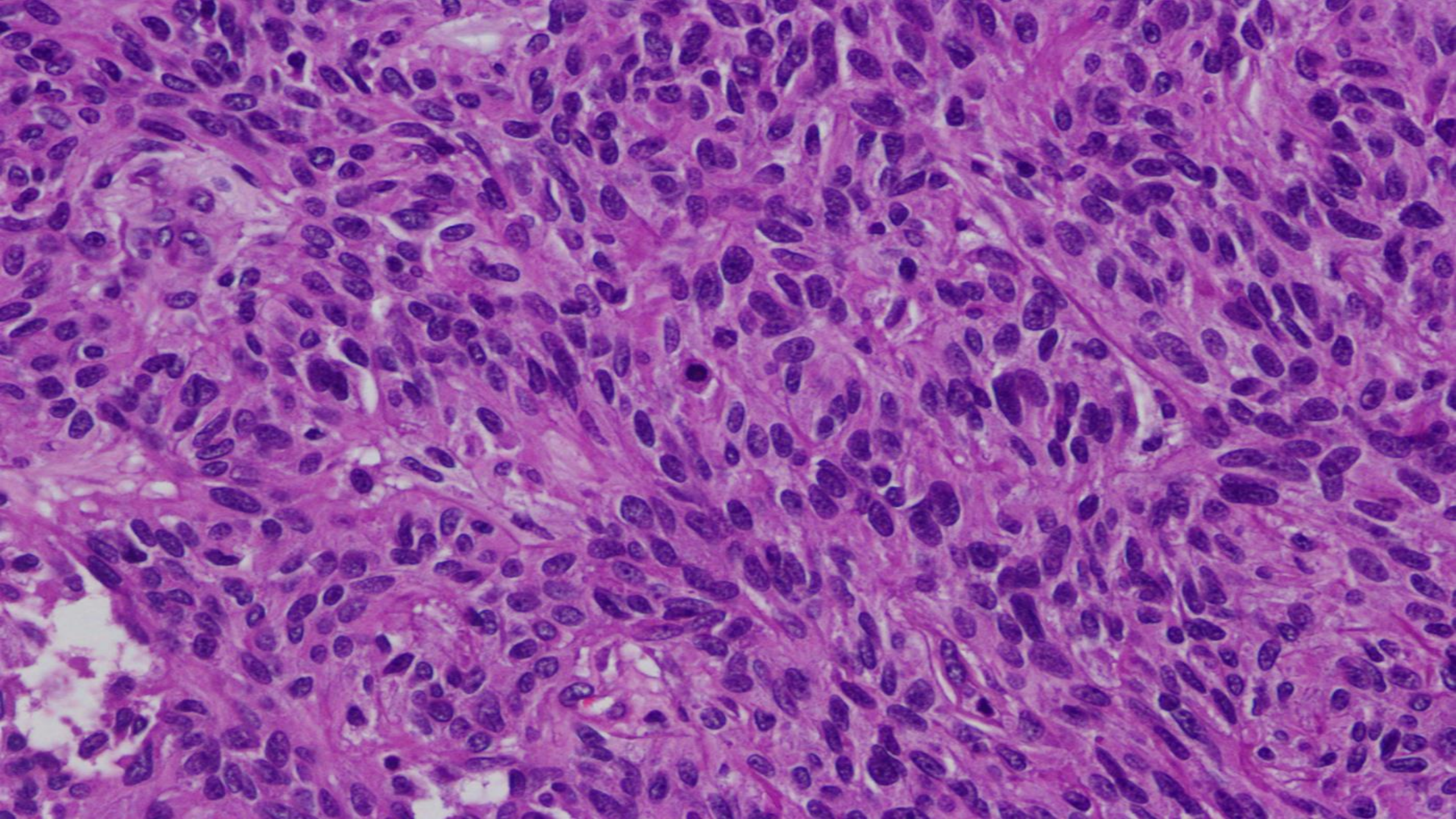


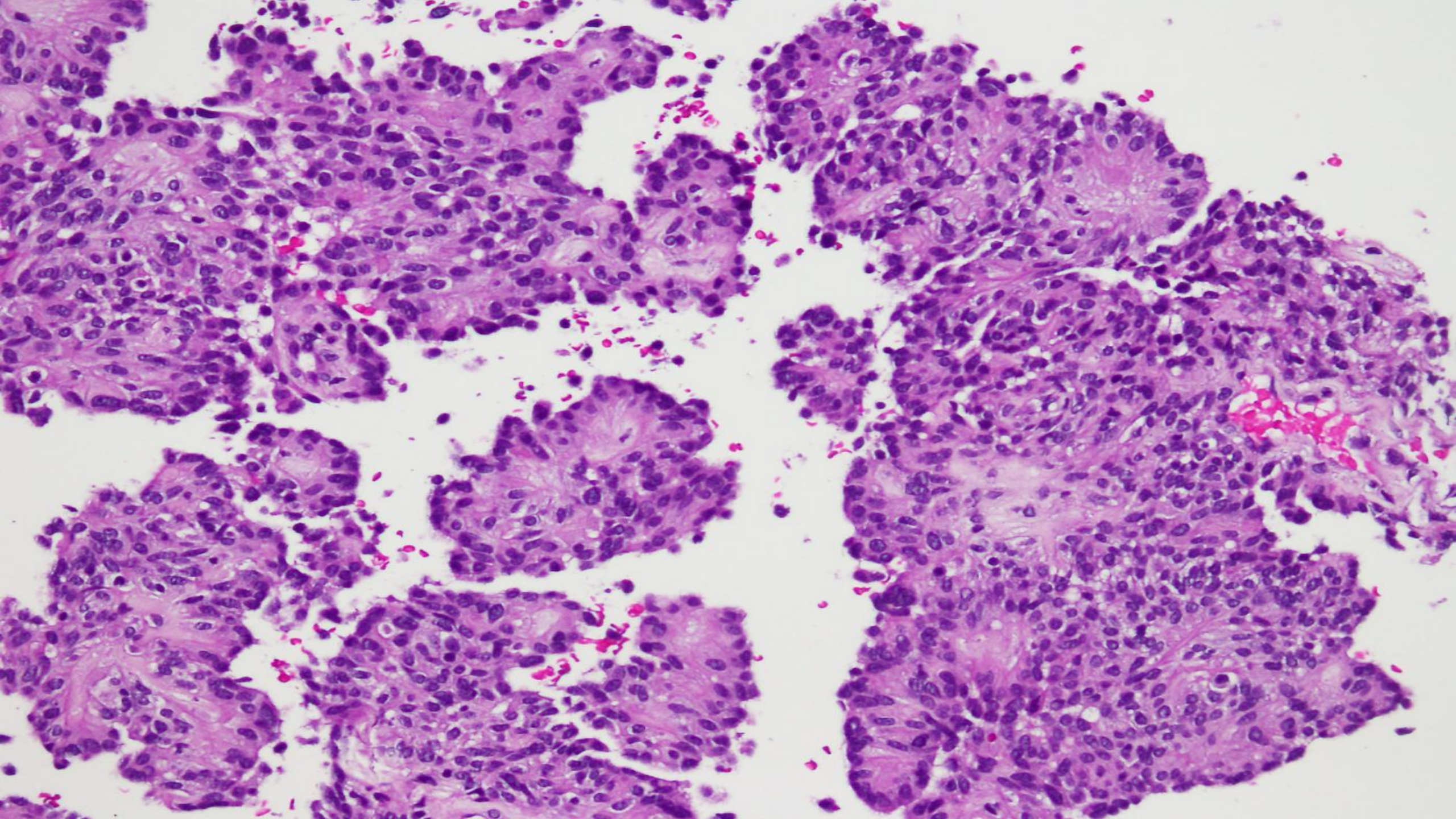


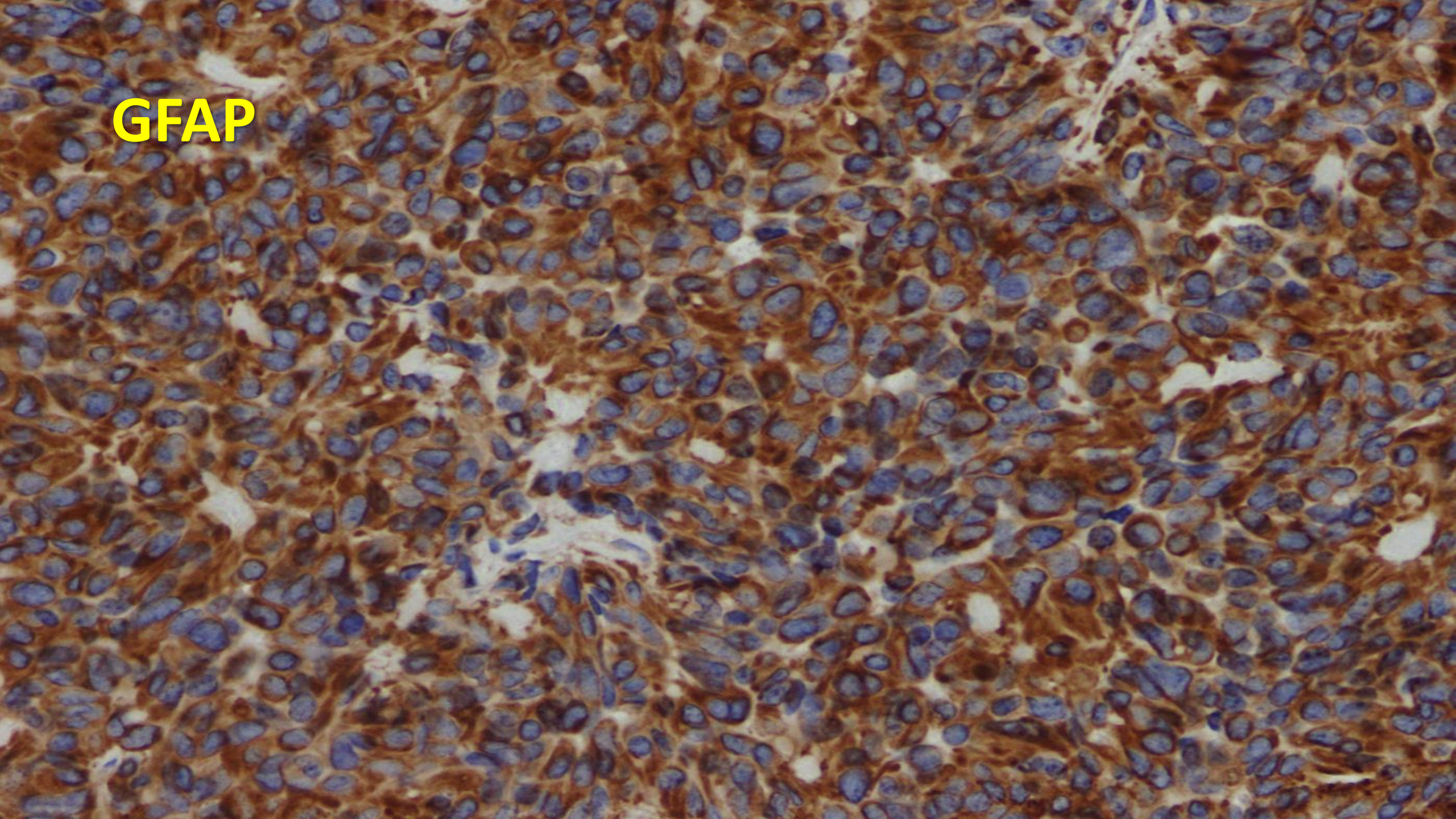

Case-8
P7875.21 A 6-year-old female patient with frontal and intra-ventricular brain tumor

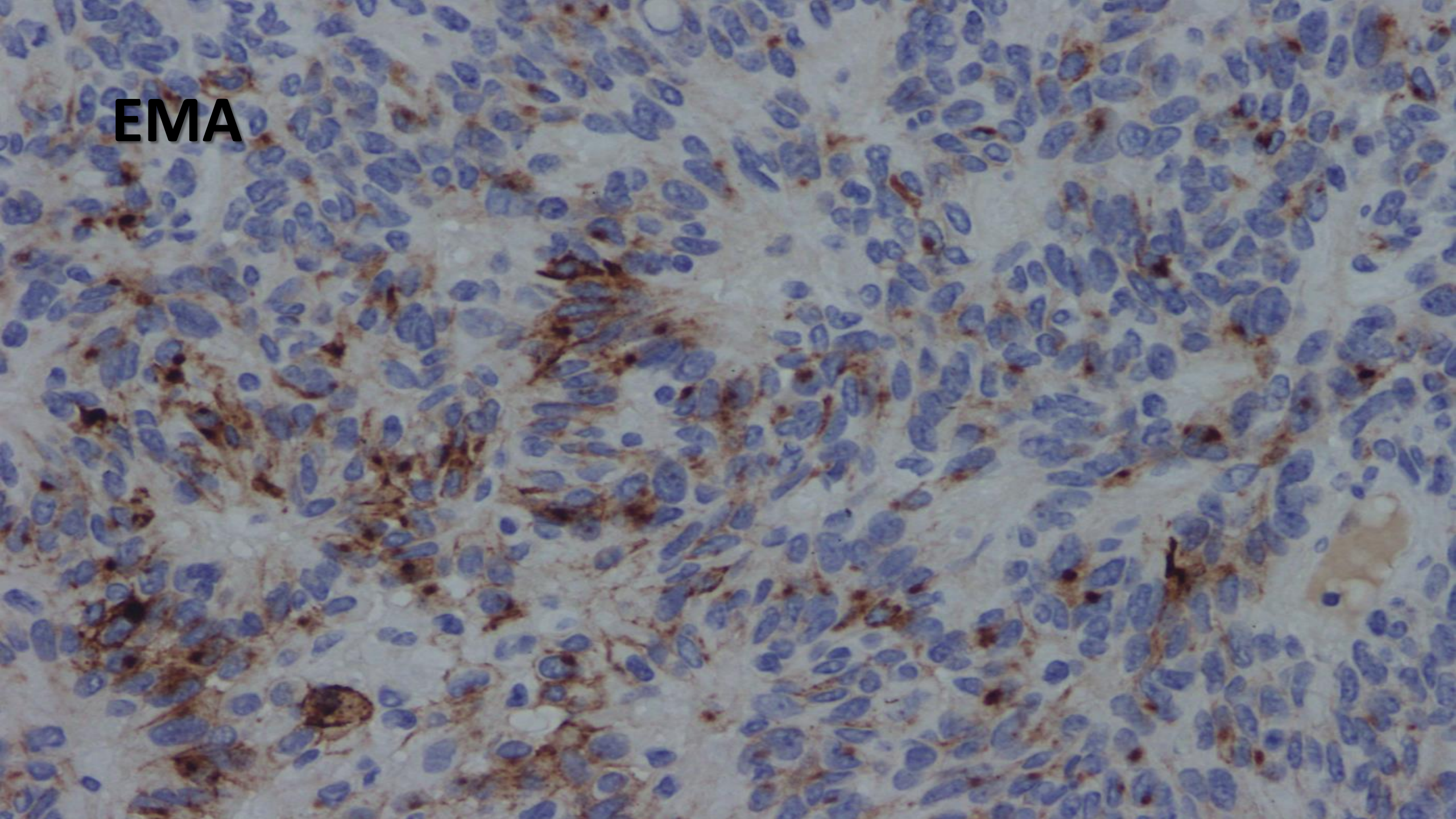


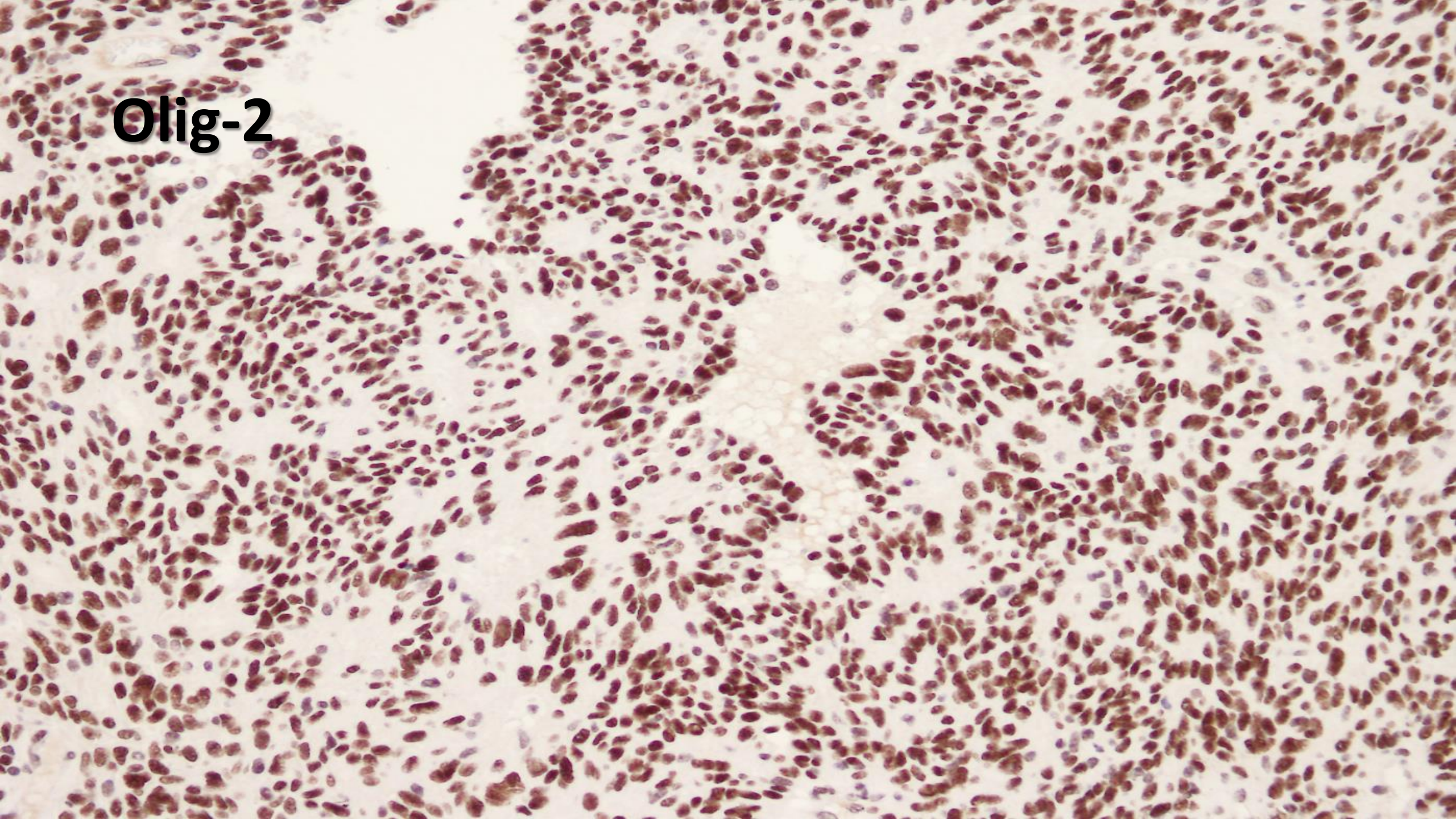


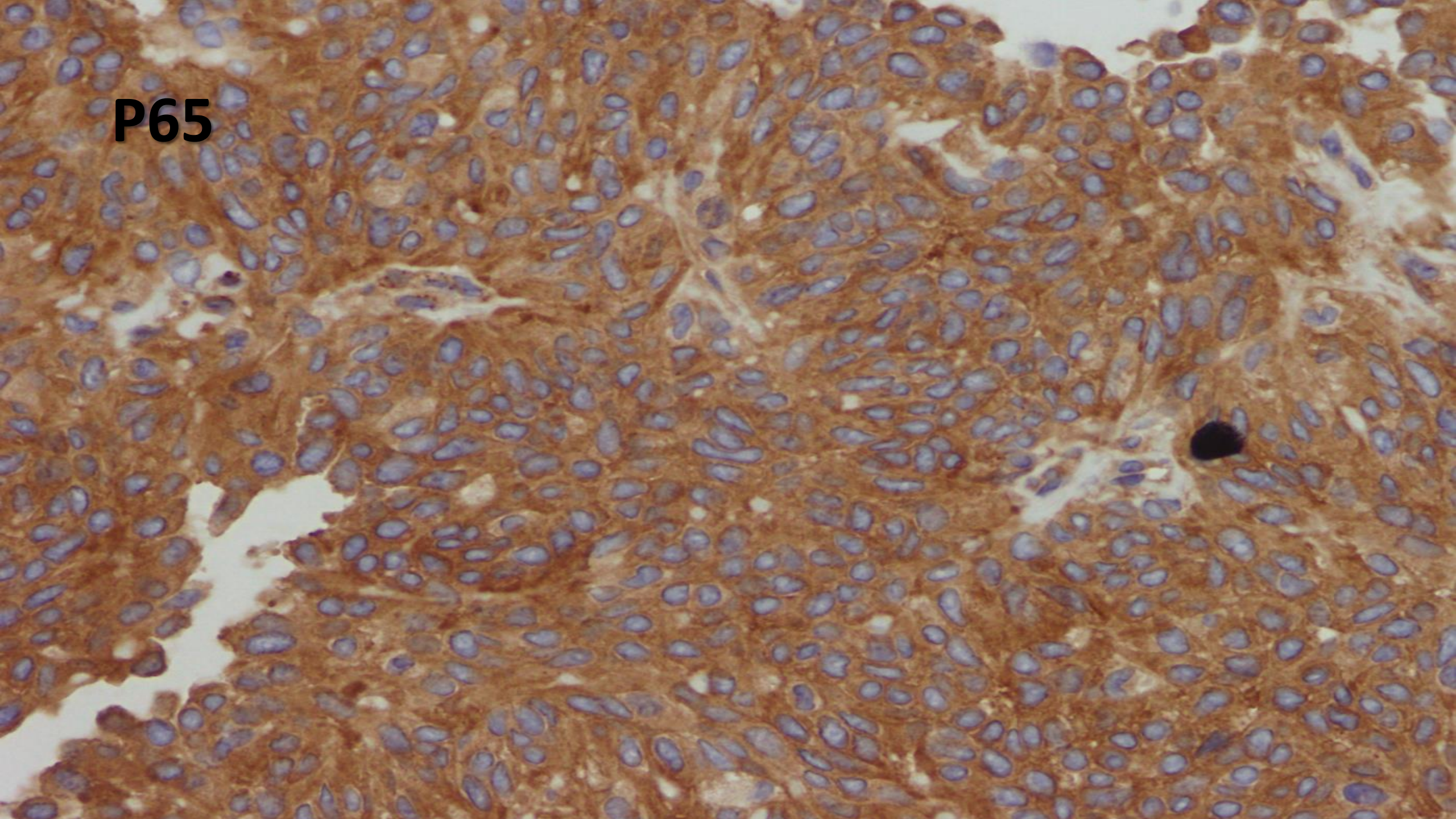


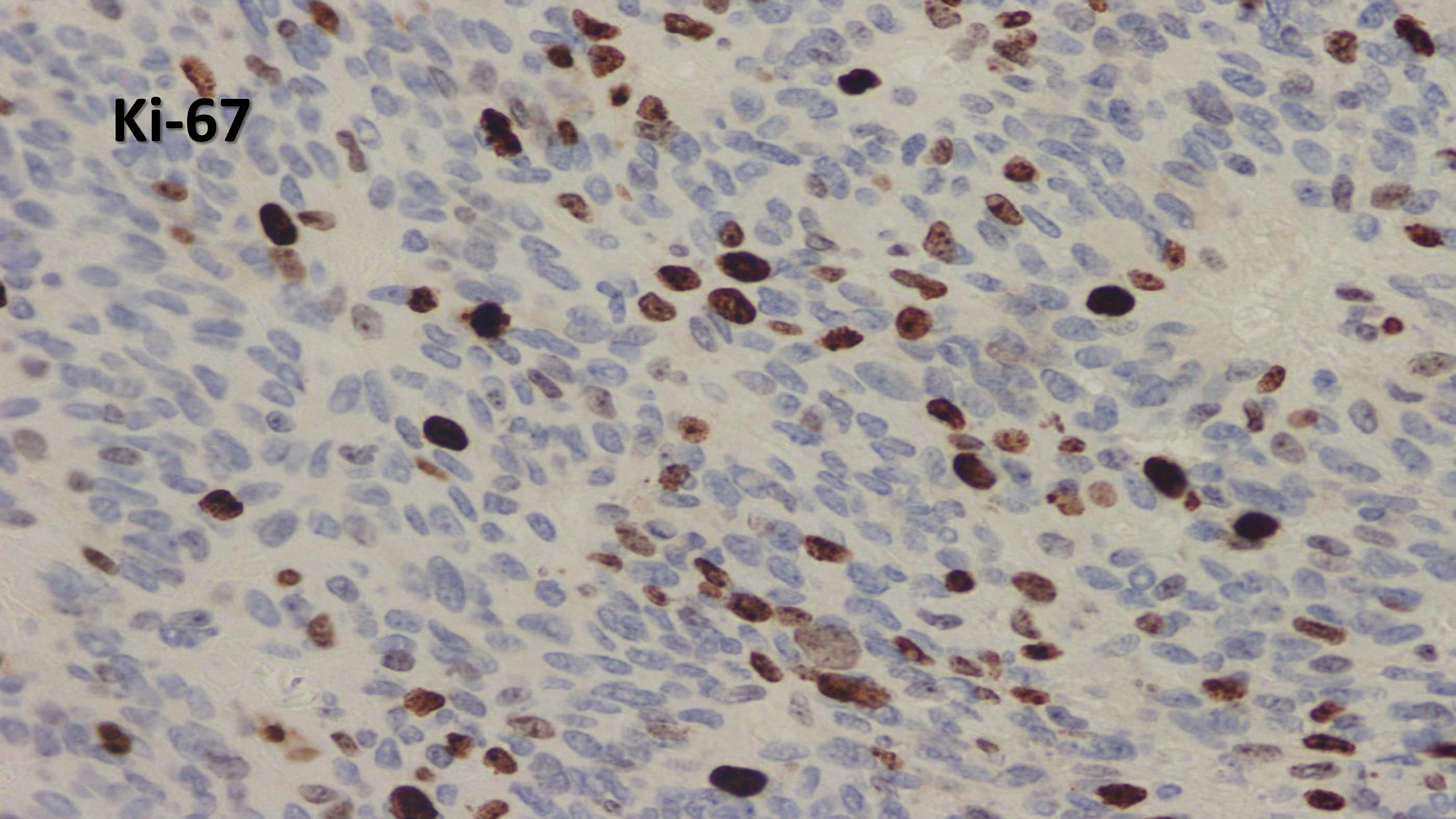


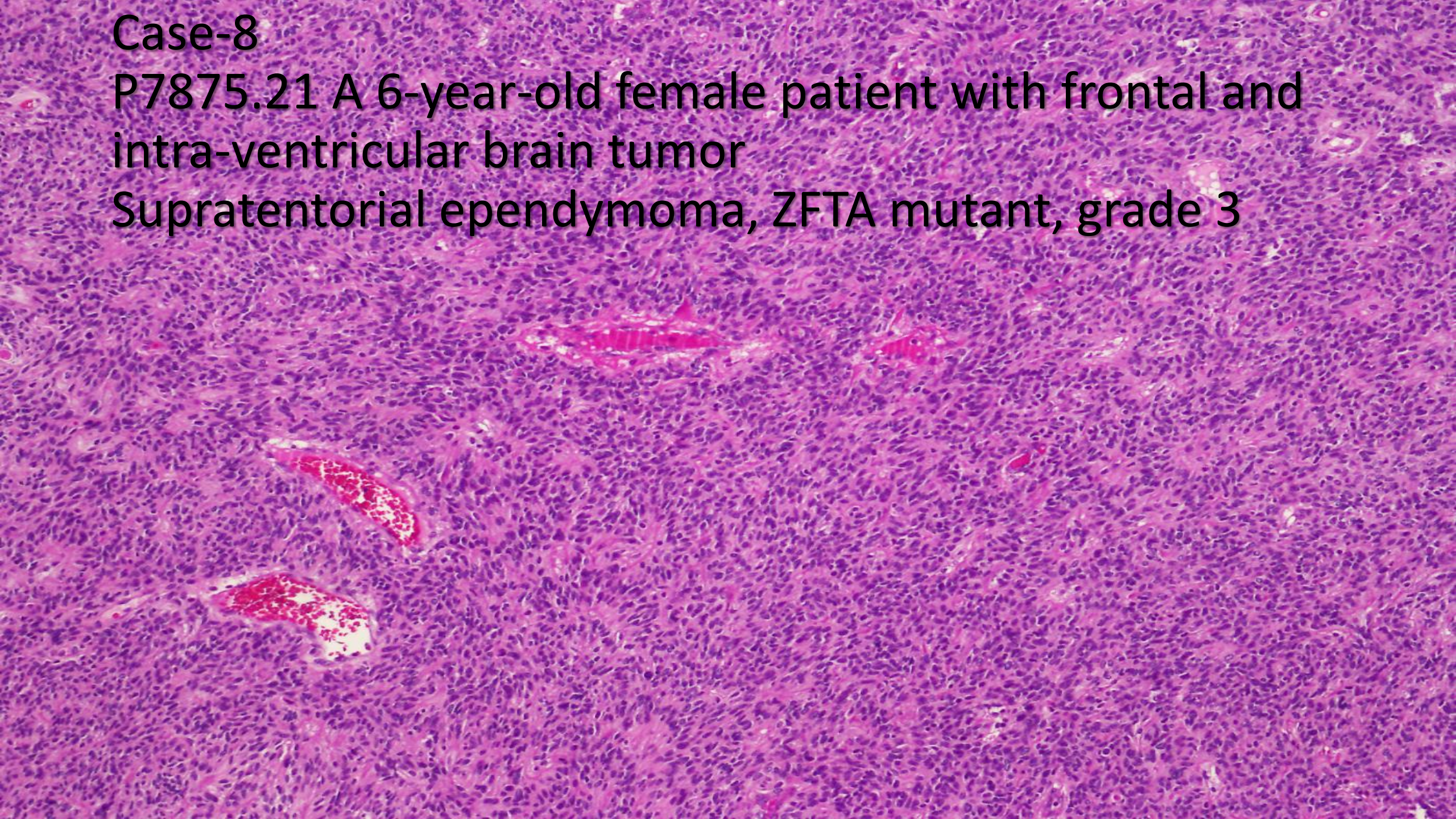

GFAP


EMA


Olig-2


P65

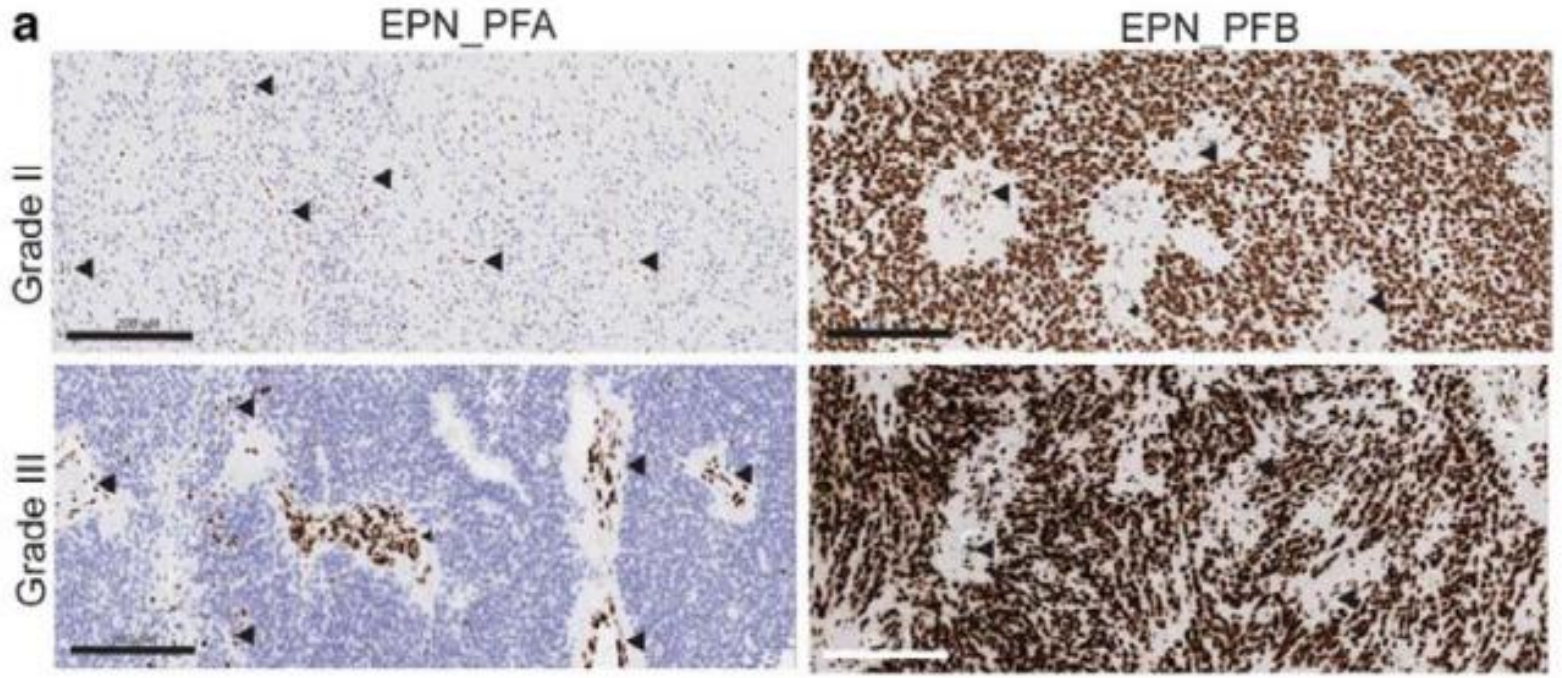

Ki-67

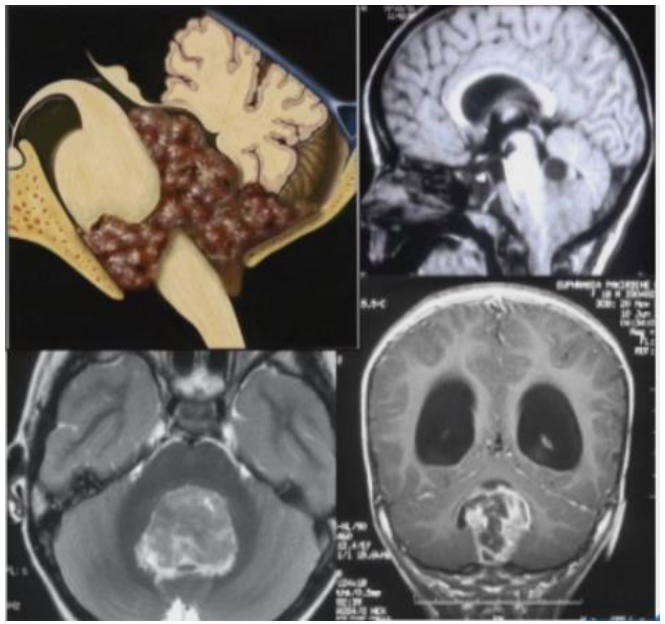

Case-8
P7875.21 A 6-year-old female patient with frontal and intra-ventricular brain tumor
Supratentorial ependymoma, ZFTA mutant, grade 3

Posterior Fossa Ependymoma

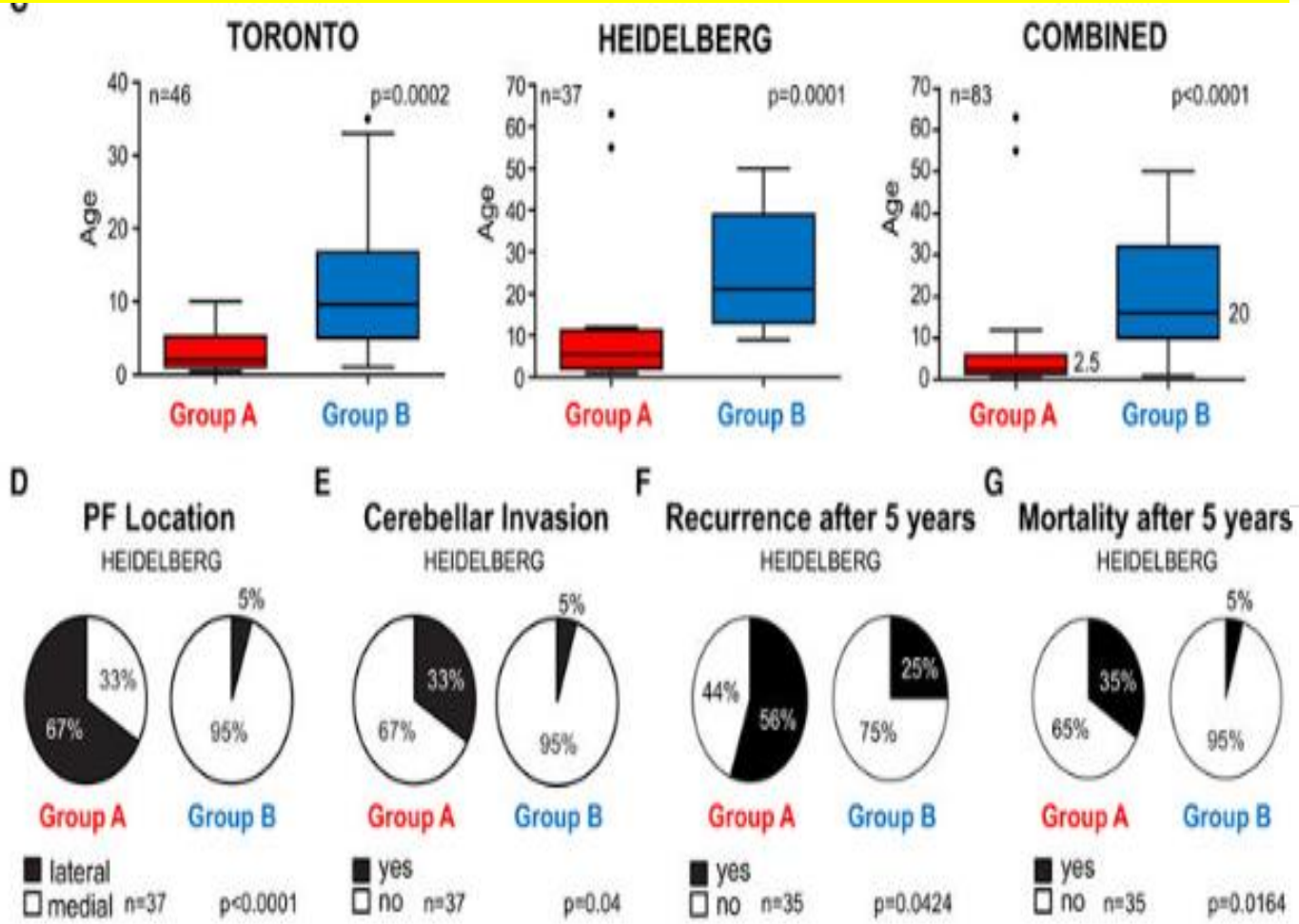
Immunohistochemical analysis of H3K27me3 demonstrates global reduction in group-A childhood posterior fossa ependymoma and is a powerful predictor of outcome

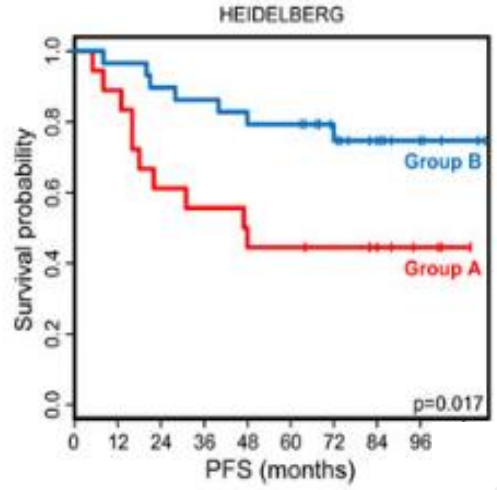
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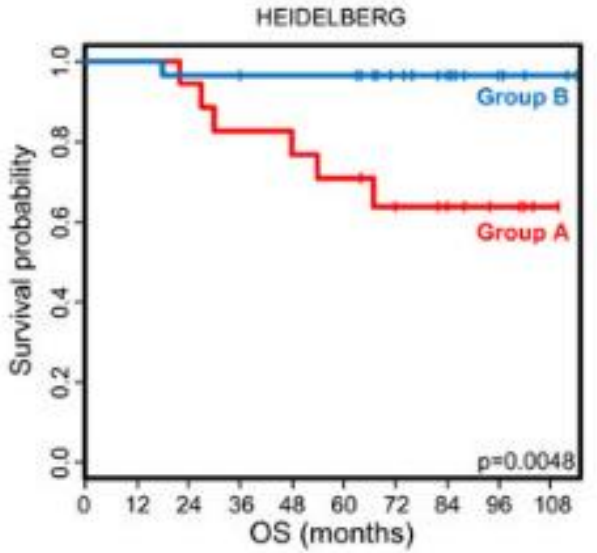




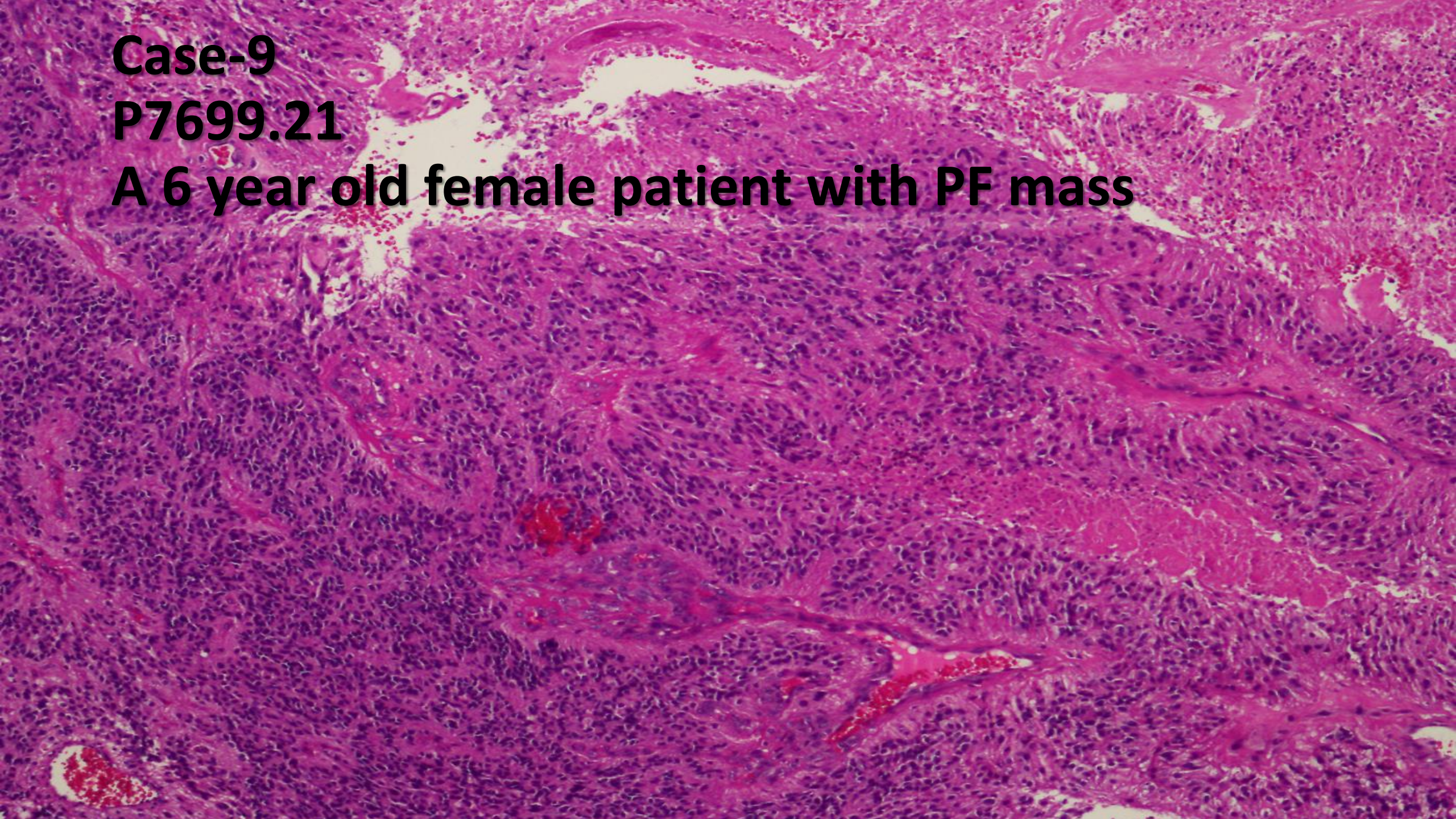
Posterior Fossa Ependymoma

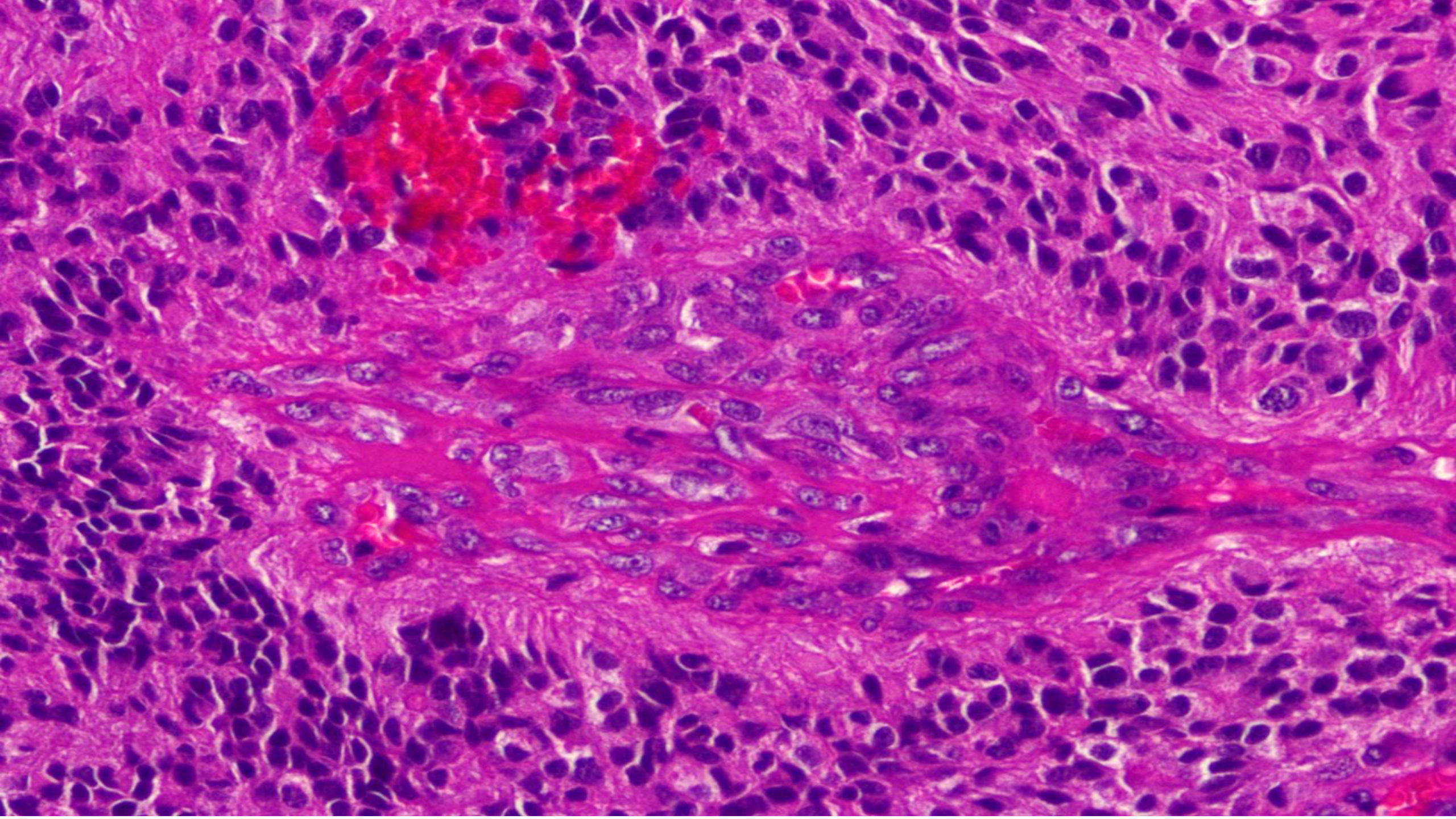


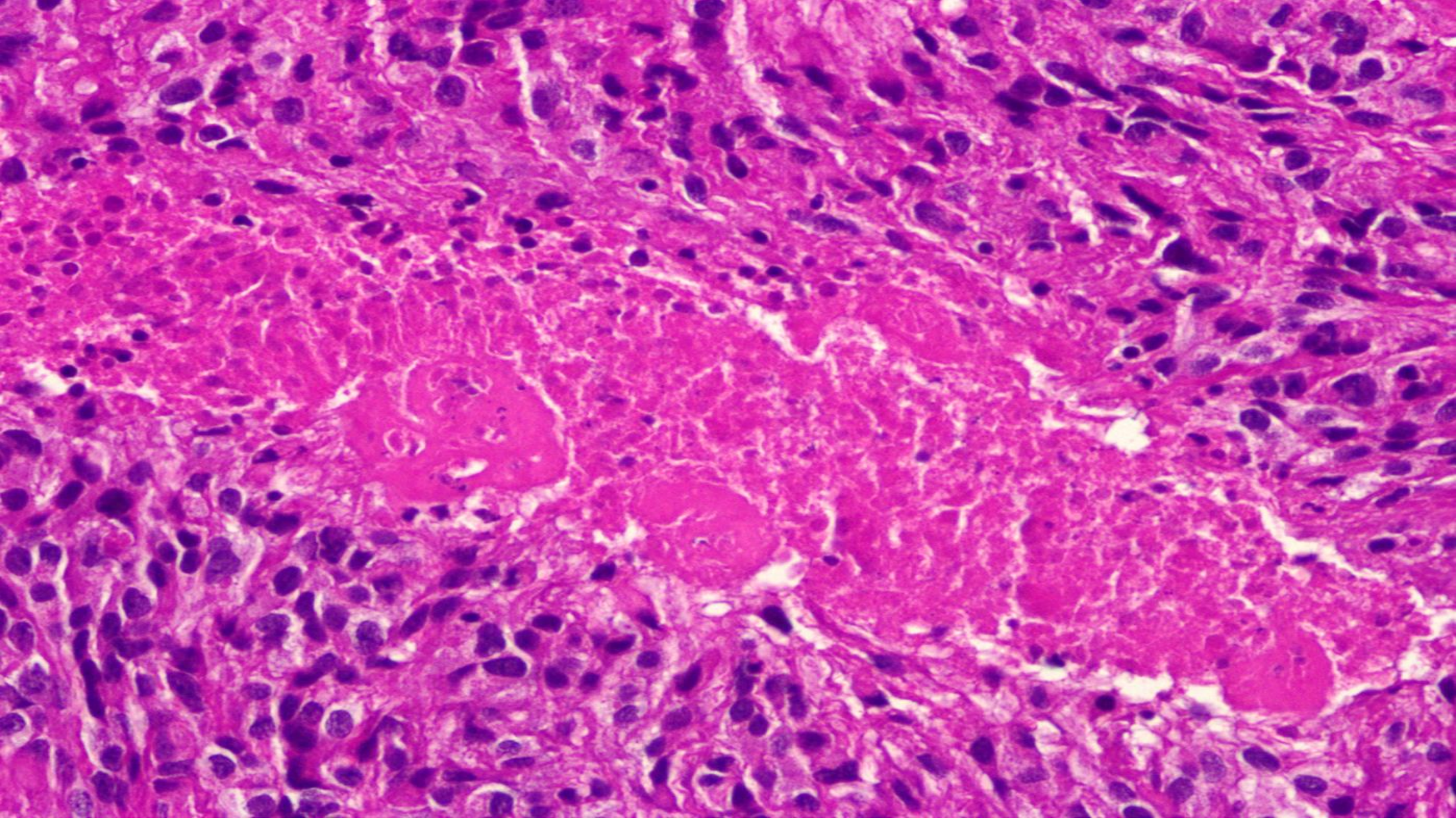


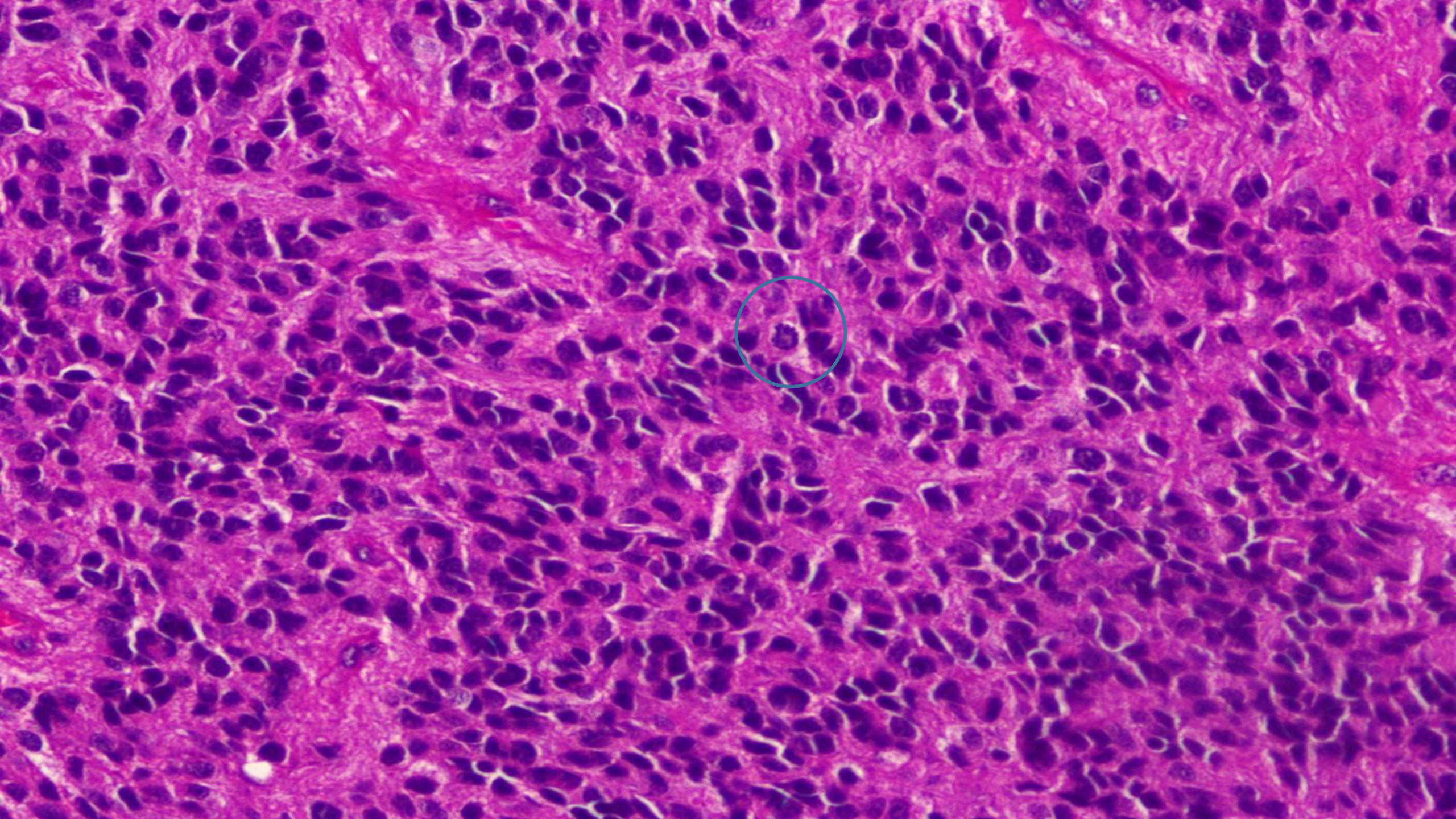


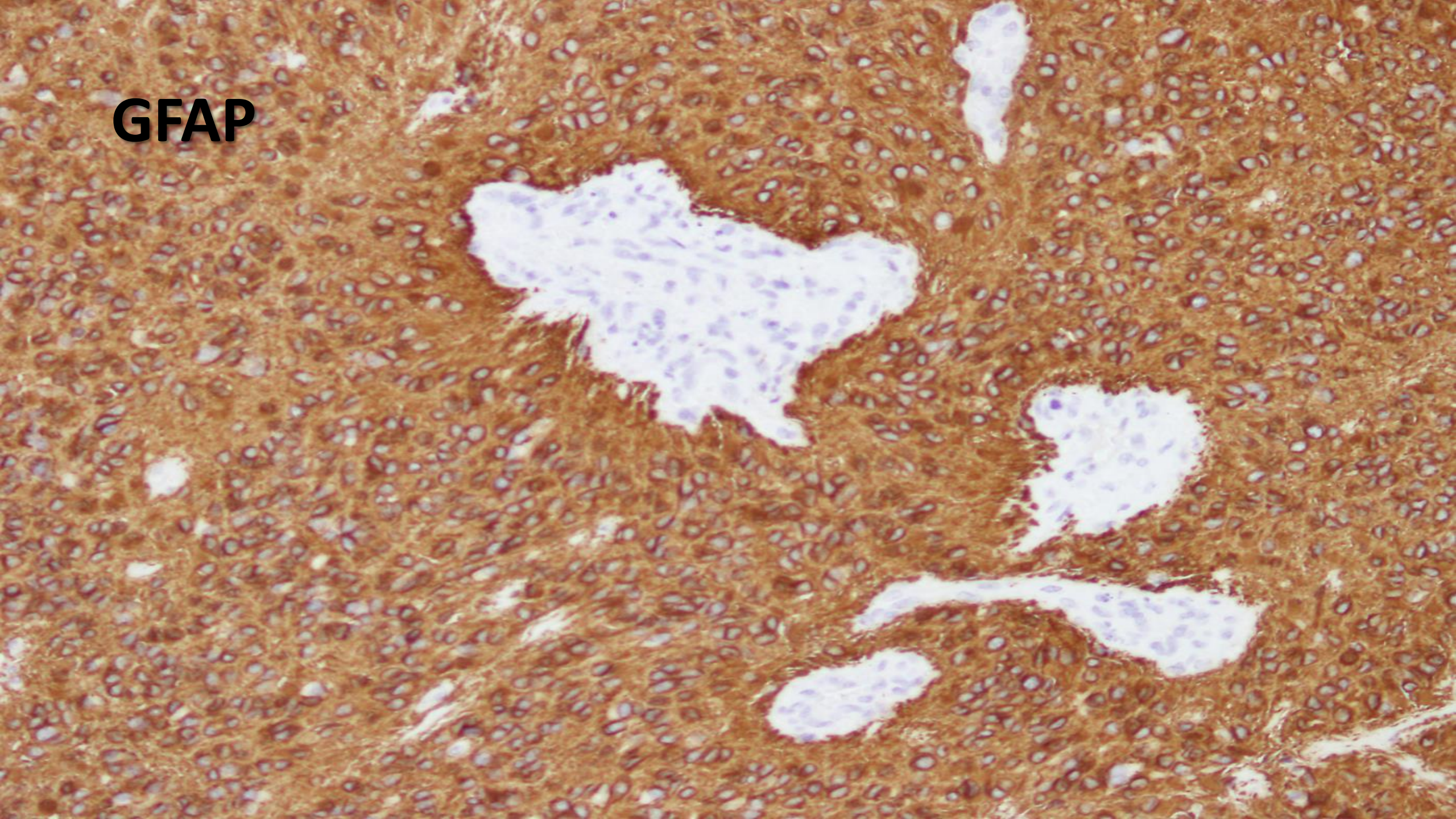
Witt H. Cancer Cell. 2011 Aug 16;20(2):143-57. doi: 10.1016/j.ccr.2011.07.007

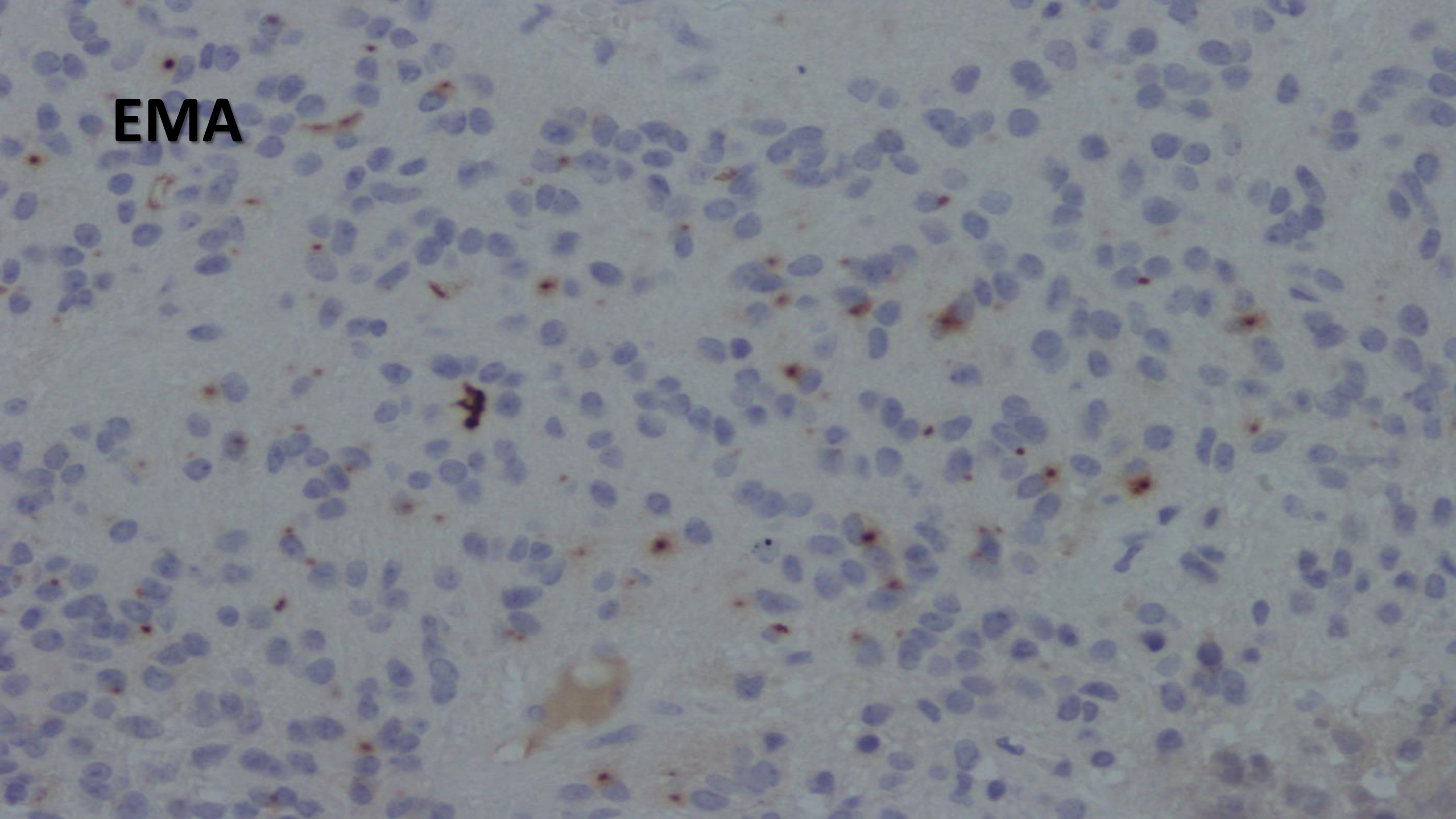

Case-9
P7699.21
A 6 year old female patient with PF mass

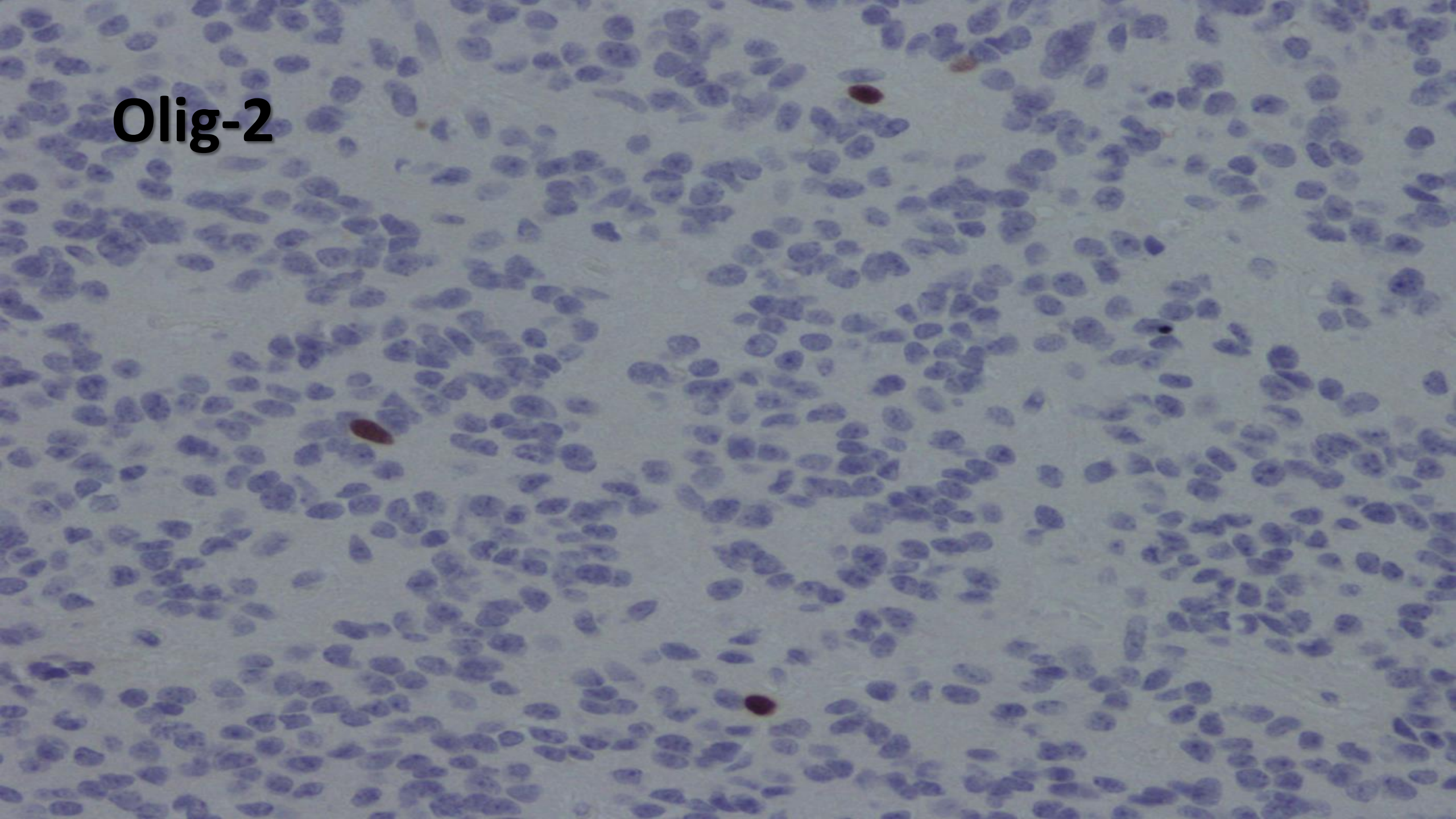


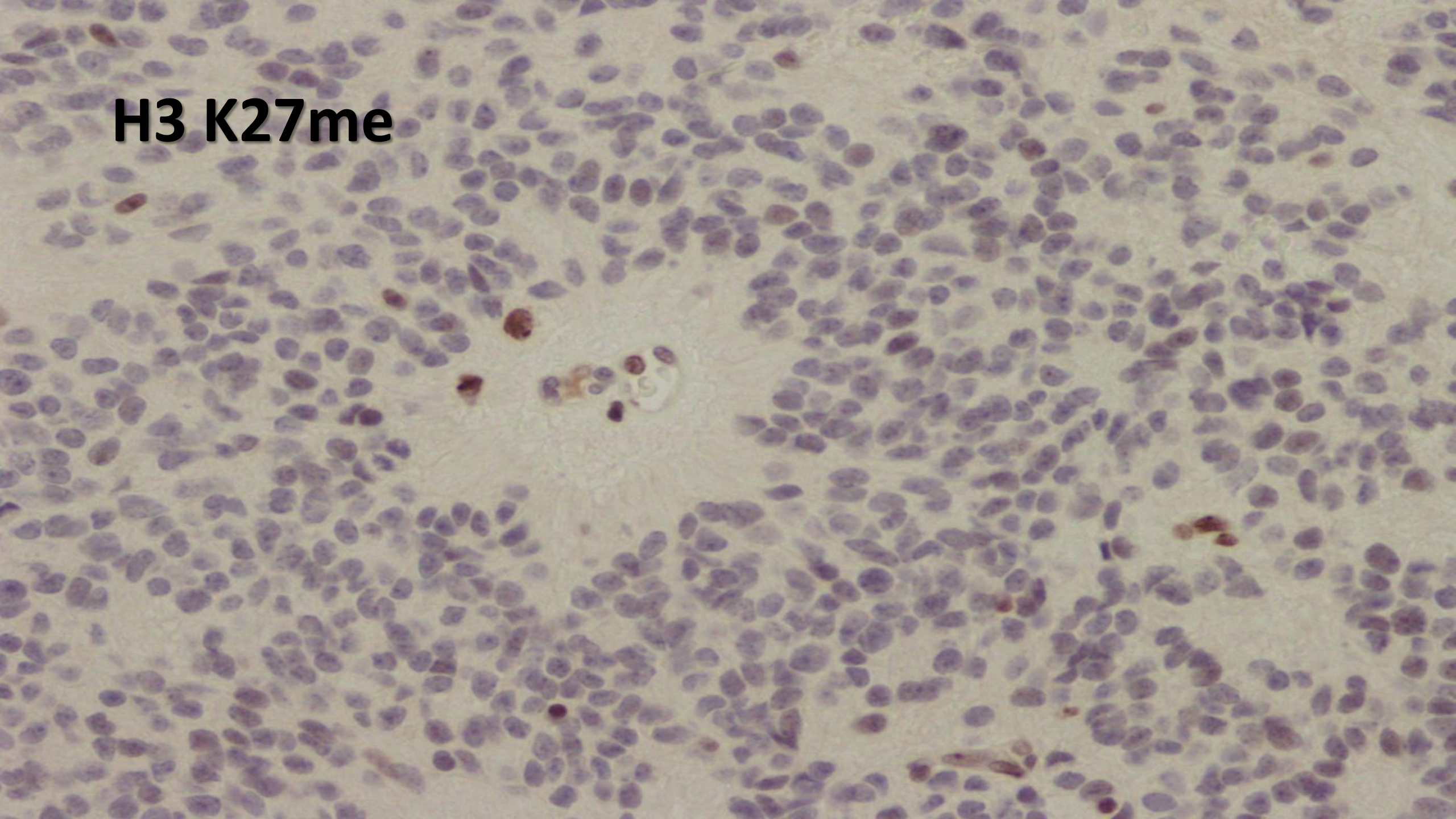


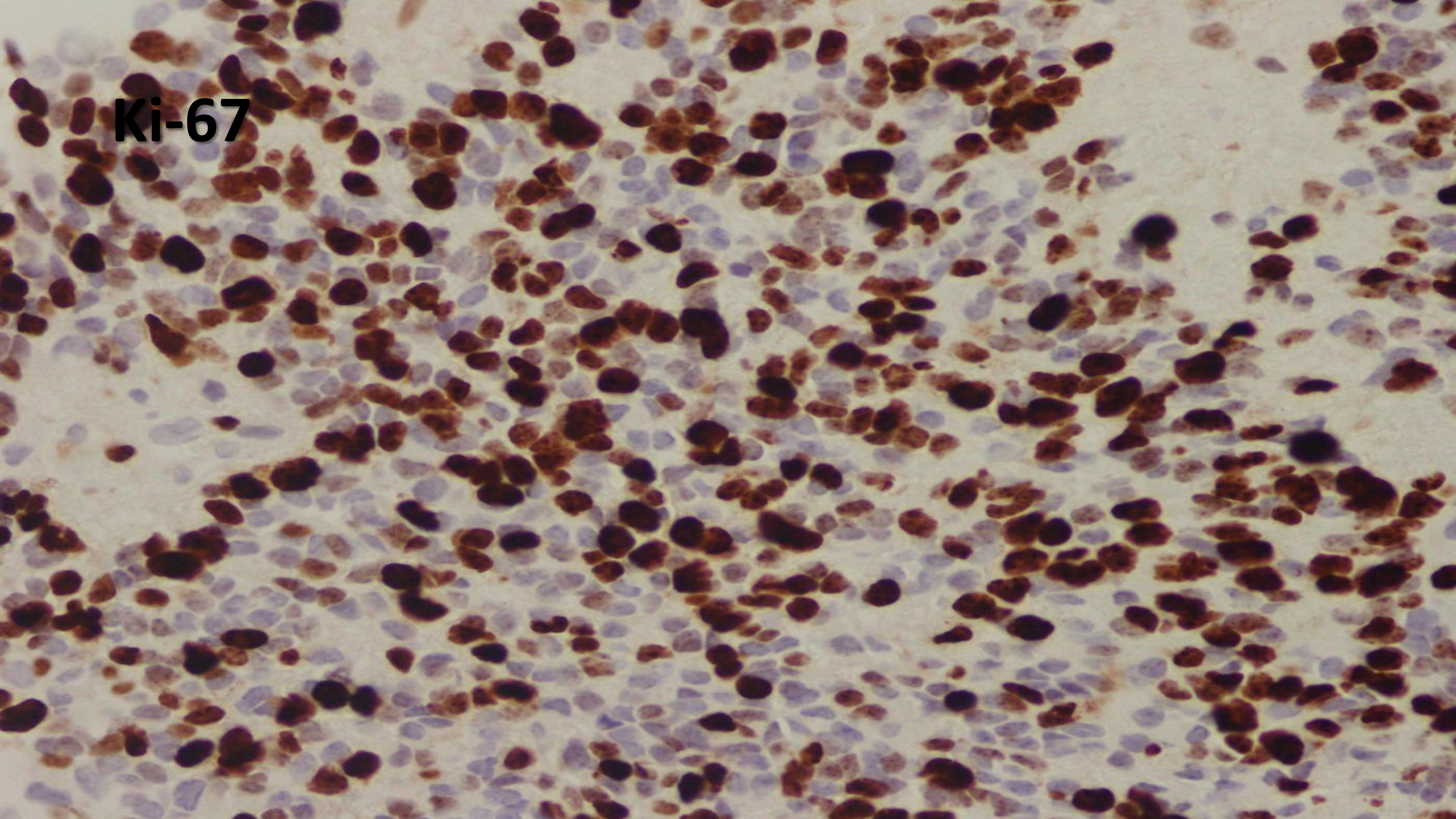


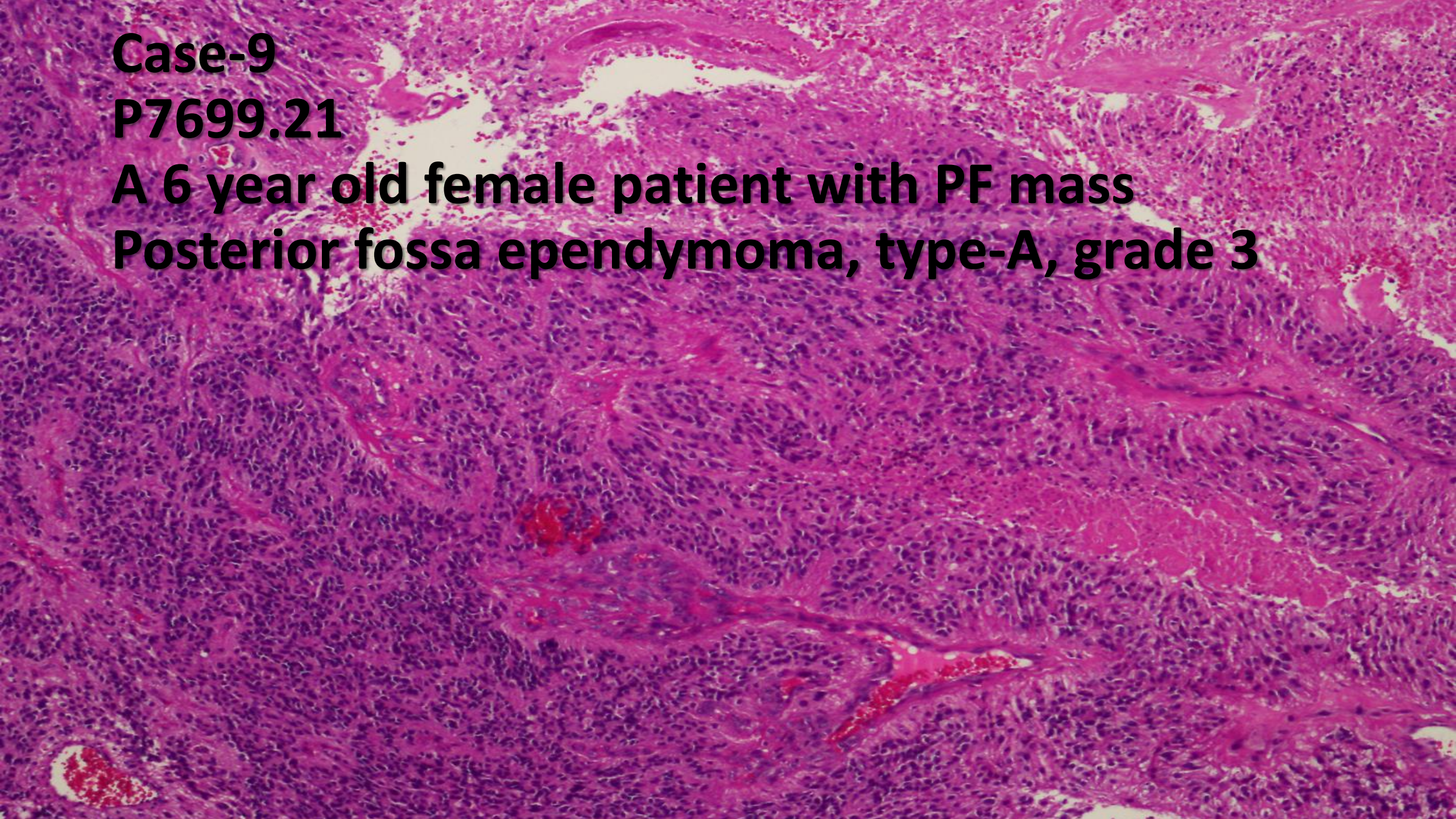

GFAP


EMA


Olig-2

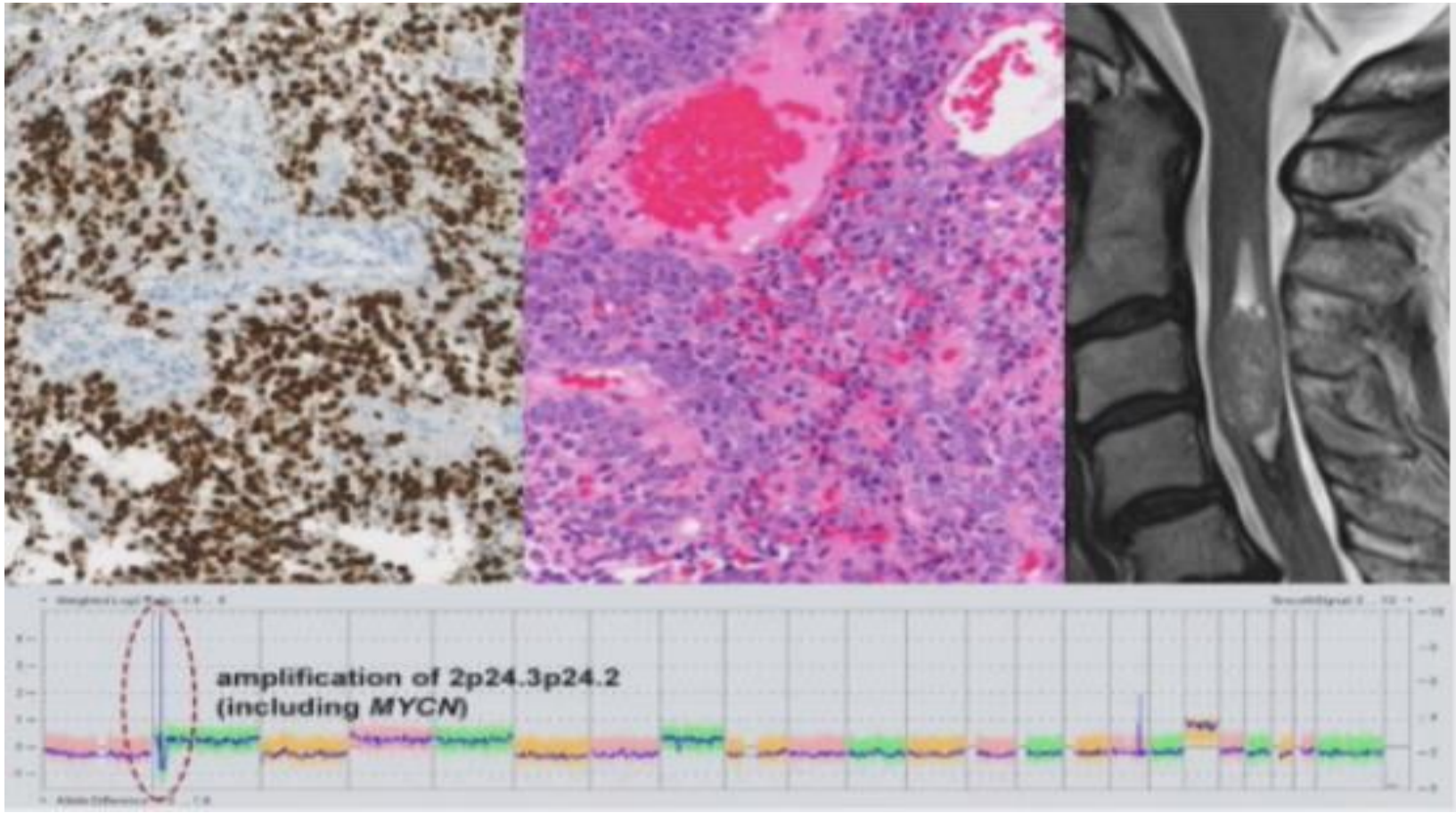

H3 K27me

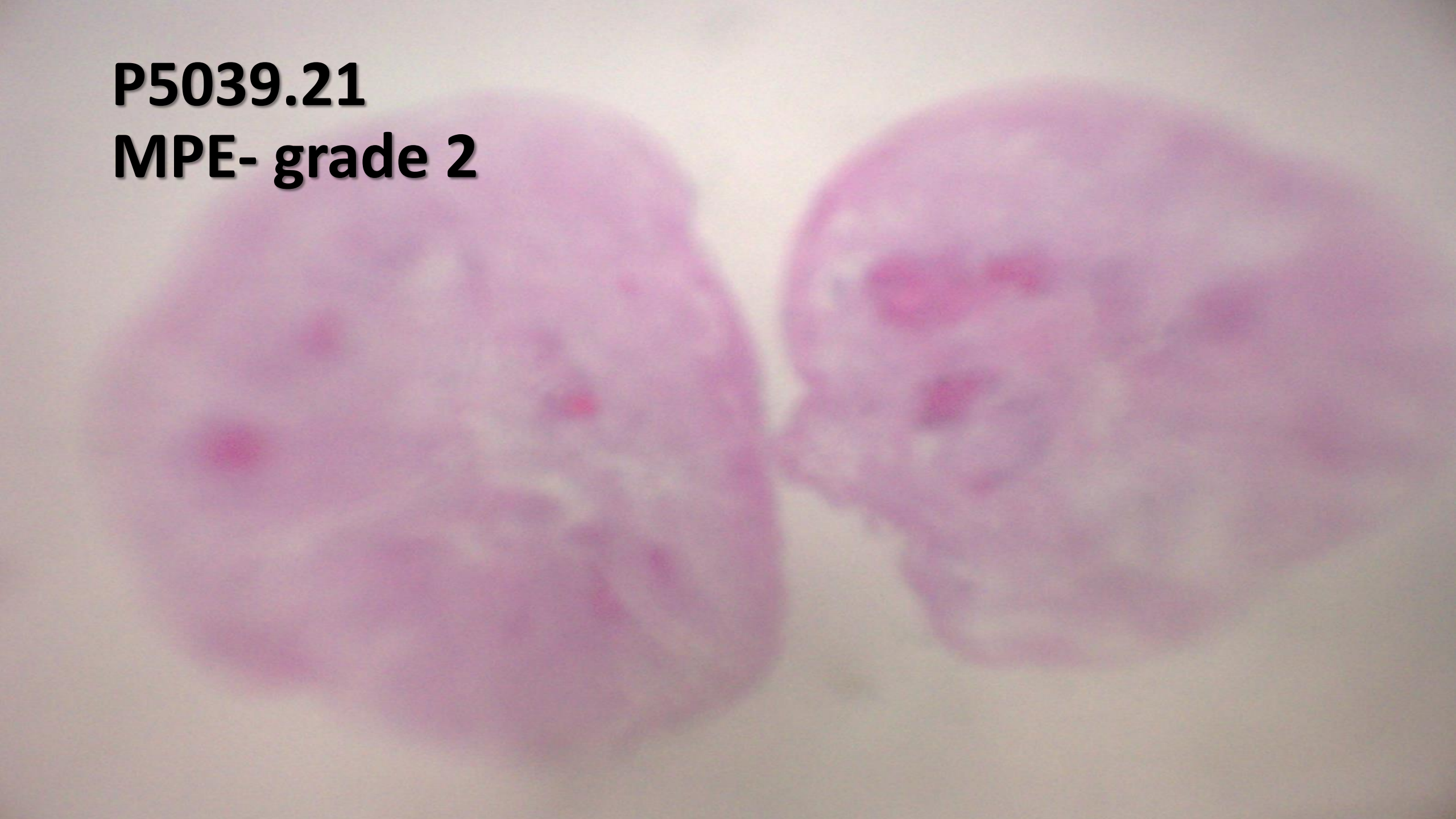

Ki-67


Case-9
P7699.21
A 6 year old female patient with PF mass
Posterior fossa ependymoma, type-A, grade 3

Spinal ependymoma, MYCN mutant

- Usually intradural, extramedullary with invasion of the spinal cord
- cervical and thoracic spine
- Leptomeningeal metastasis
- Poor prognosis

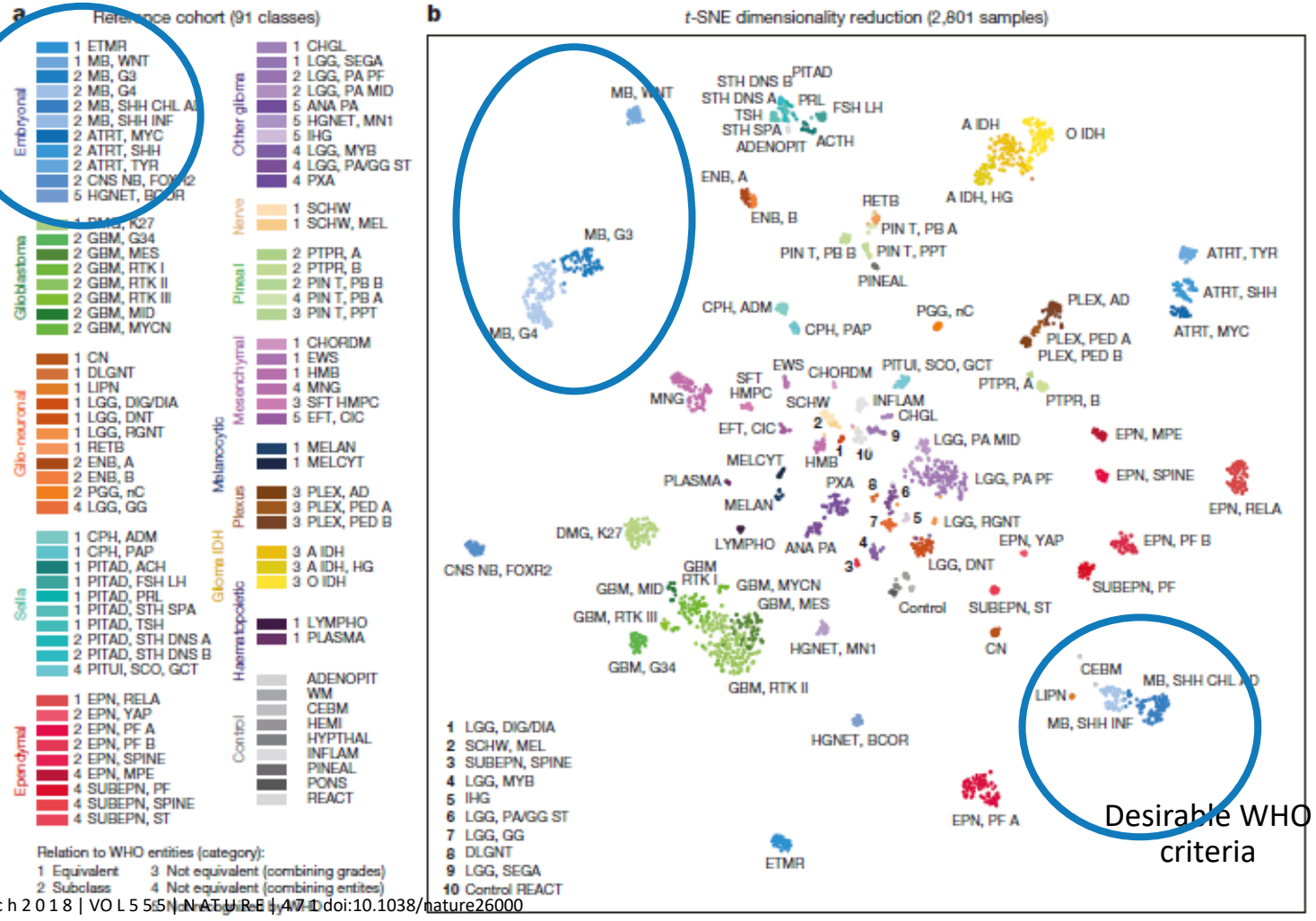



P5039.21
MPE- grade 2

6. Ependymoma should be divided by location and each location has specific molecular profile

Methylation Profile

Embryonal tumors- Medulloblastoma



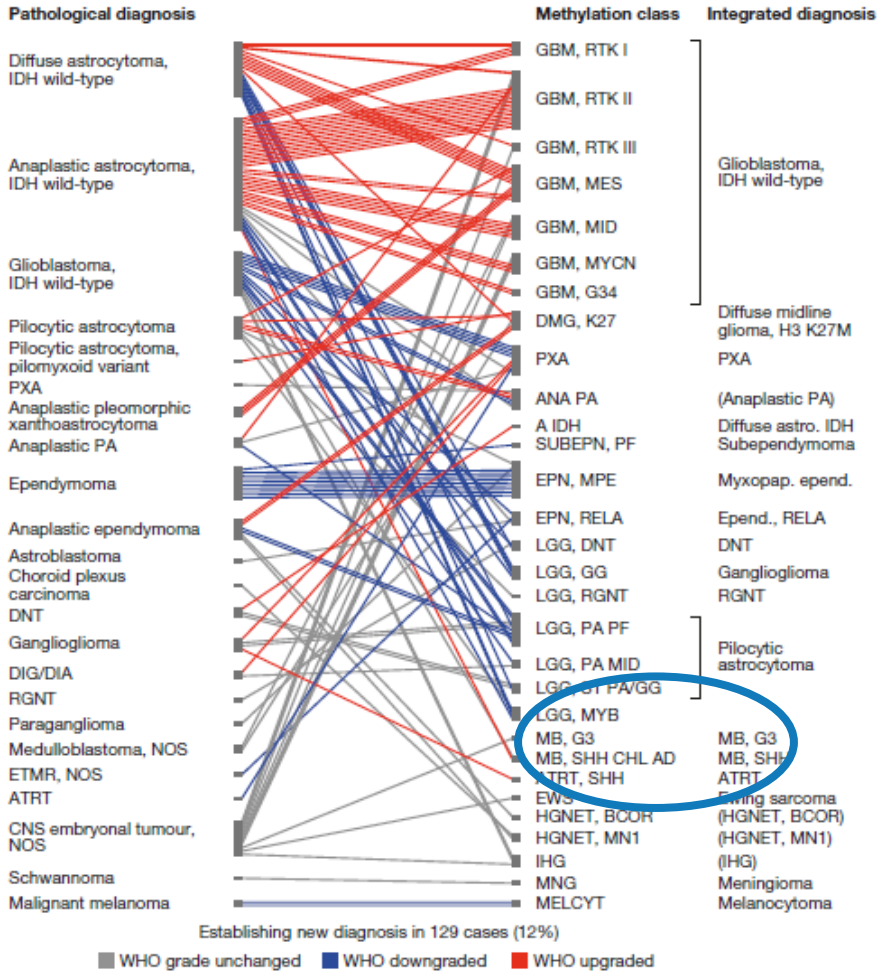


Figure 4 | Reassessment of discrepant cases and establishment of

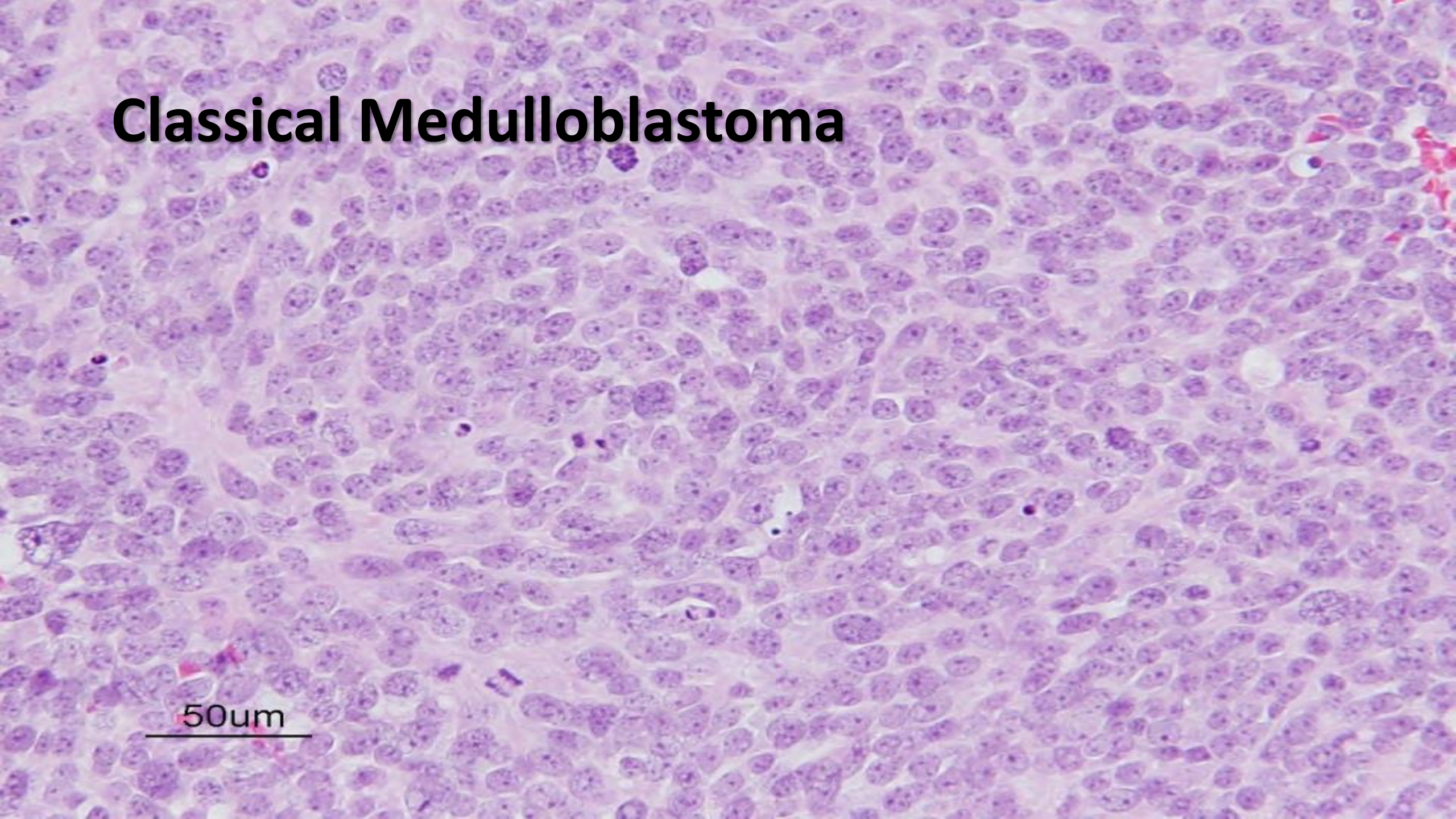
22 march 2018 | VOL 555 | NATURE | 471 doi:10.1038/nature26000

Medulloblastoma

- **Medulloblastoma, Molecular classification**
  - Medulloblastoma Wnt activated
  - Medulloblastoma, SHH activated and p53 wt
  - Medulloblastoma, SHH activated and p53 mt
  - Medulloblastoma, non-Wnt, non-SHH

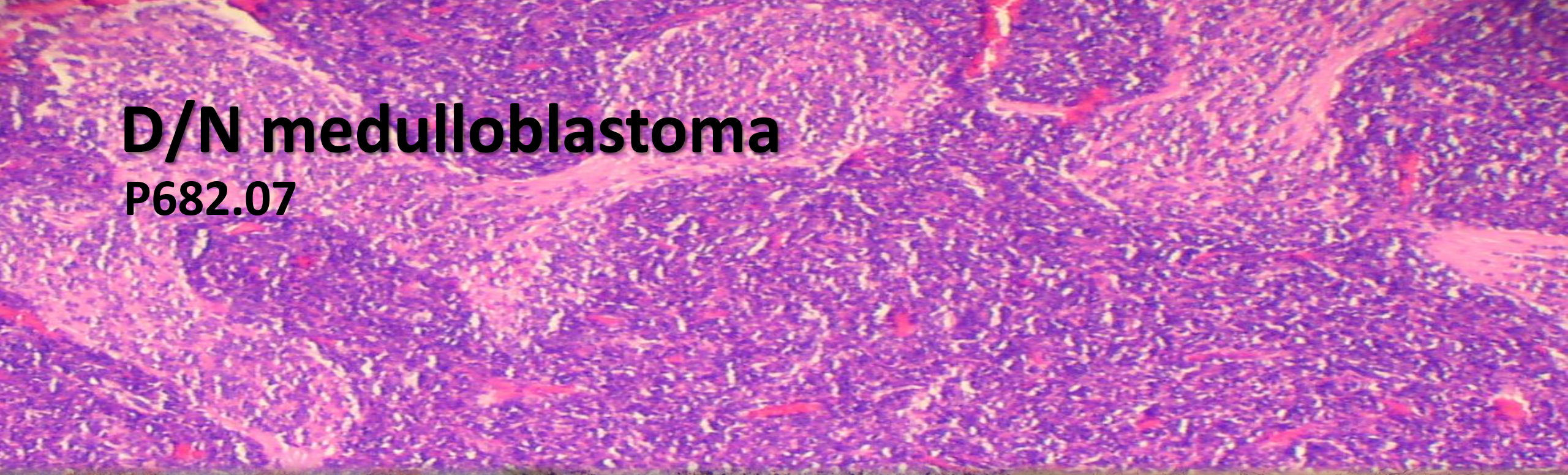
- **Medulloblastoma, histologic classification**

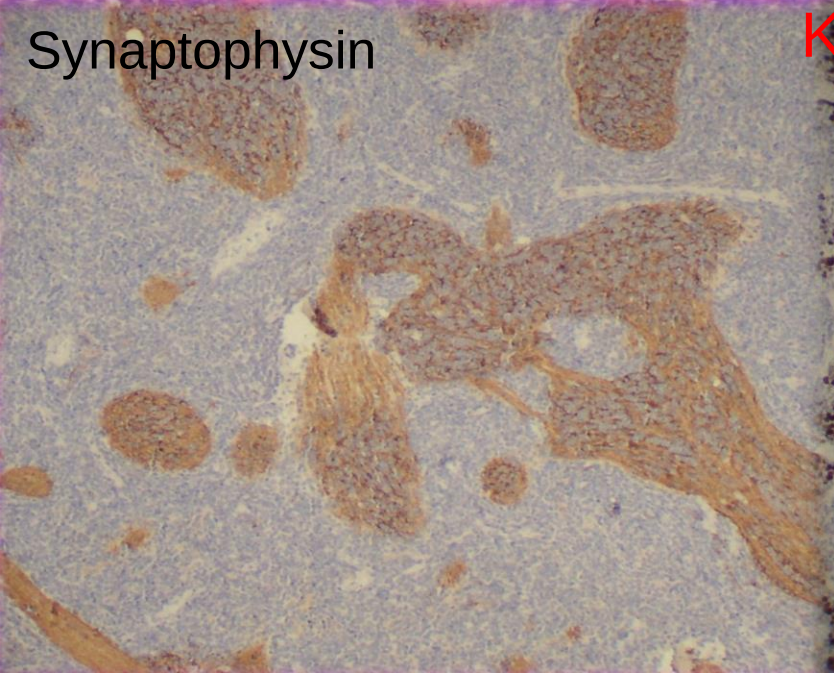
Classical Medulloblastoma

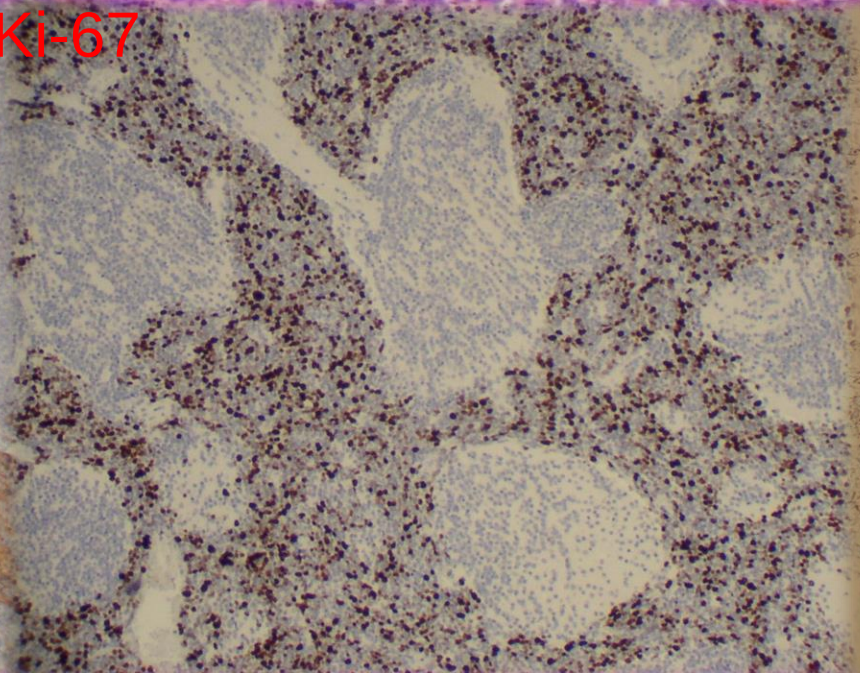


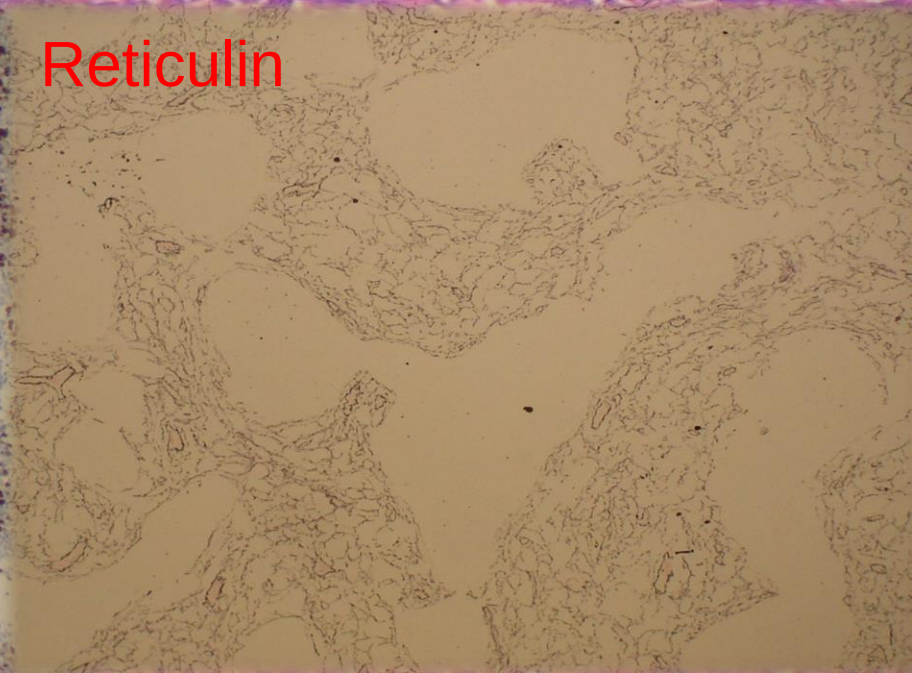
D/N medulloblastoma

P682.07

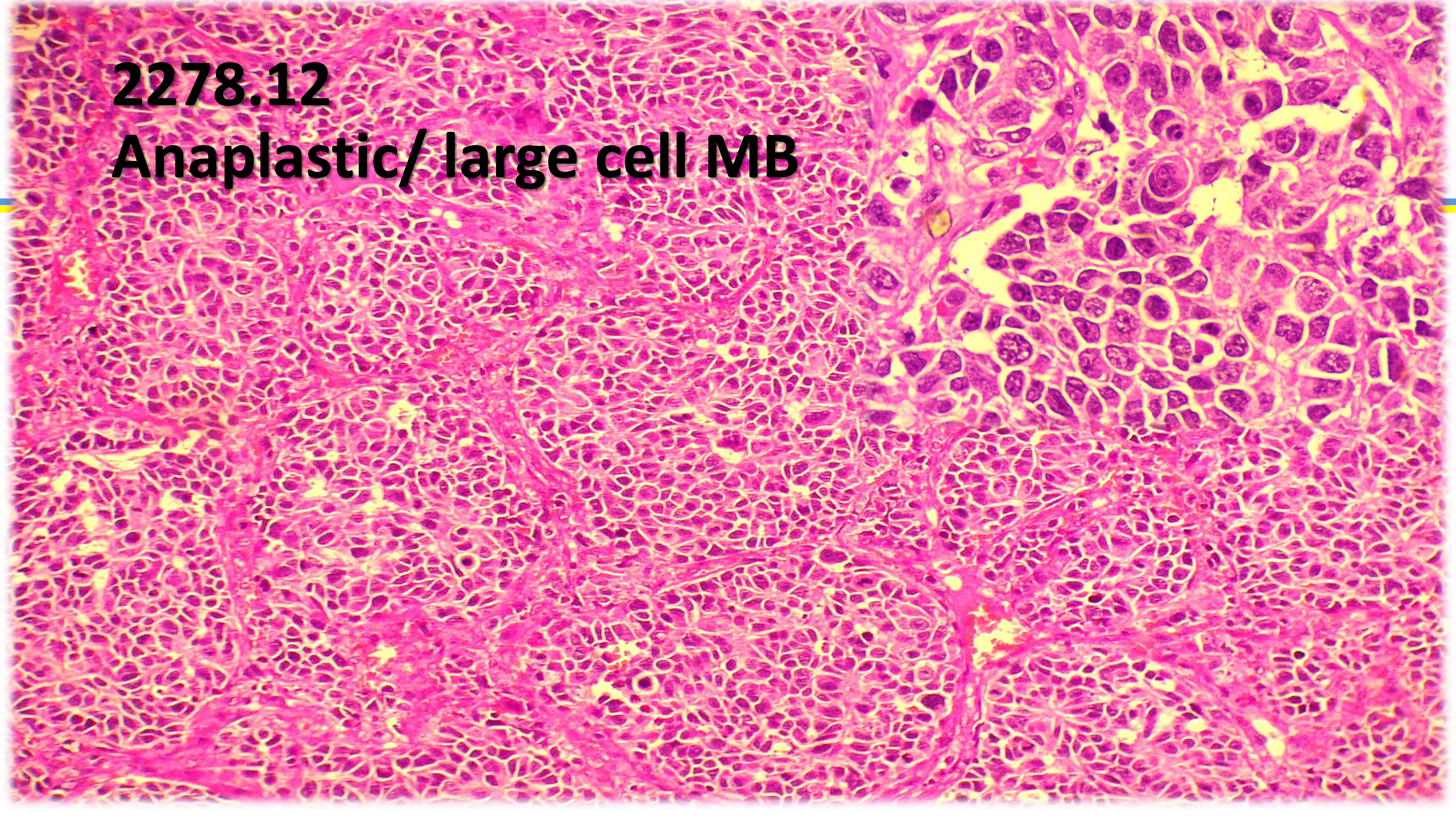




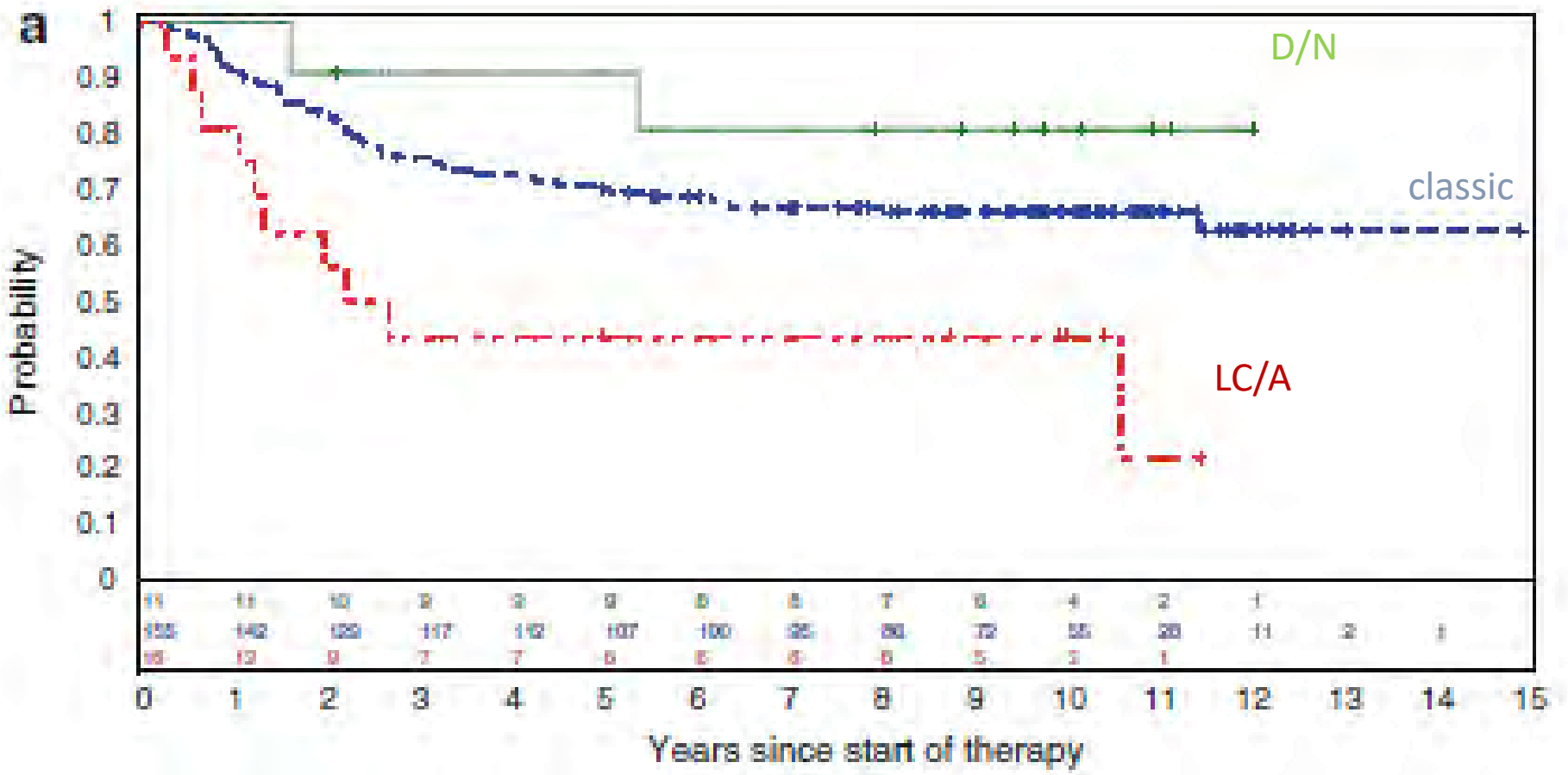




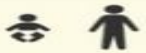
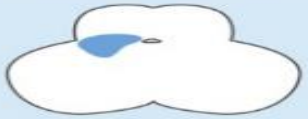
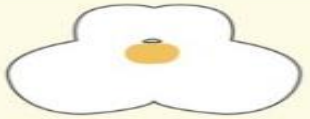
2278.12
Anaplastic/ large cell MB



Outcome and Histologic Variant



Ellison et al. Acta Neuropath, 2011

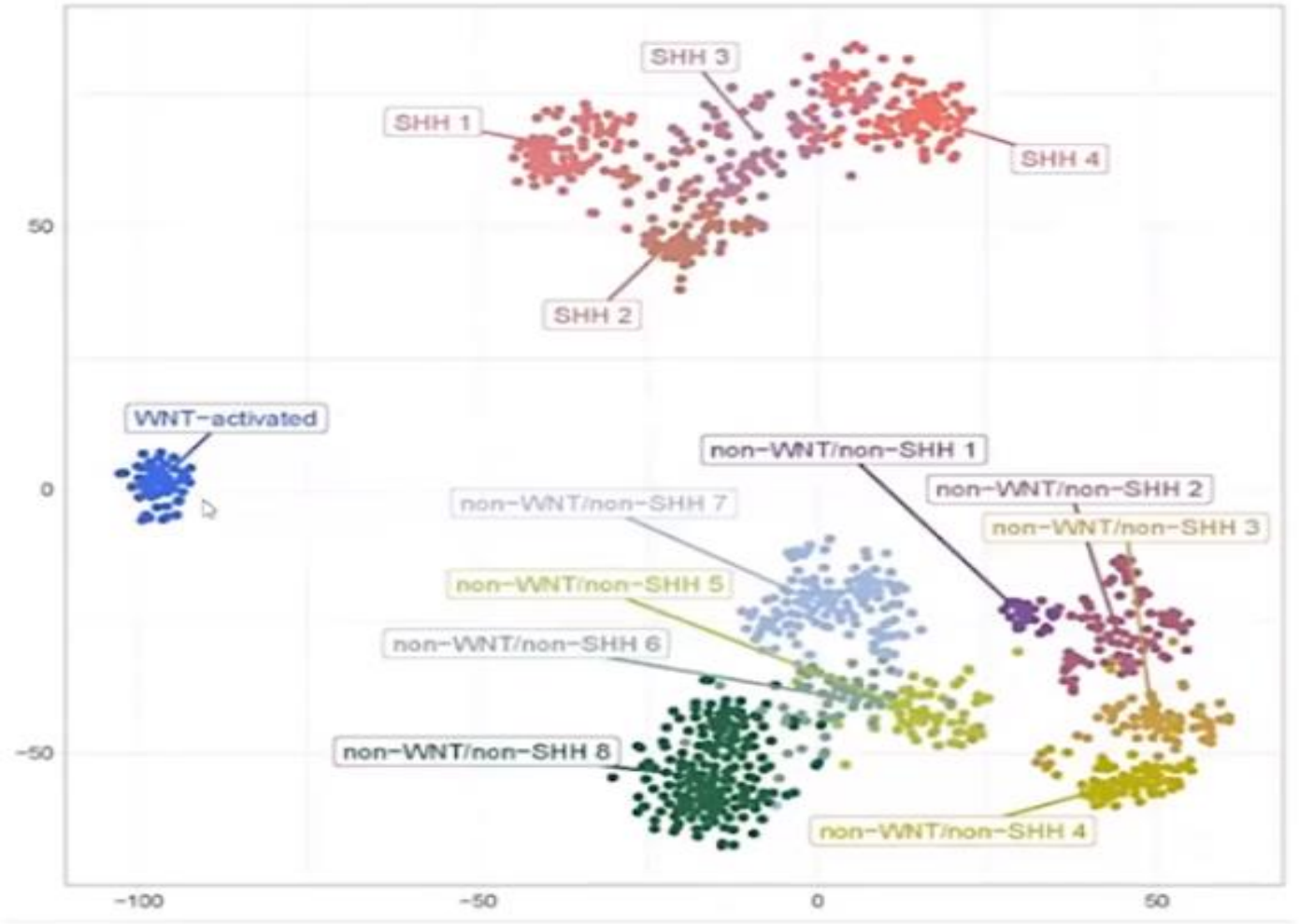
	Subgroup	WNT	SHH	Group 3	Group 4
Clinical Characteristics	% of Cases	10	30	25	35
	Age at Diagnosis				
	Gender Ratio (M:F)	1:1	1:1	2:1	3:1
	Anatomic Location				
	Histology	Classic, Rarely LCA	Desmoplastic, Classic, LCA	Classic, LCA	Classic, LCA
	Metastasis at Diagnosis (%)	5-10	15-20	40-45	35-40
	Recurrence Pattern	Rare; Local or metastatic	Local	Metastatic	Metastatic
	Prognosis	Very good	Infants good, others intermediate	Poor	Intermediate
Molecular Characteristics	Proposed Cell of Origin	Progenitor cells in the lower rhombic lip	Granule precursors of the external granule layer	Neural stem cells	Unipolar brush cells
	Recurrent Gene Amplifications	-	*MYCN* *GLI1* or *GLI2*	*MYC* *MYCN* *OTX2*	*SNCAIP* *MYCN* *OTX2* *CDK6*
	Recurrent SNVs	*CTNNB1* *DDX3X* *SMARCA4* *TP53*	*PTCH1* *TERT* *SUFU* *SMO* *TP53*	*SMARCA4* *KBTBD4* *CTDNEP1* *KMT2D*	*KDM6A* *ZMYM3* *KTM2C* *KBTBD4*
	Cytogenetic Events ■ Gain ■ Loss	6	3q, 9p 9q, 10q, 17p	1q, 7, 18 8, 10q, 11, 16q i17q	7, 18q 8, 11p, X i17q
	Other Recurrent Genetic Events	-	-	*GFI1* and *GFI1B* enhancer hijacking	*PRDM6*, *GFI1*, and *GFI1B* enhancer hijacking

Age: Infant Child Adult

Juraschka and Taylor. J Neurosurg Pediatr. 2019;24(4):353–

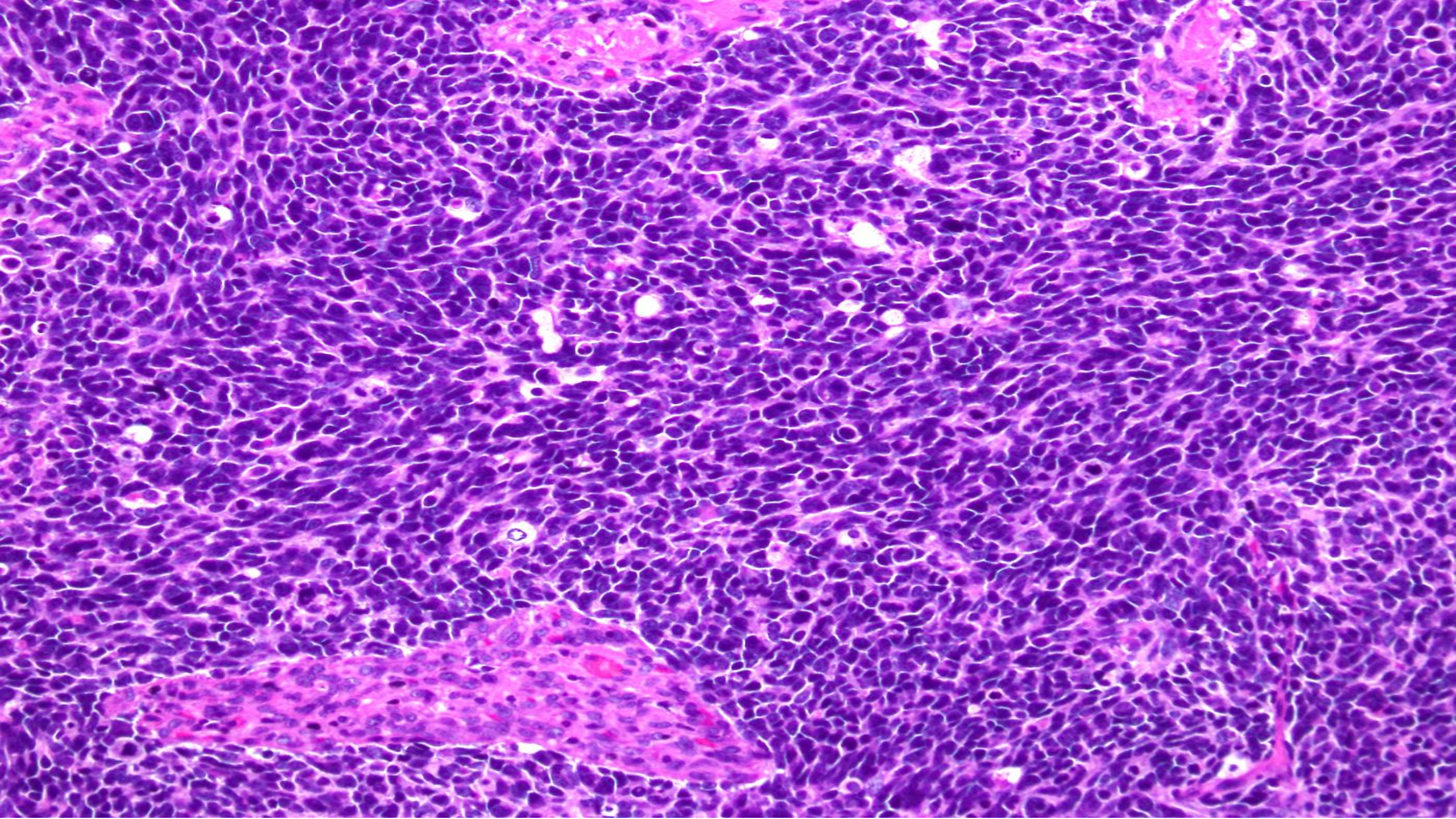
Zhao et al. *J Neurooncol.* 2018;139(2):333–

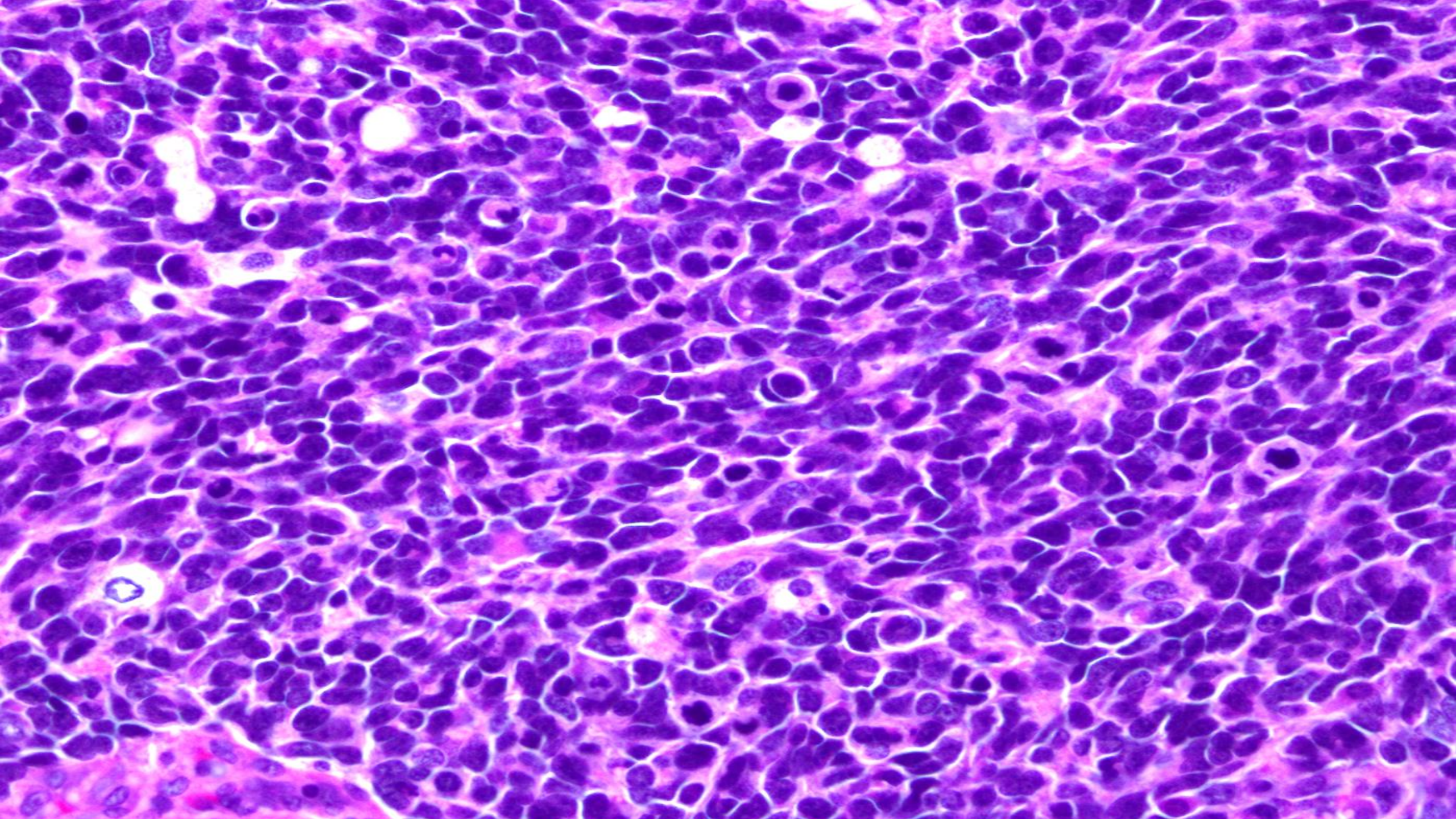
Medulloblastoma

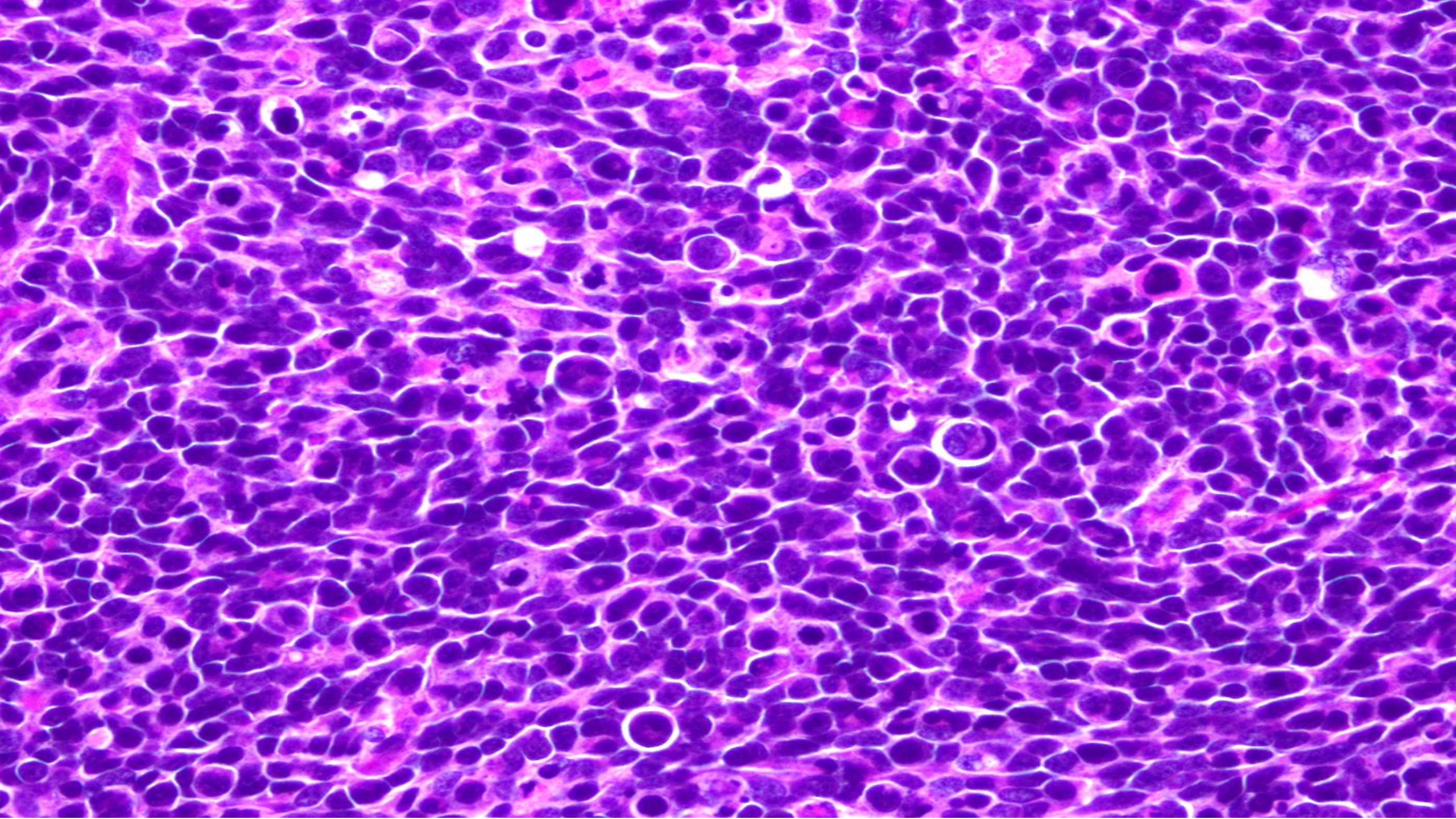


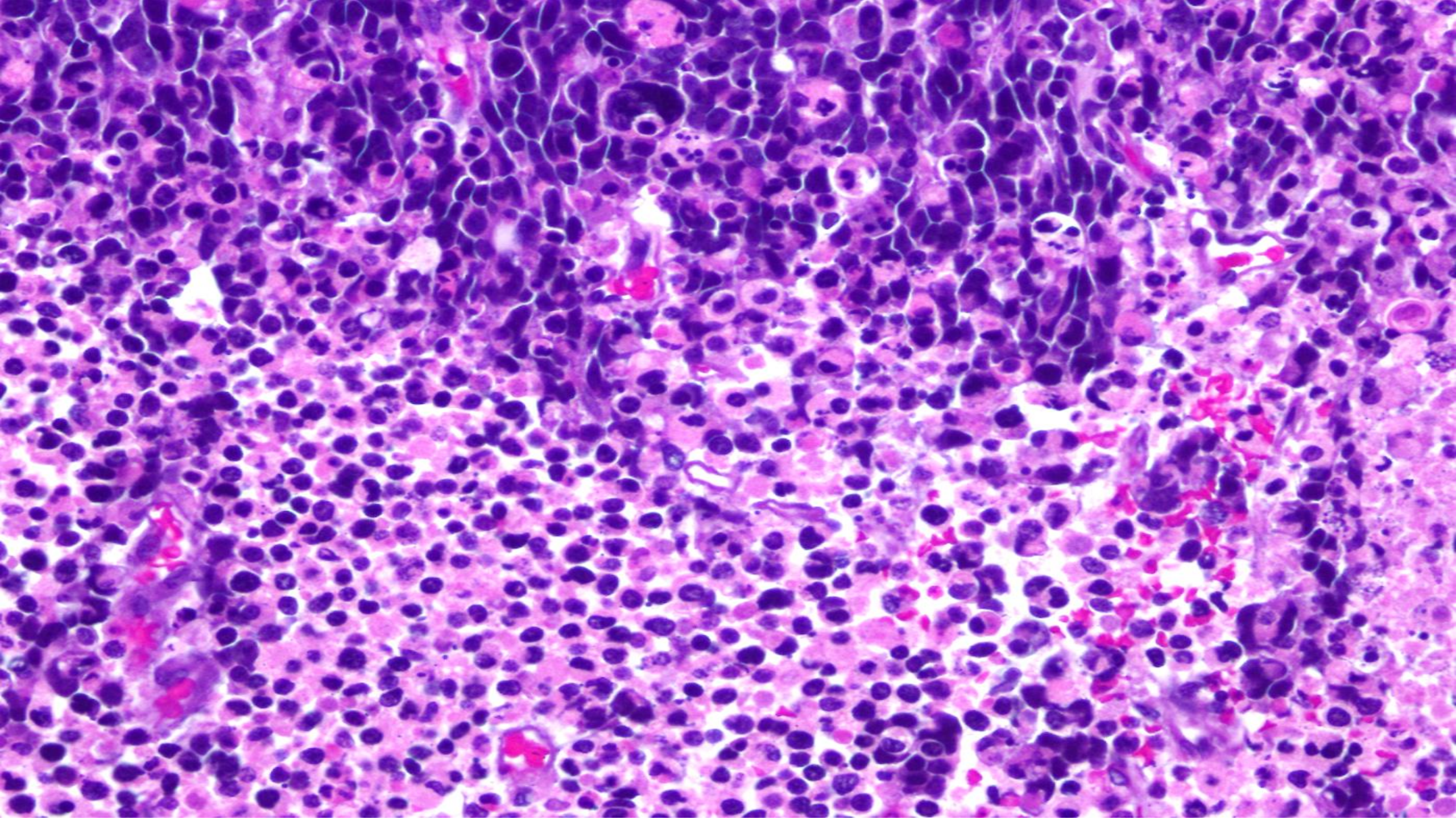
Case-10
MRN 221421/ P9108.22

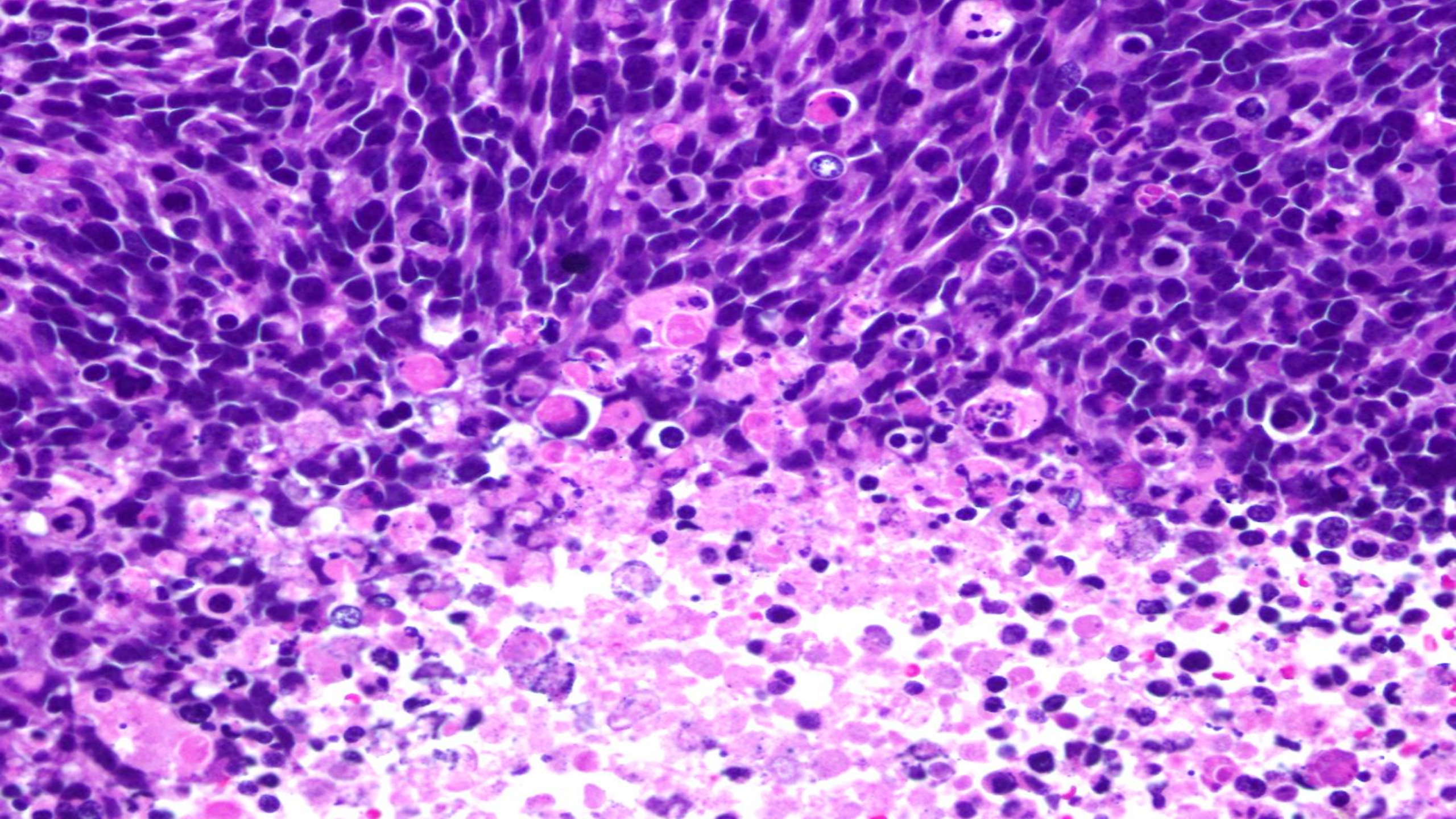
- An 11-year-old previously healthy child, noted 2 months ago to have headaches, and later had altered level of consciousness and went to ER were CT brain done showed hydrocephalus and post fossa tumor.
- Brain MRI , there is mild heterogeneous contrast enhancing lesion centred at the right cerebellar hemisphere.

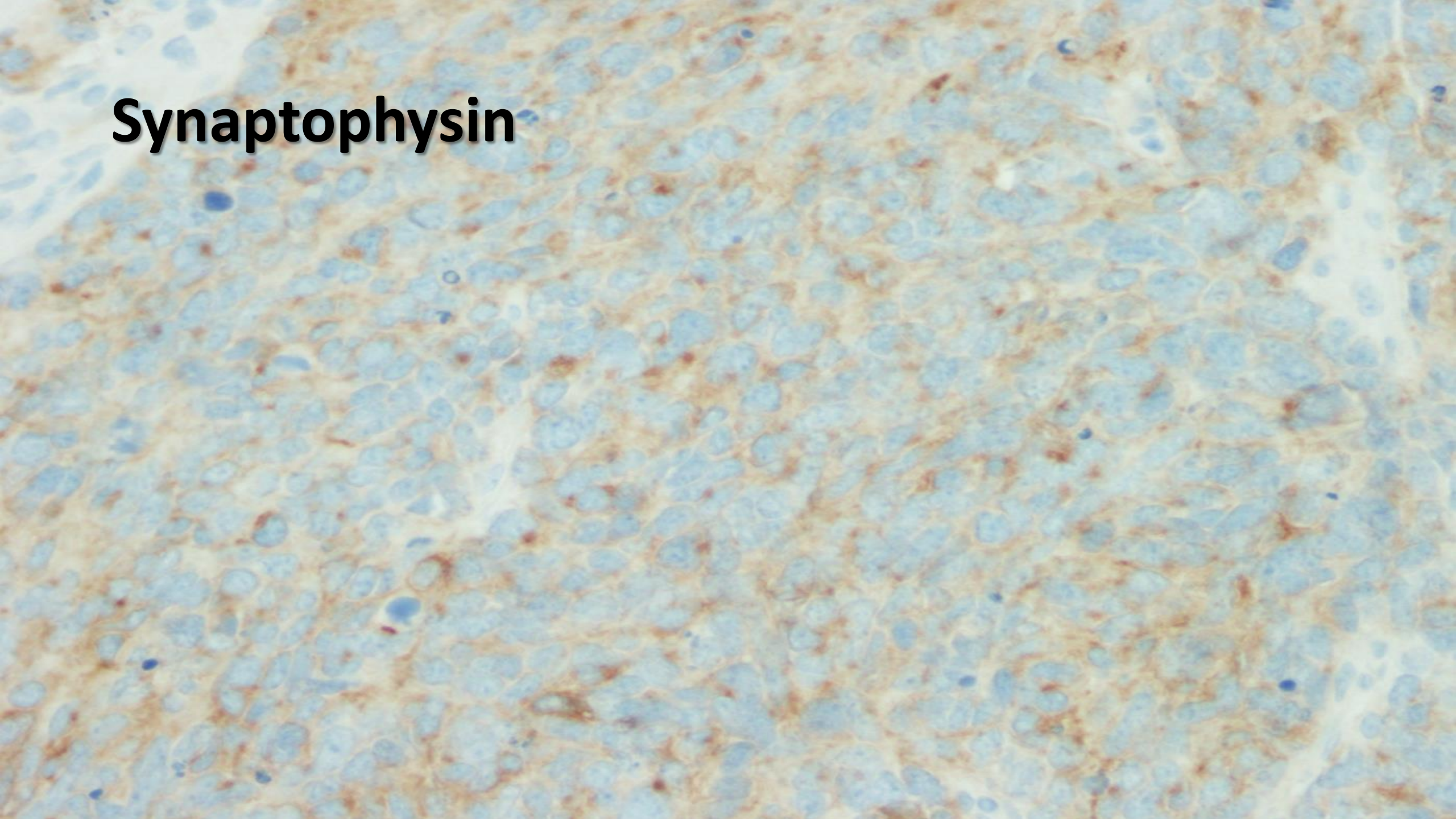


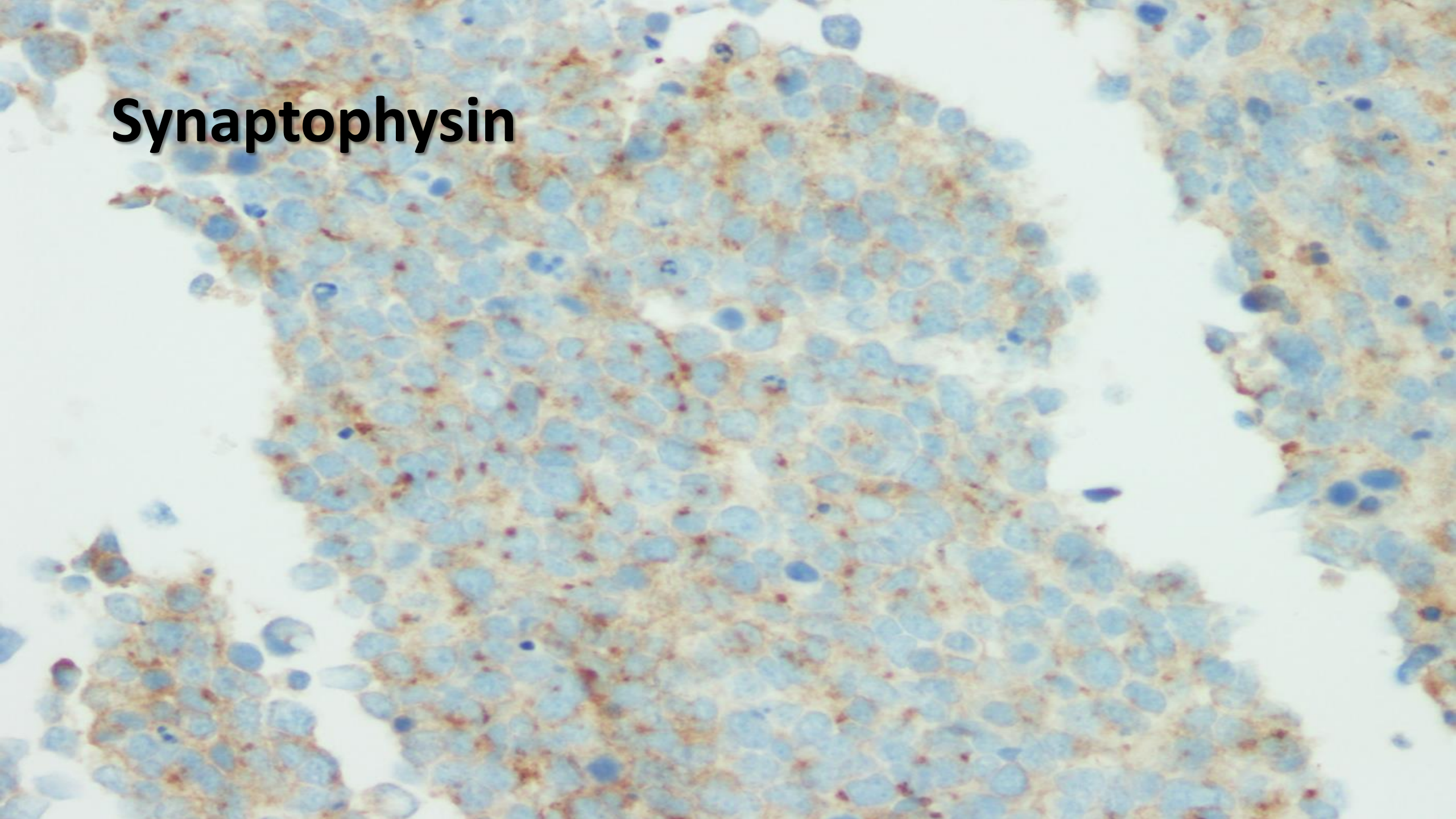


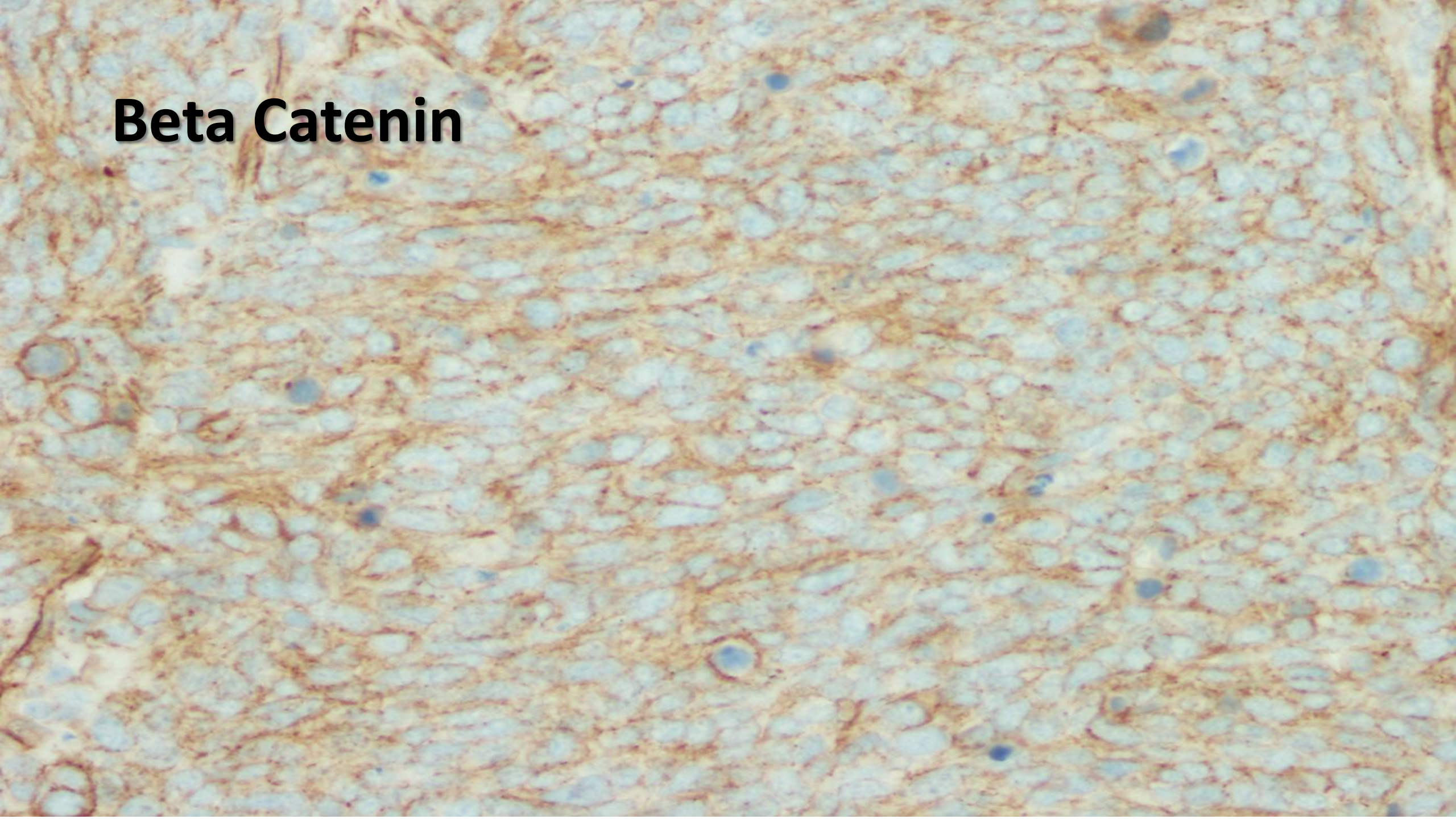


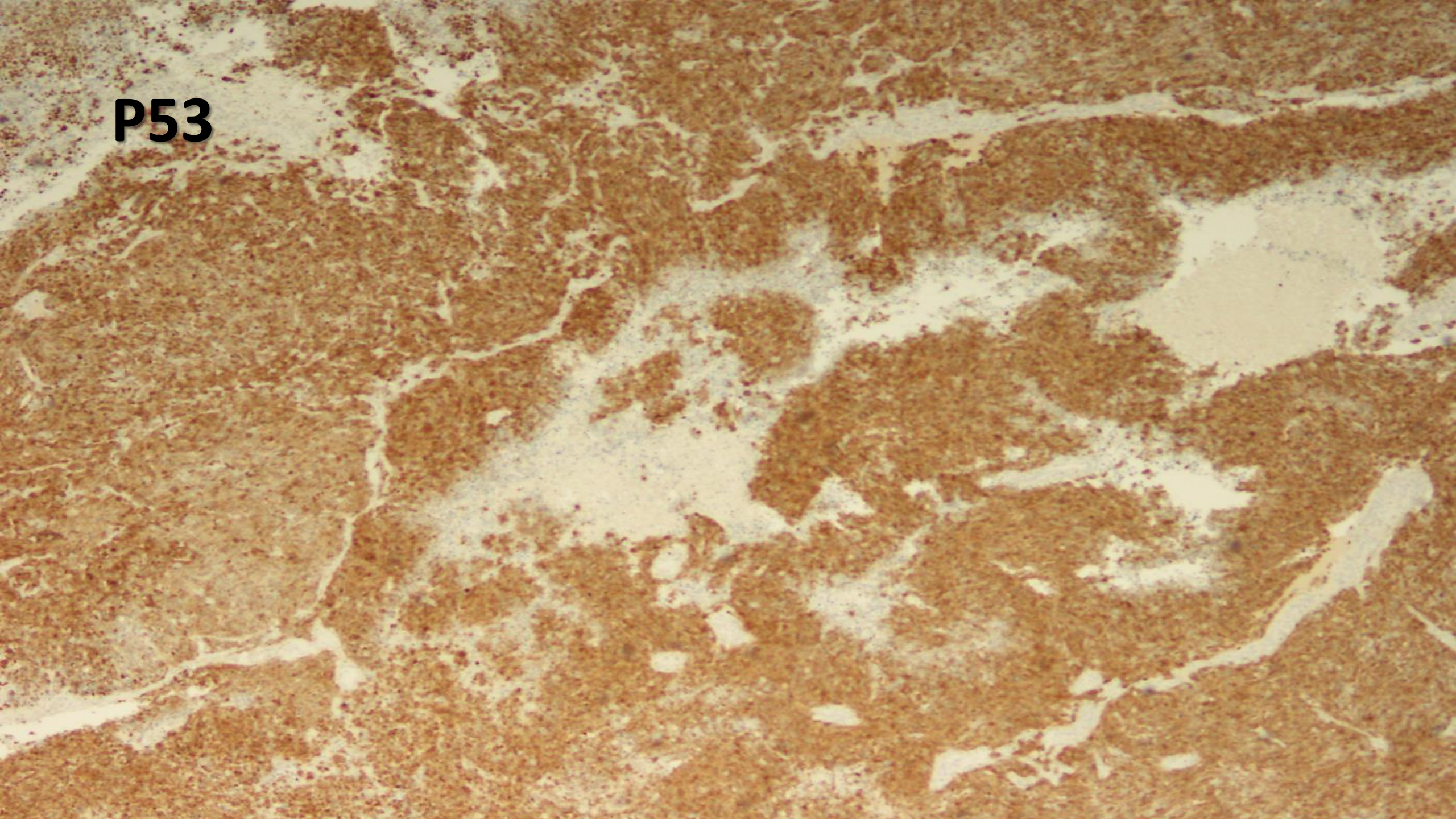


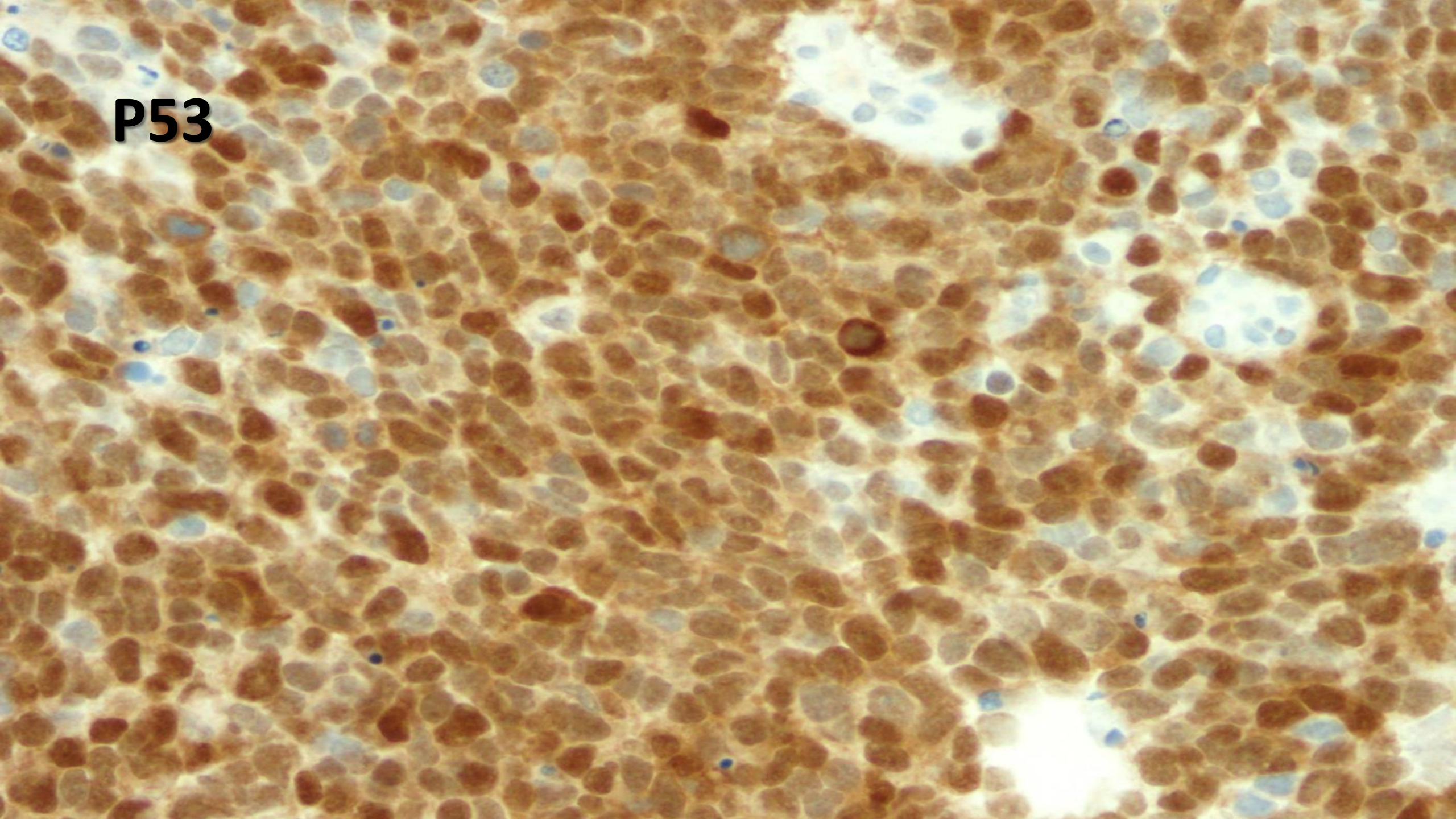


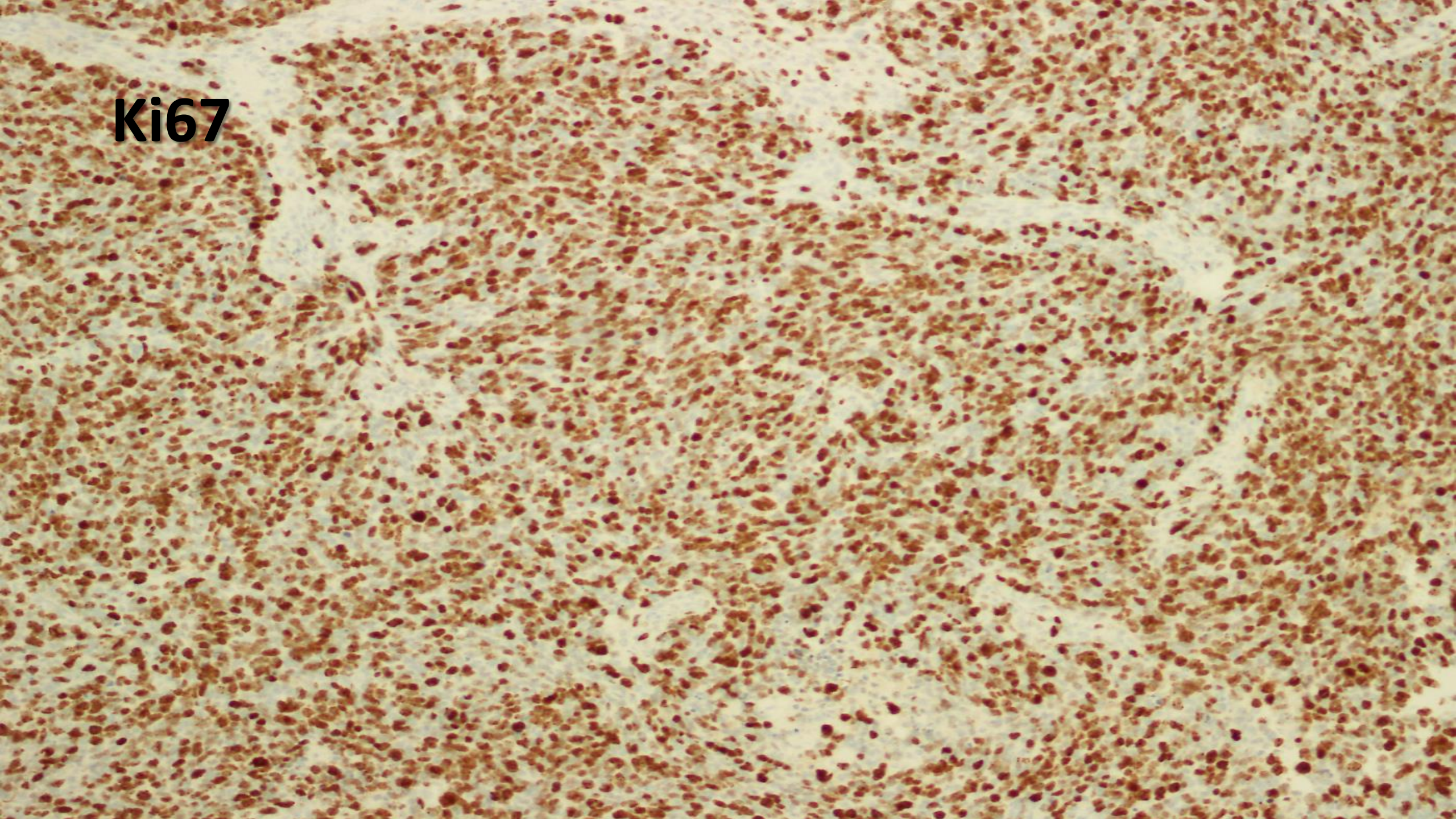

Synaptophysin

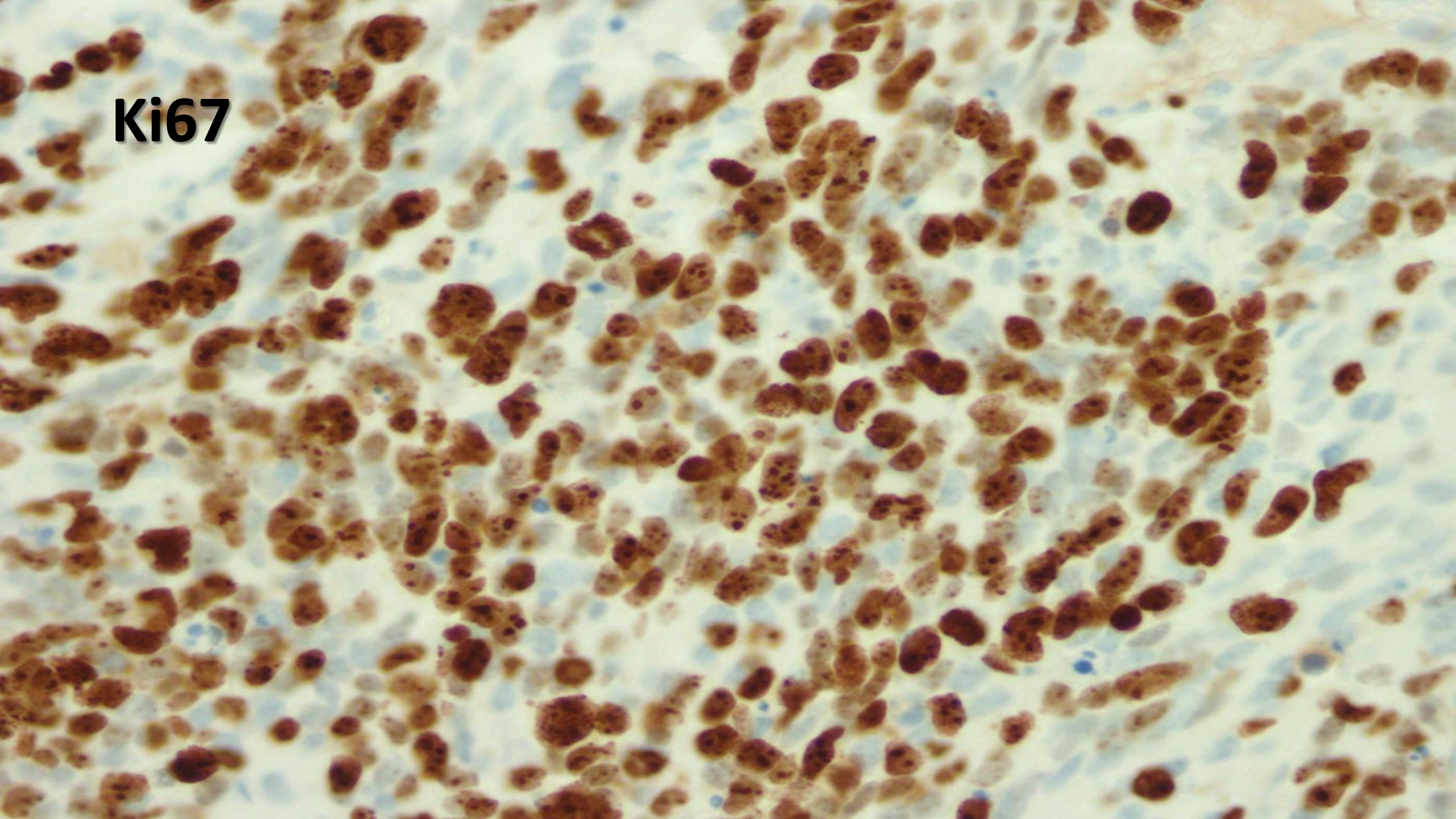

Synaptophysin


Beta Catenin


P53


P53


Ki67


Ki67

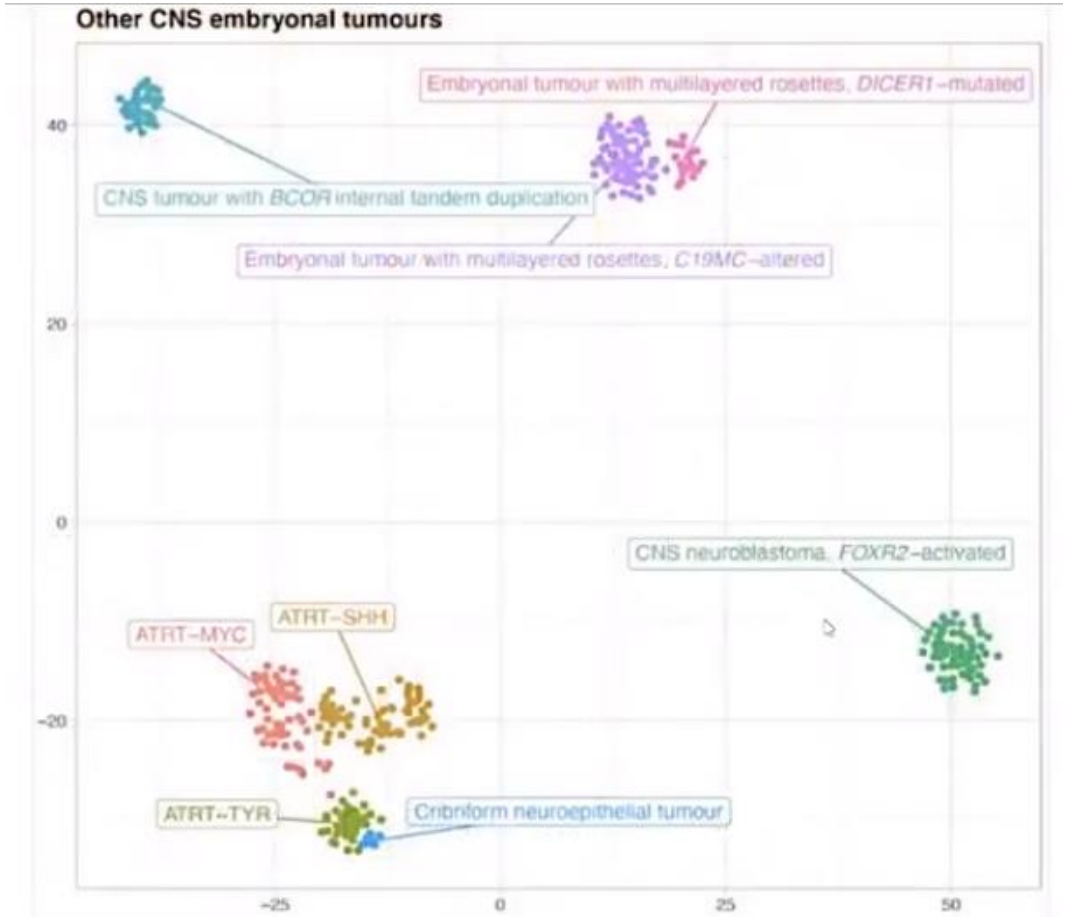
Case-10
MRN 221421/ P9108.22

- Medulloblastoma, Anaplastic/ large cell type, P53 mutant, WHO grade 4.

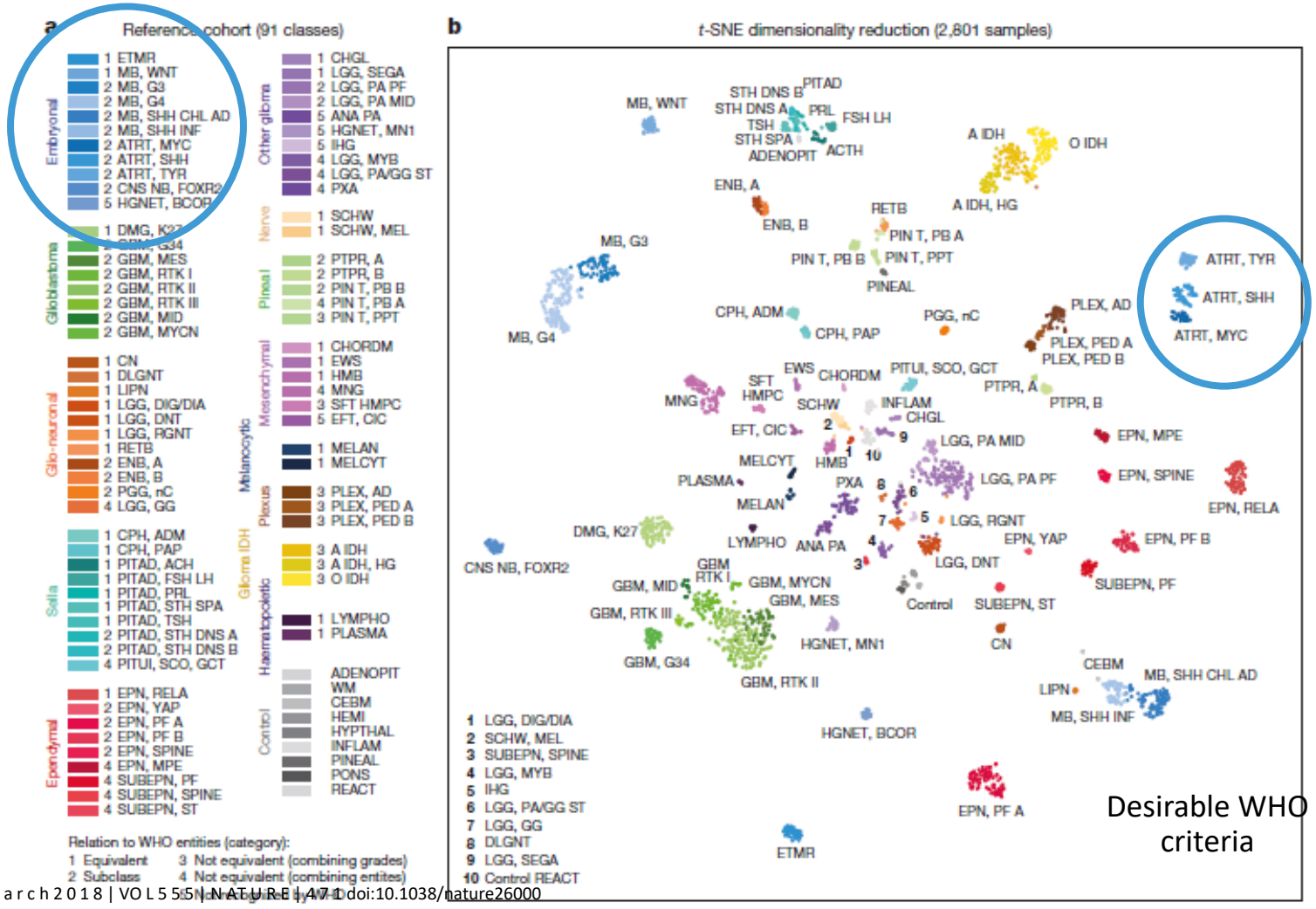
7. Medulloblastoma should undergo molecular classification (some surrogate markers include P53, beta-catenin, and cMYC)

Other Embryonal Tumors

- Atypical teratoid rhabdoid tumor (AT/RT)
- Cribriform neuroepithelial tumor
- Embryonal tumor with multi-layered rosettes (ETMR)
- CNS neuroblastoma FOXR2 activated
- CNS tumor with BCOR internal tandem duplication



Methylation Profile
Embryonal tumor- AT/RT



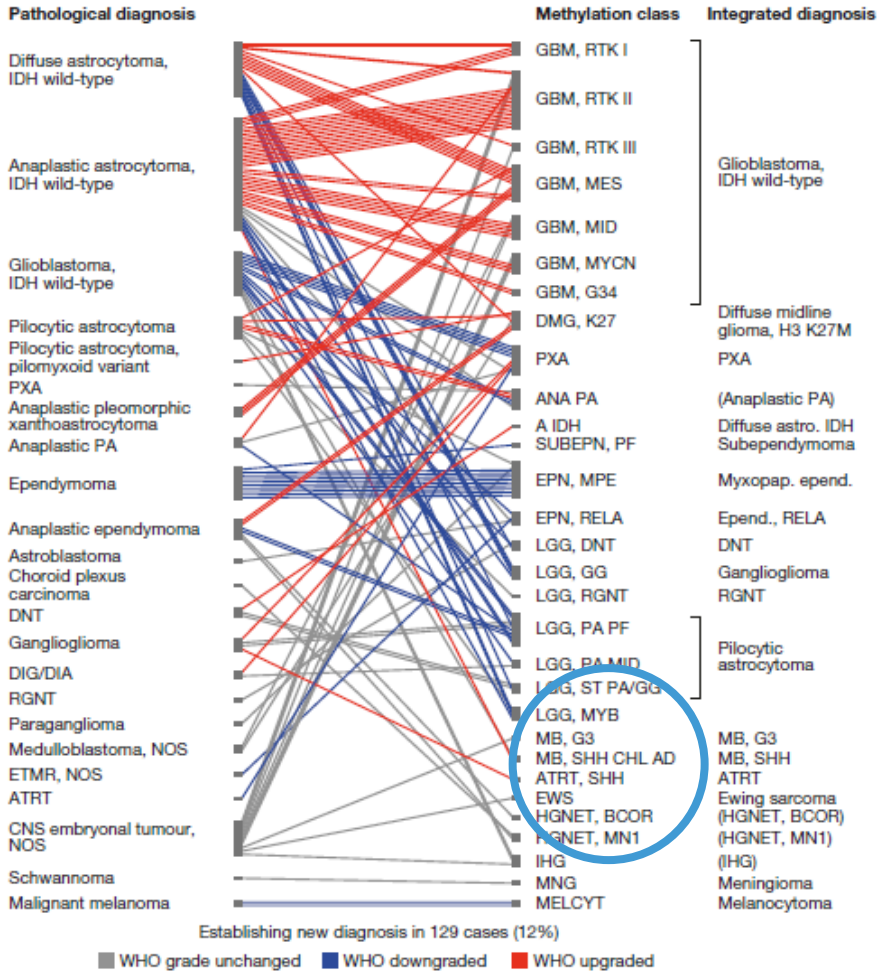
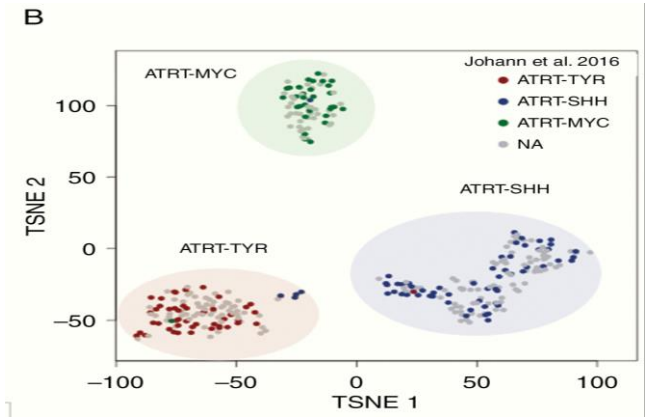
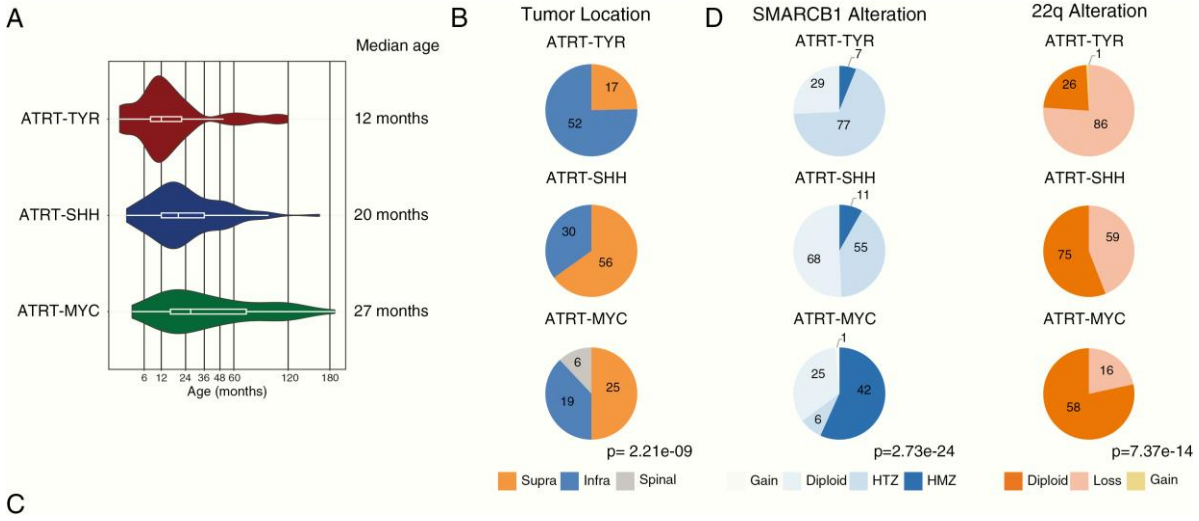


Figure 4 | Reassessment of discrepant cases and establishment of

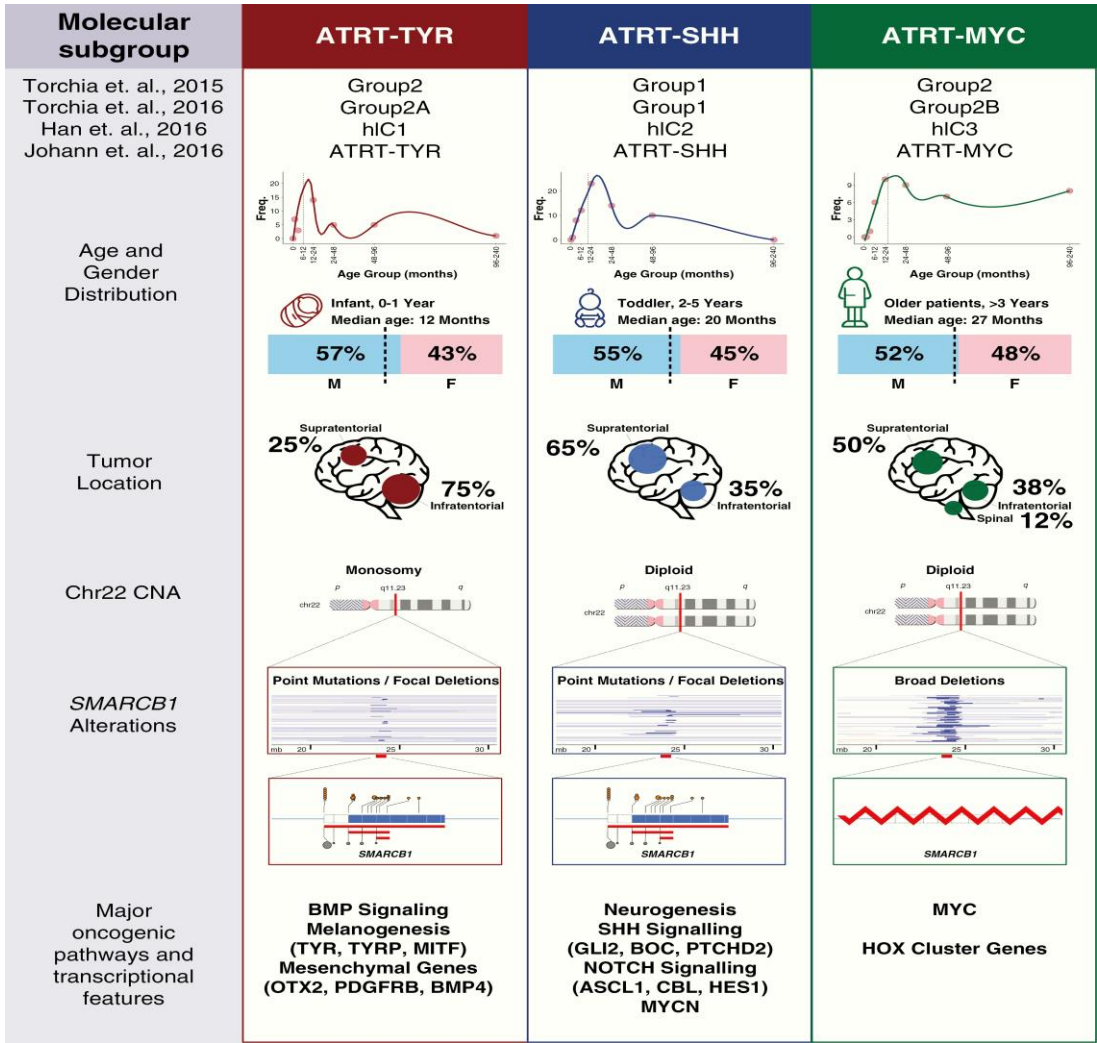
22 march 2018 | VOL 555 | NATURE | 471 doi:10.1038/nature26000

Atypical Teratoid Rhabdoid Tumor

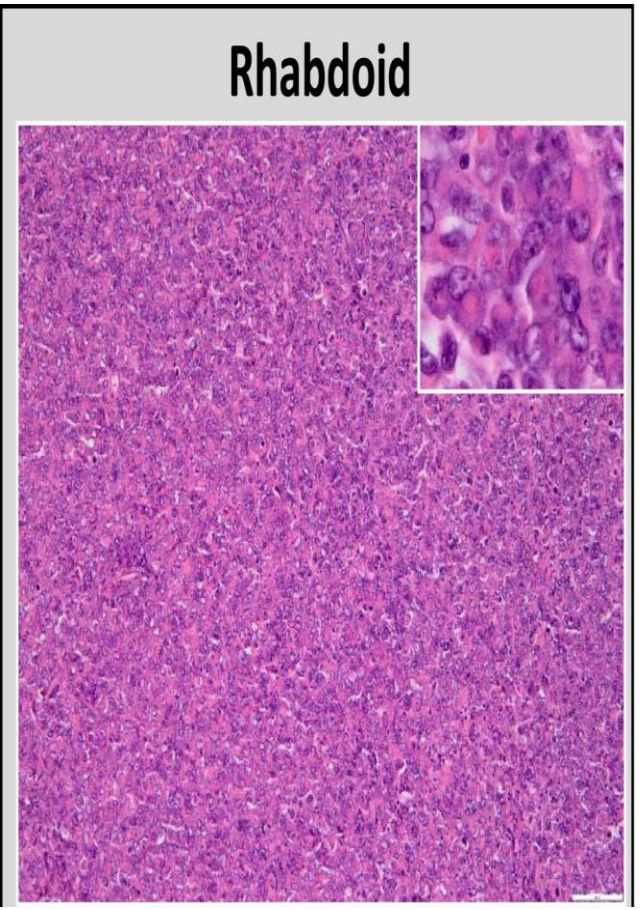




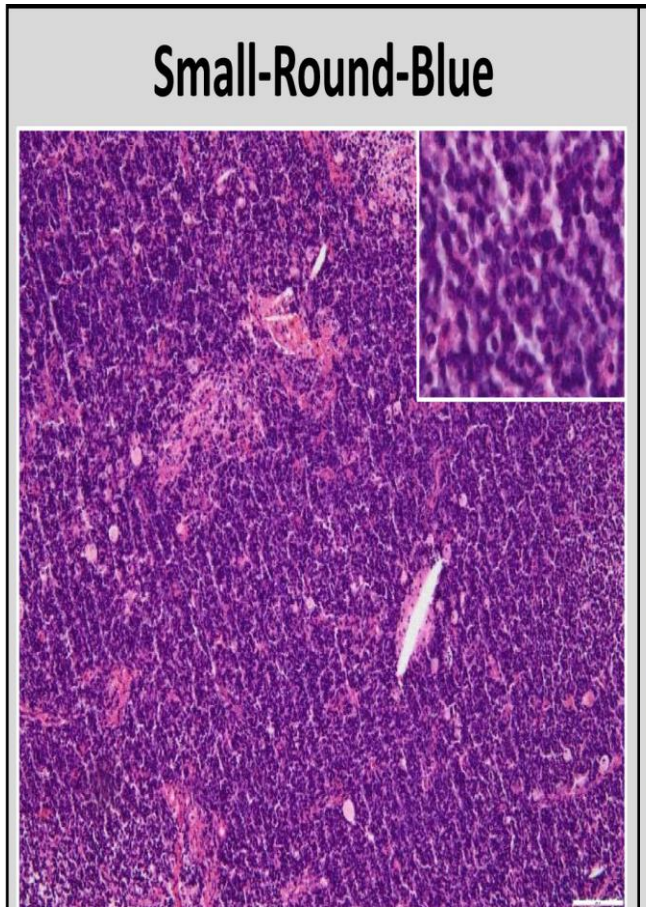
Neuro Oncol, Volume 22, Issue 5, May 2020, Pages 613–624, https://doi.org/10.1093/neuonc/noz235



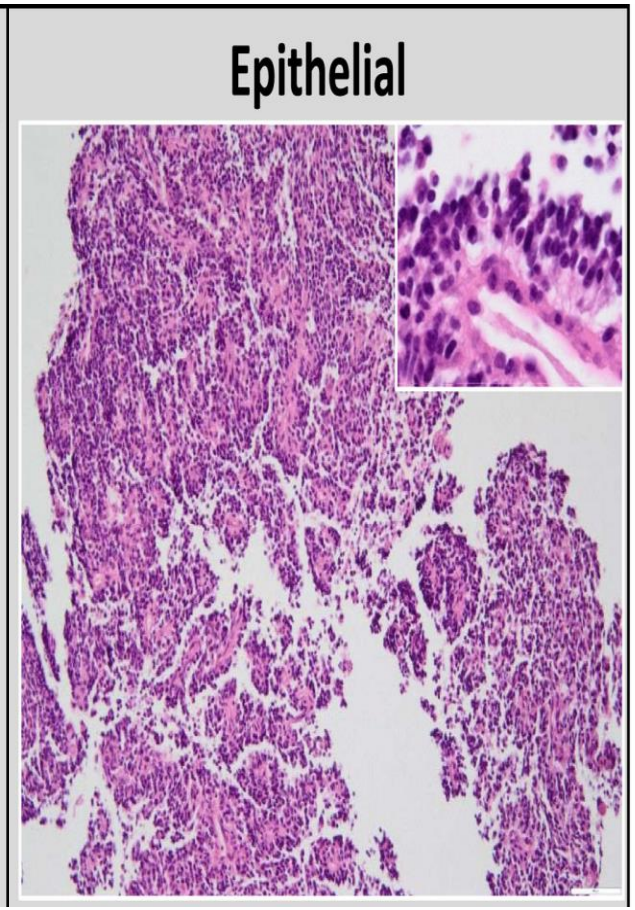
Correlation of Morphology with Molecular subtyping



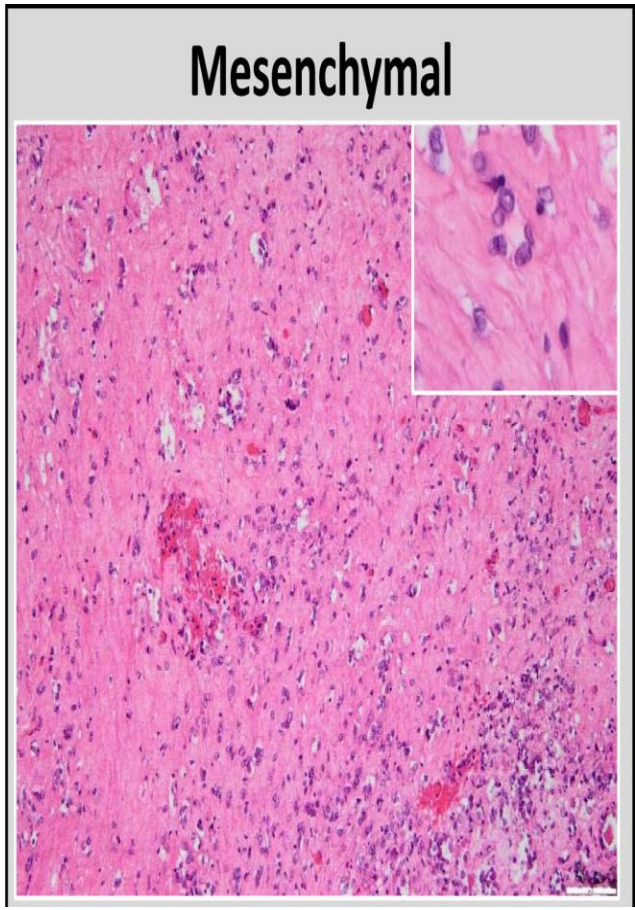
ATRT-MYC



ATRT-SHH



ATRT-TYR

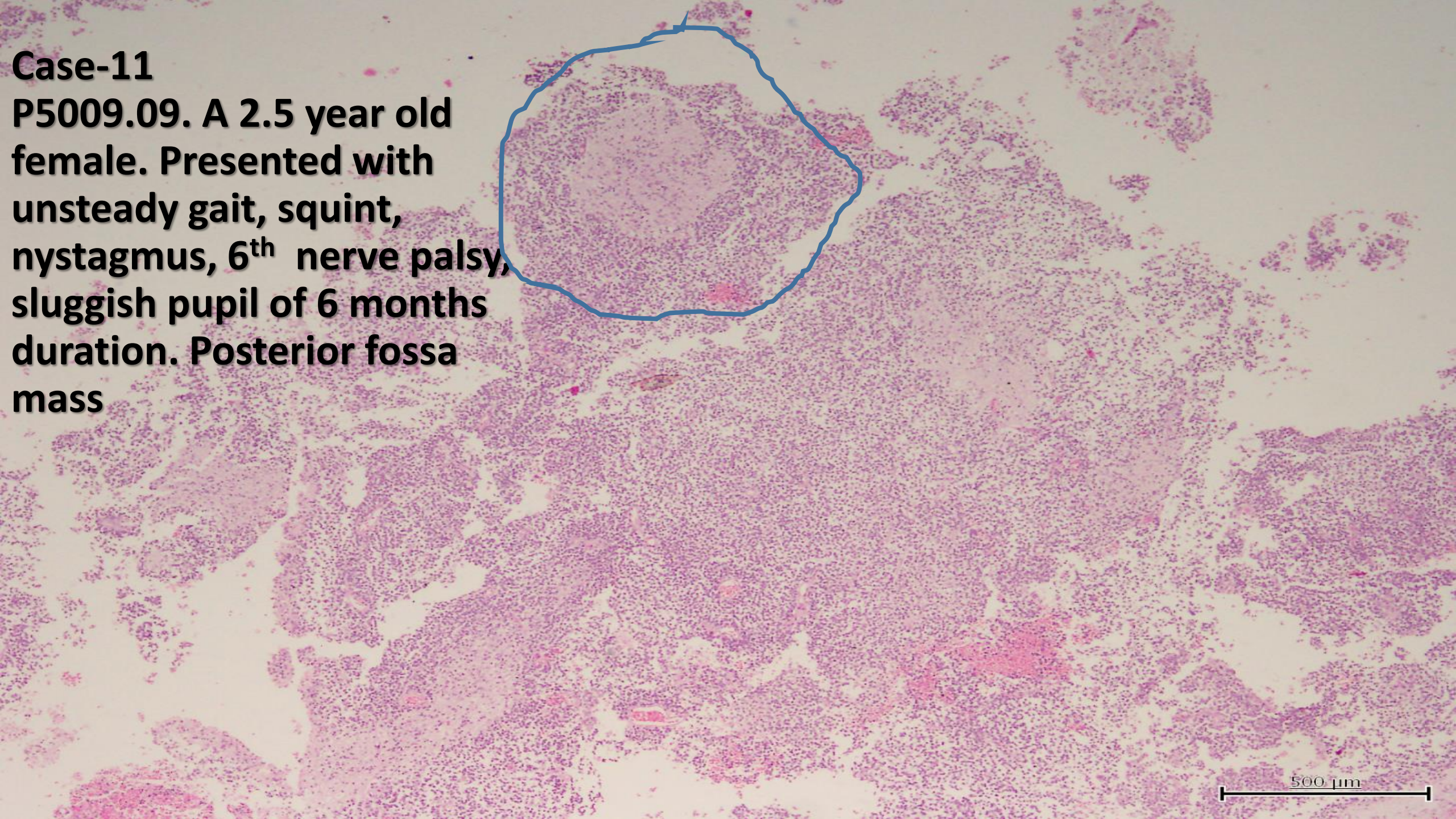


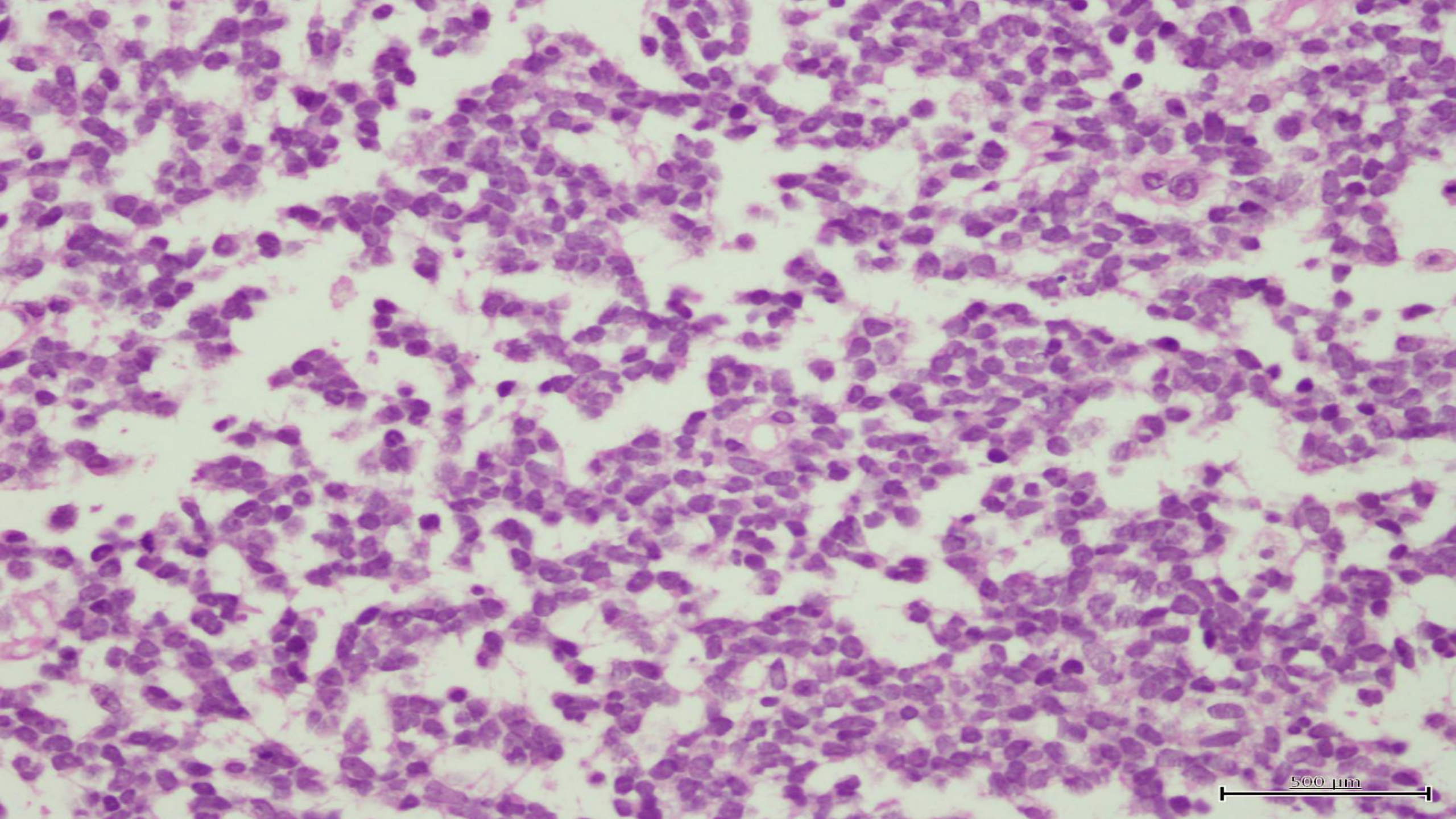
ATRT-MYC

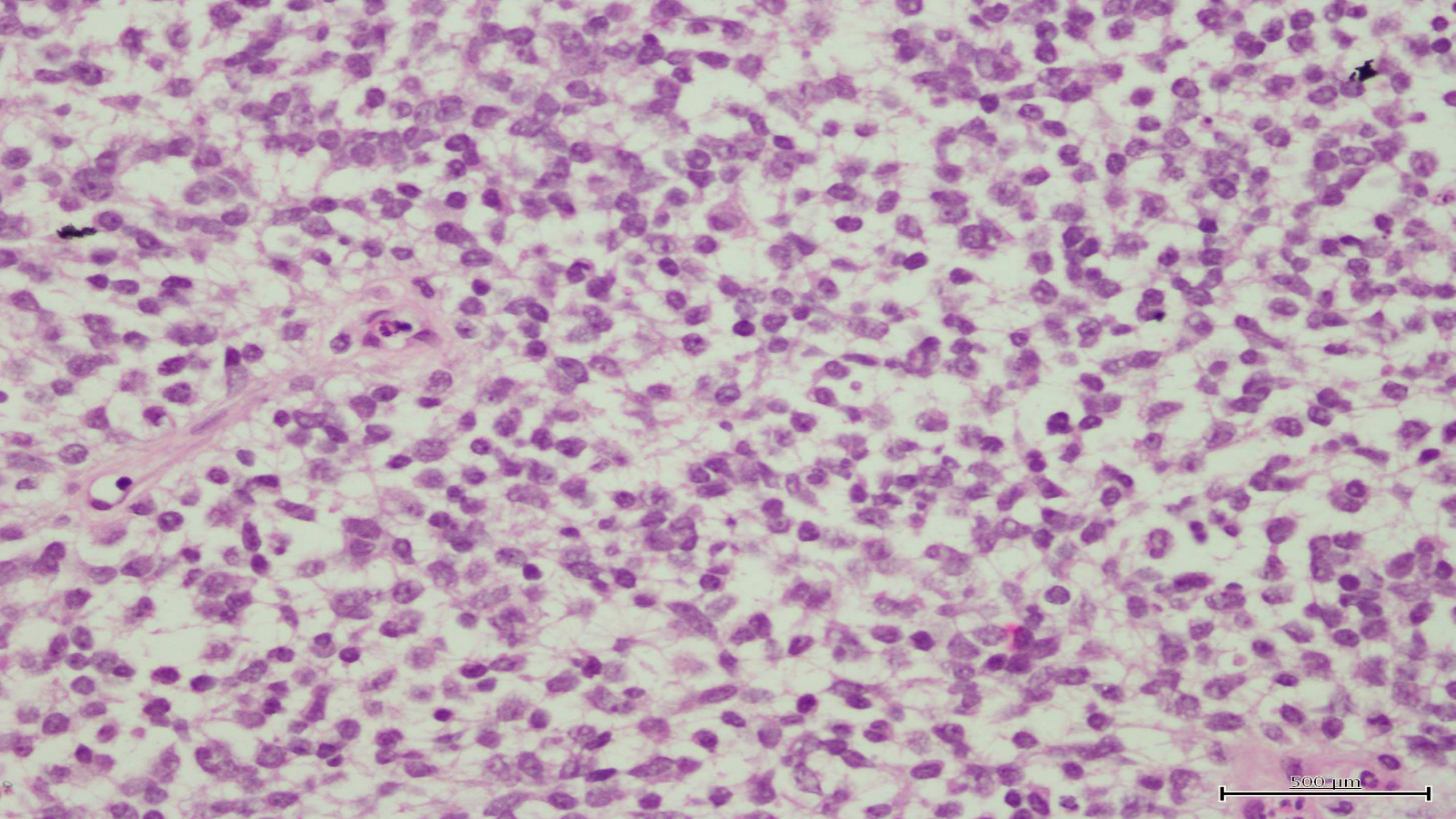
Brain Pathology, Volume: 31, Issue: 5, First published: 03 May 2021, DOI: (10.1111/bpa.12967)

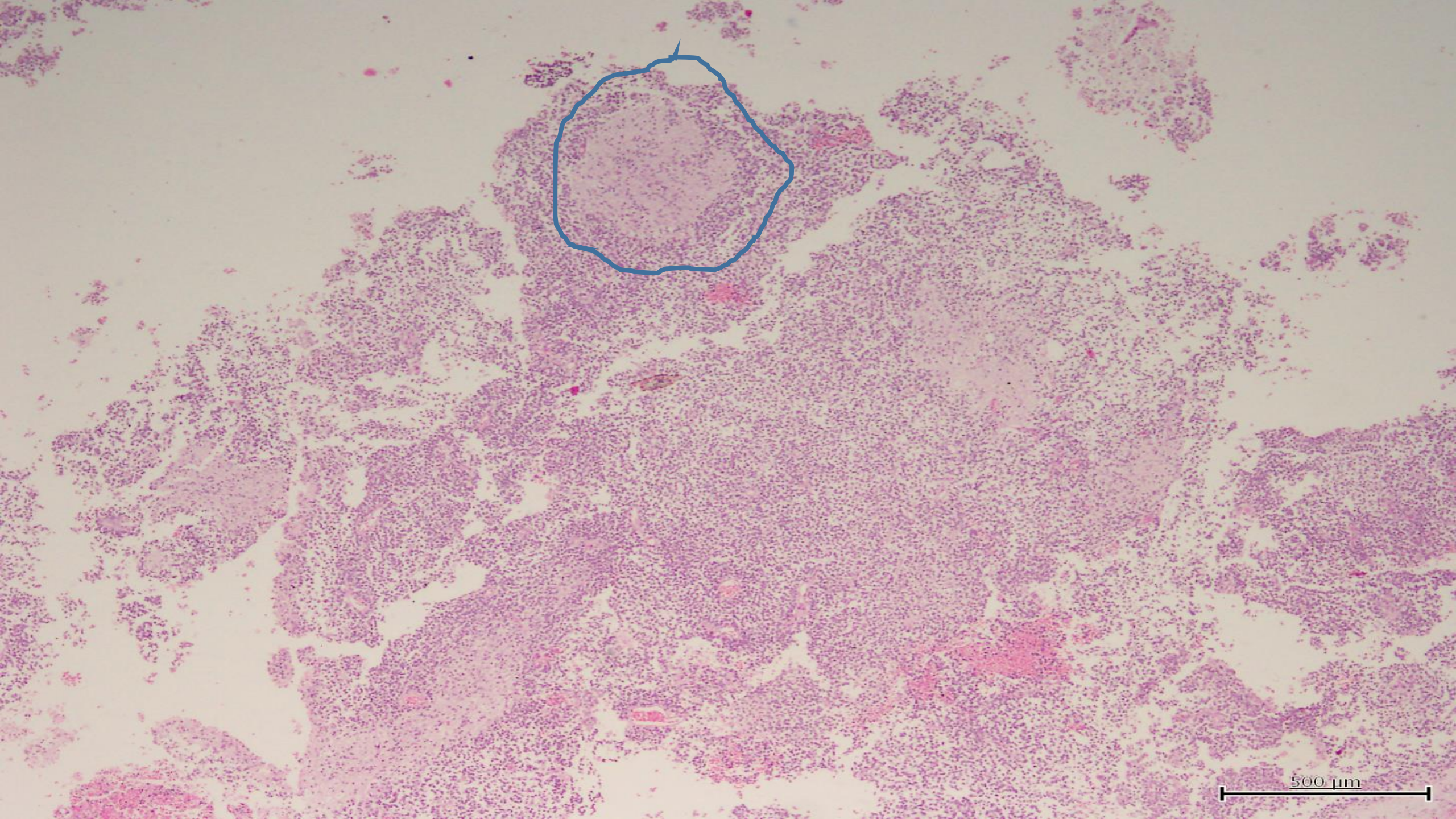
Case-11

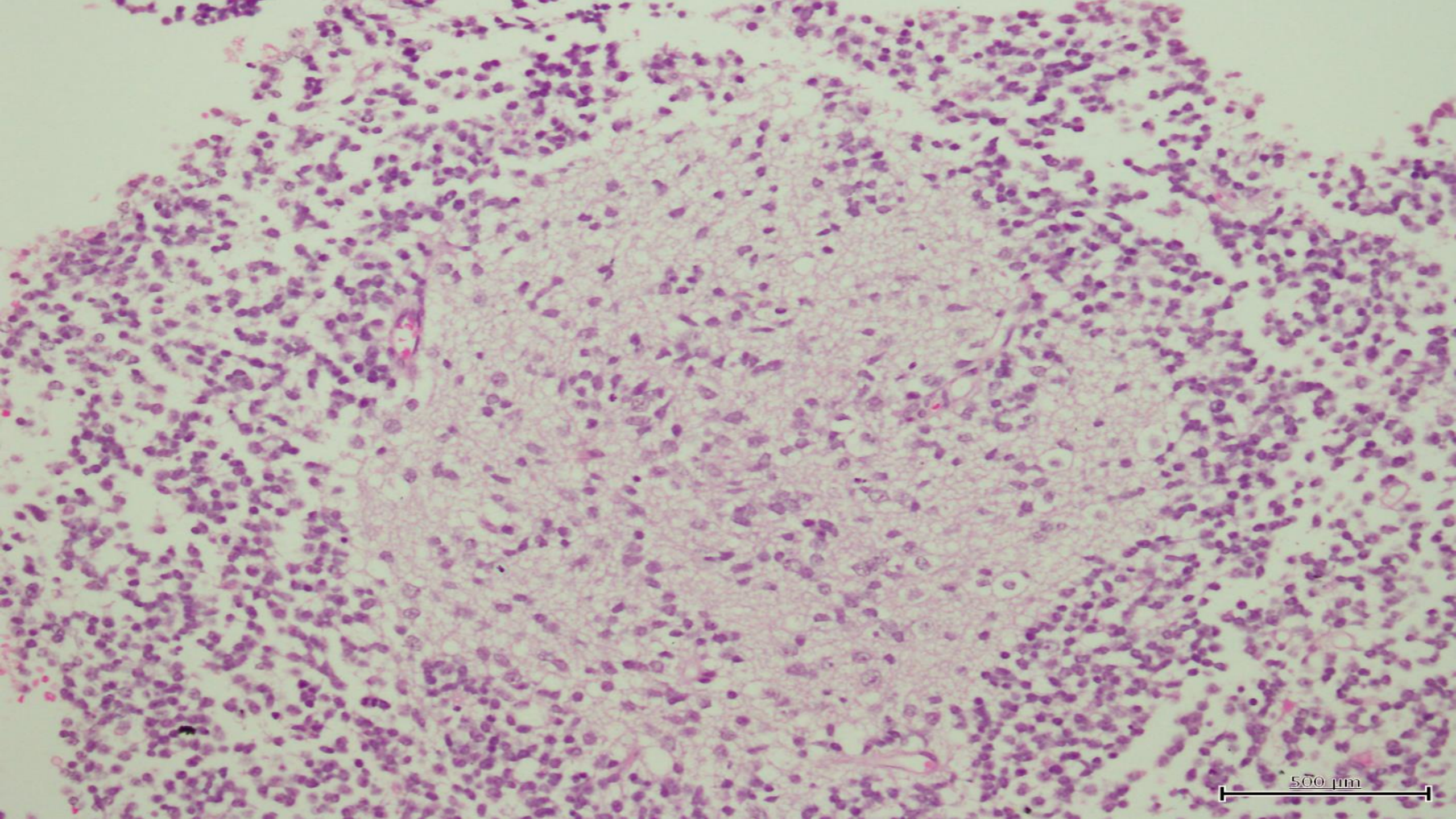
P5009.09. A 2.5 year old female. Presented with unsteady gait, squint, nystagmus, 6th nerve palsy, sluggish pupil of 6 months duration. Posterior fossa mass

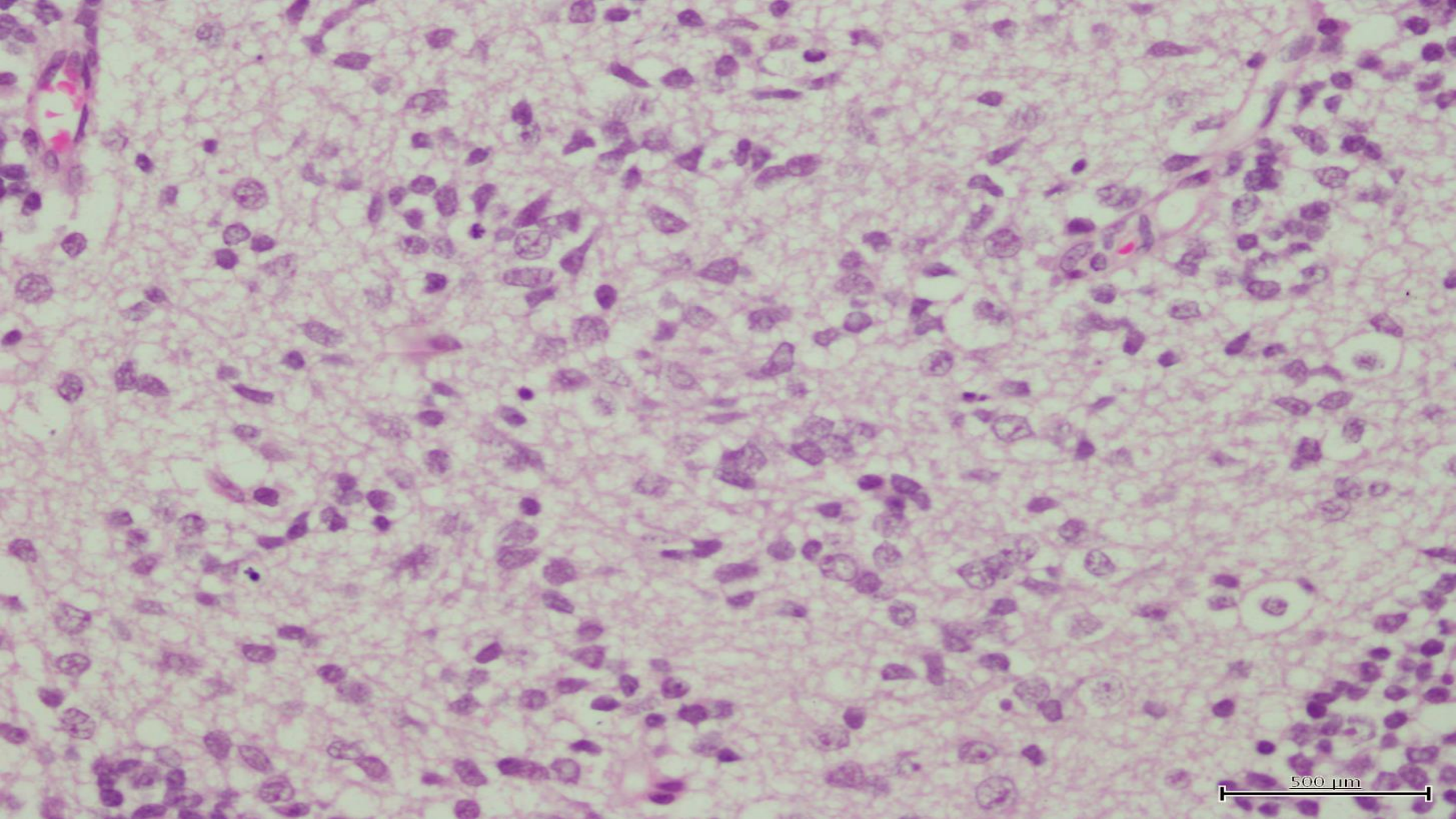



500 µm

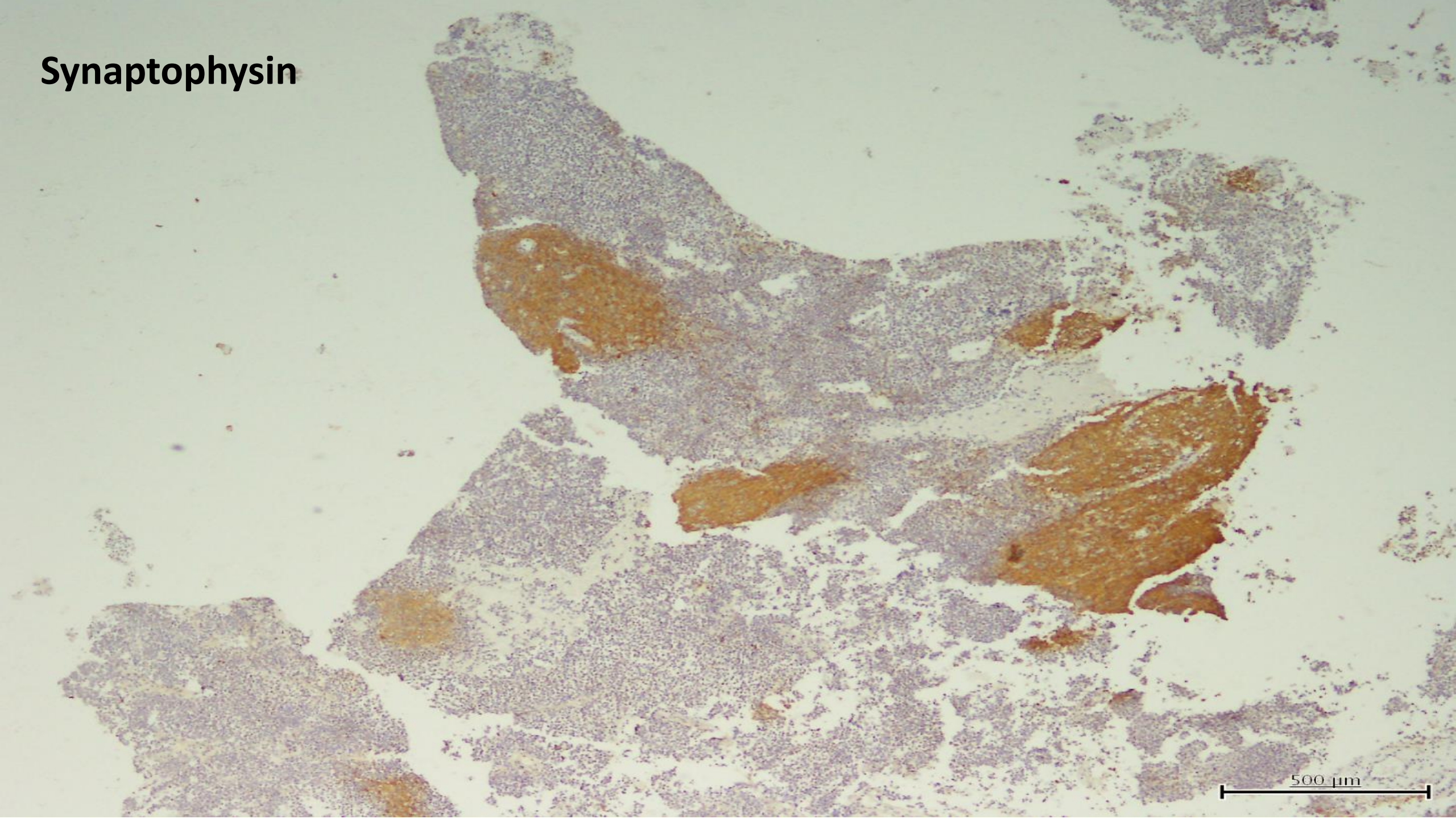

500 µm

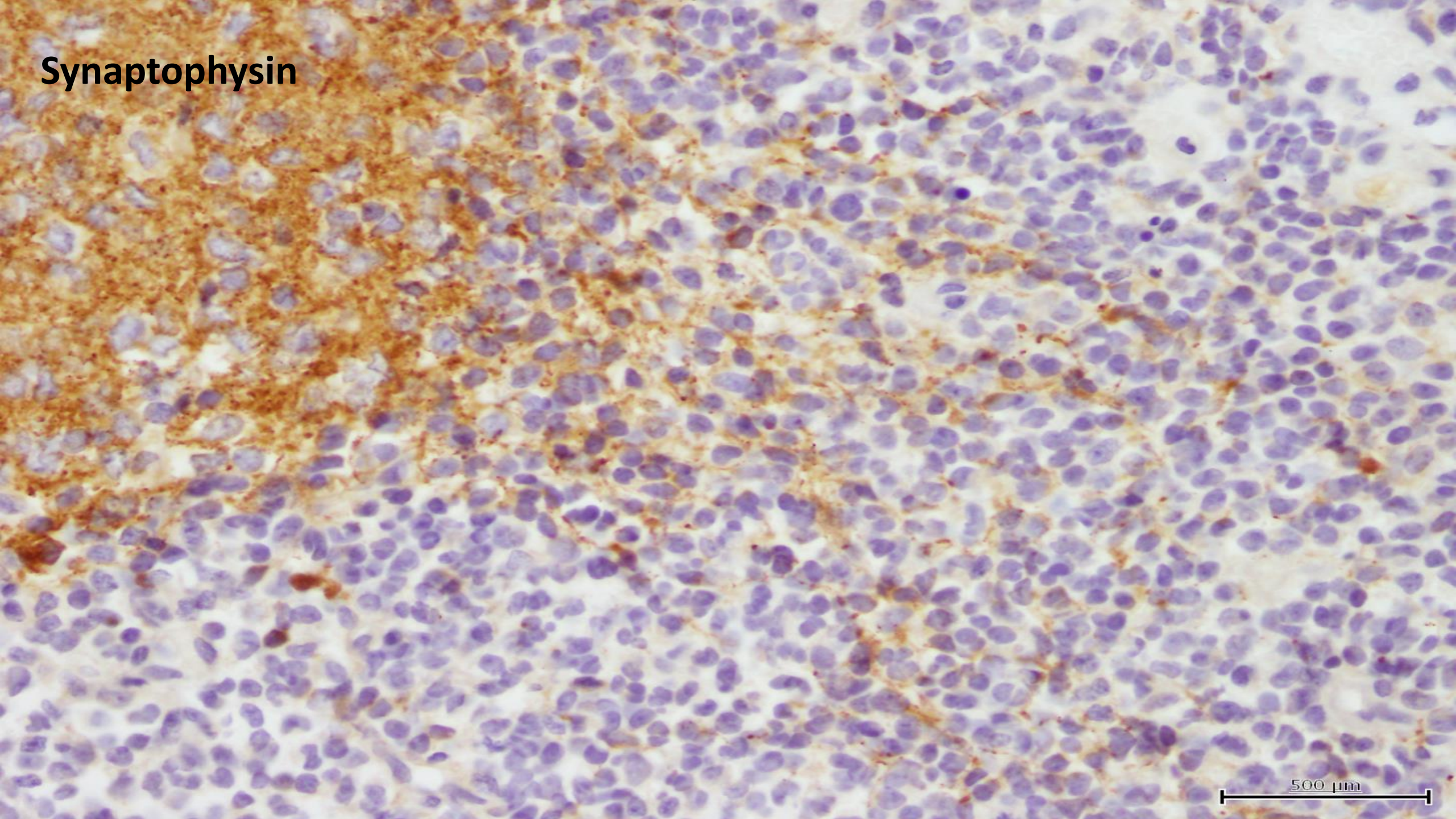

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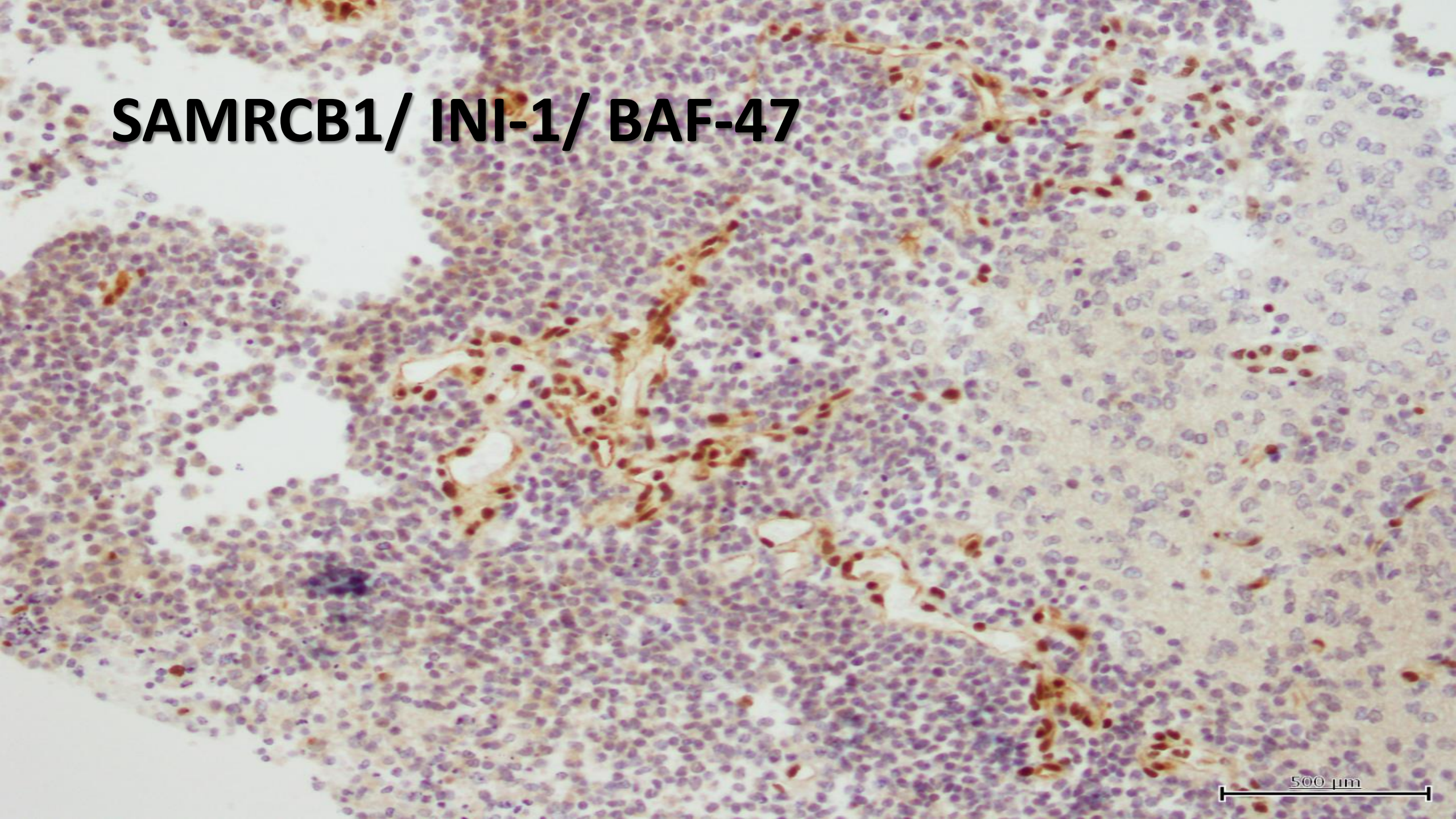

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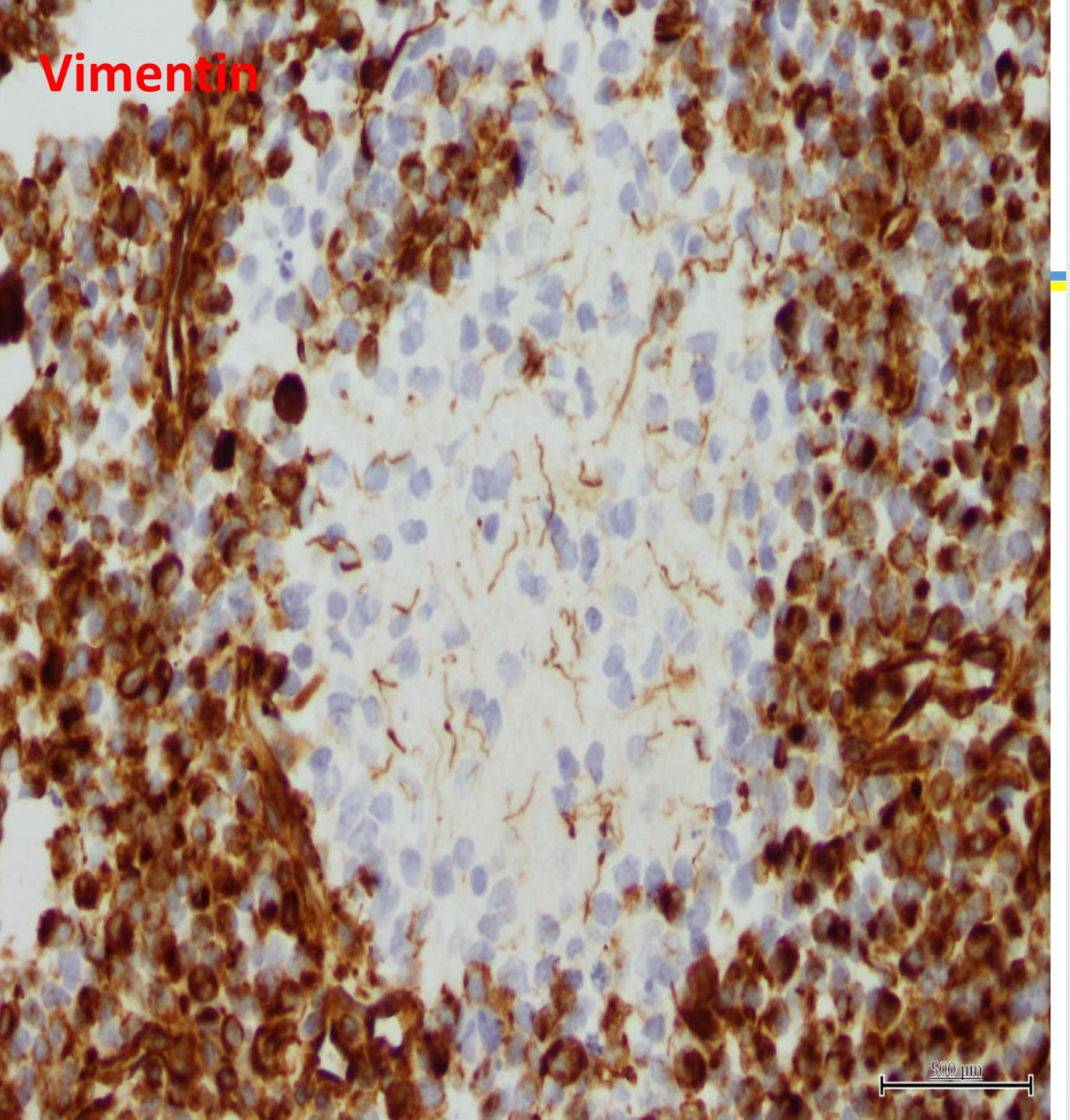

500 µm

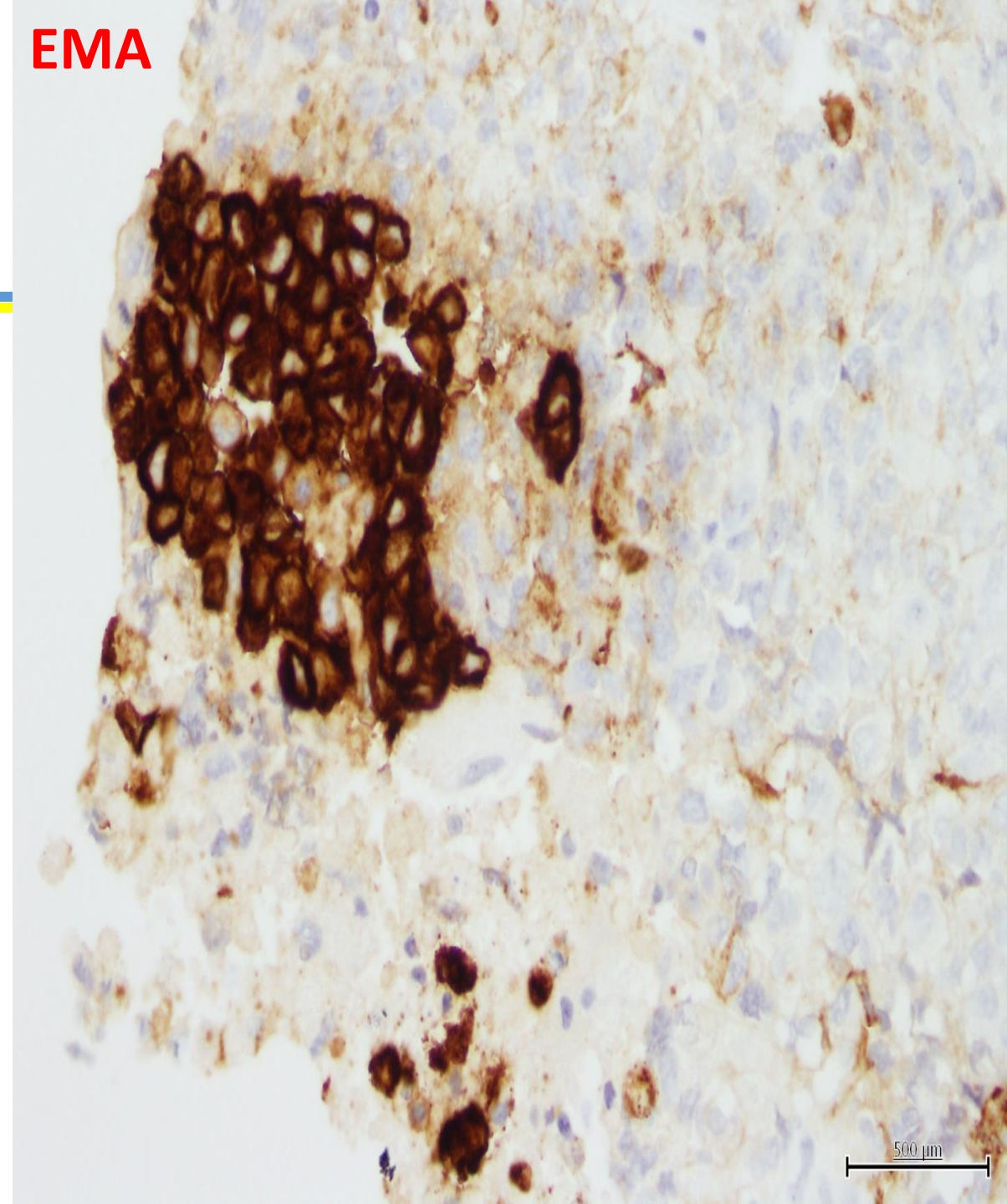
Synaptophysin

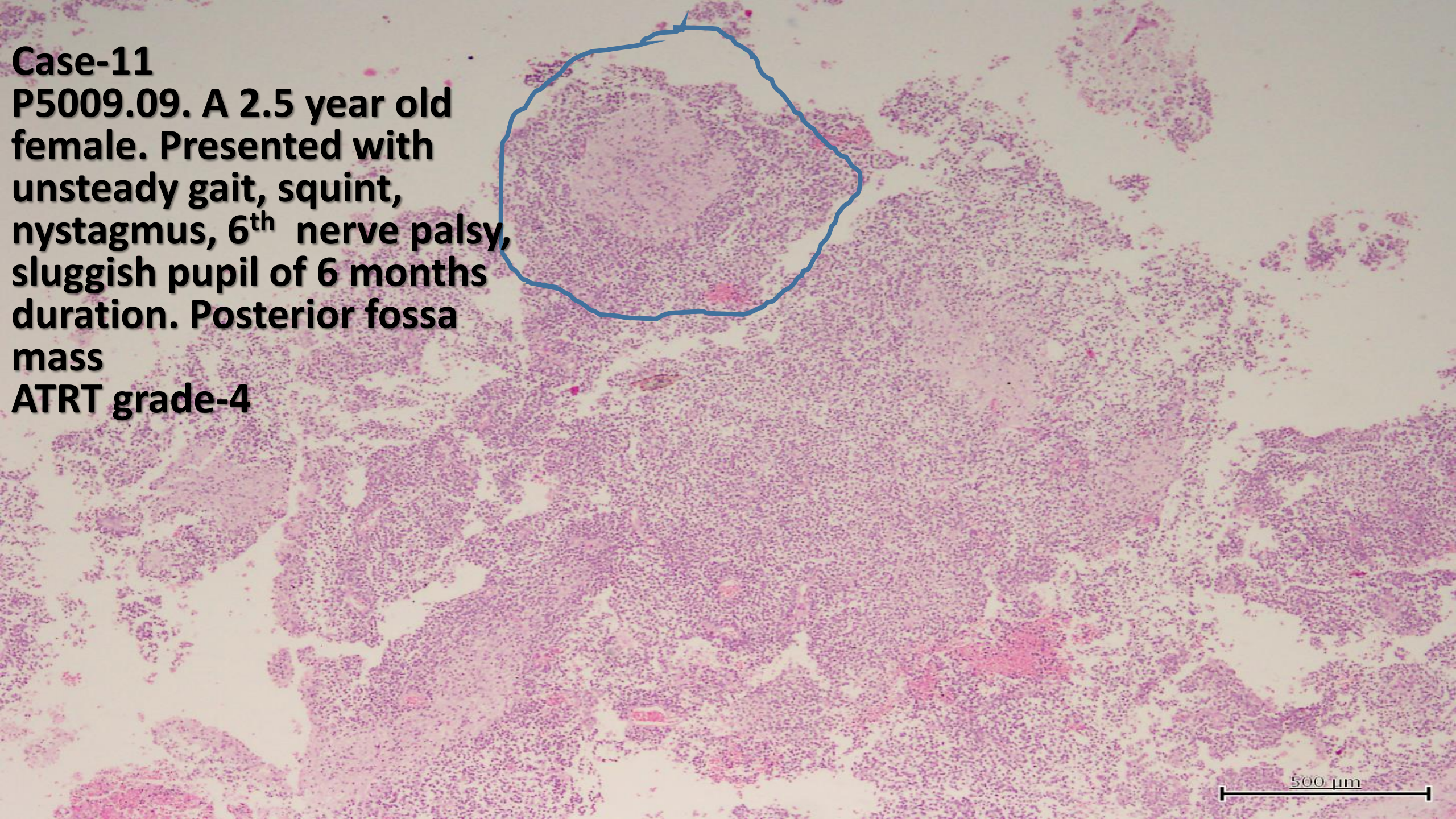



Synaptophysin
500 µm

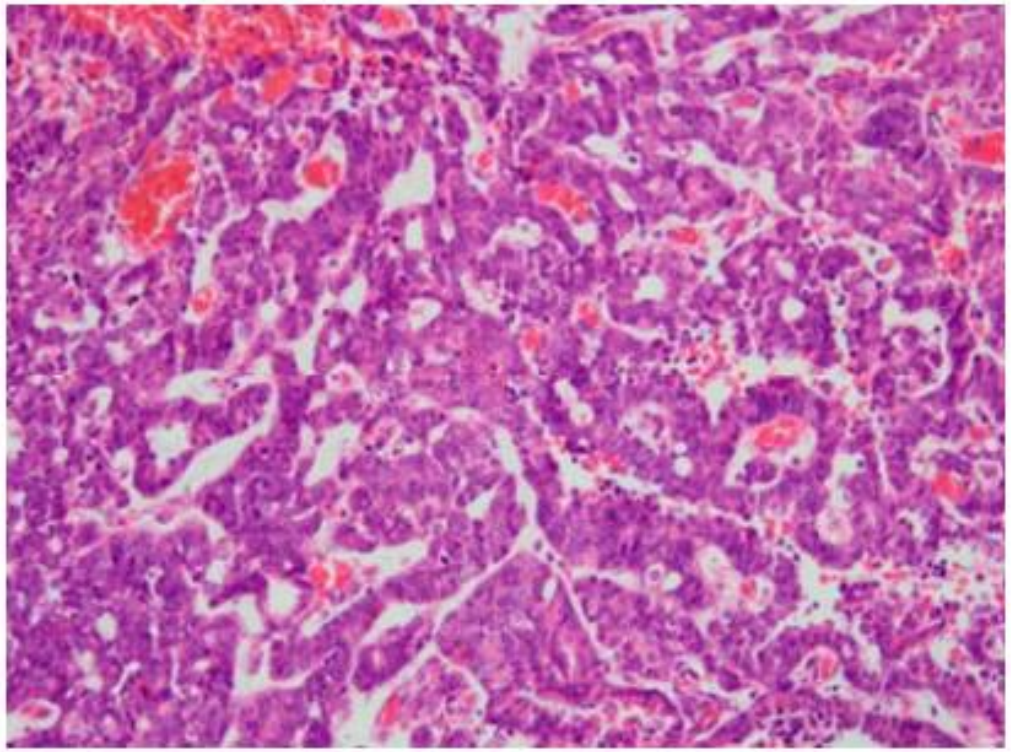

SAMRCB1/ INI-1/ BAF-47
500 µm

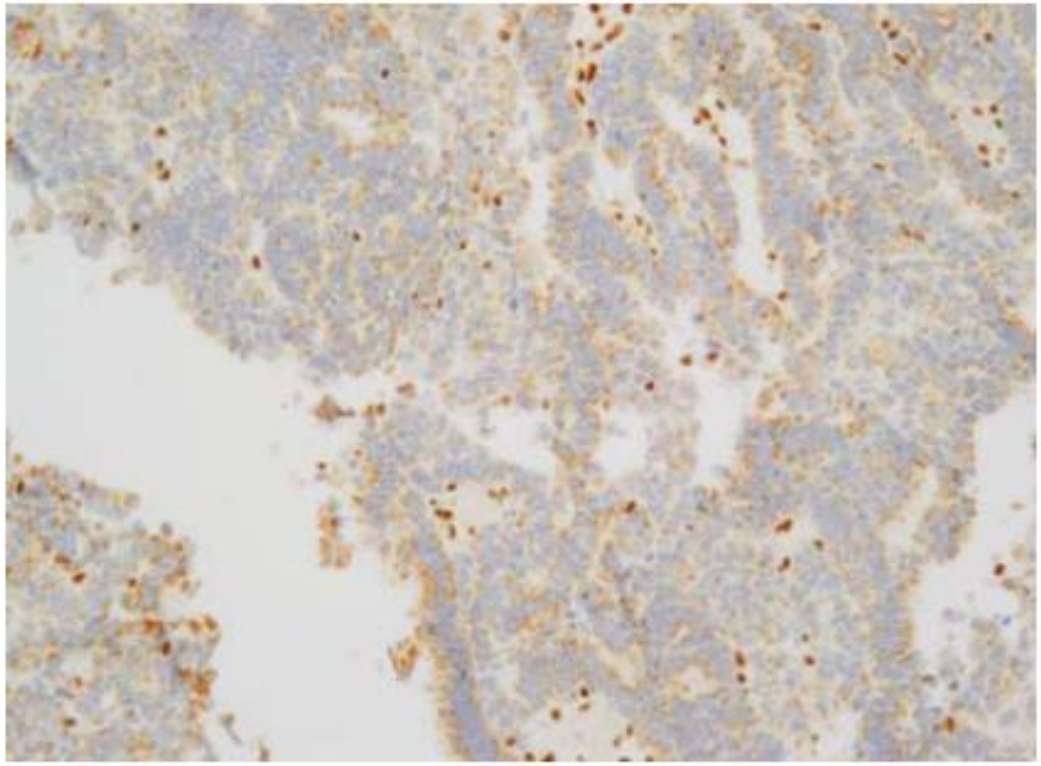

Vimentin
500 µm


EMA
500 µm


Case-11
P5009.09. A 2.5 year old female. Presented with unsteady gait, squint, nystagmus, 6th nerve palsy, sluggish pupil of 6 months duration. Posterior fossa mass
ATRT grade-4
500 µm

Embryonal tumor
Cribriform neuroepithelial tumor (CRINET)

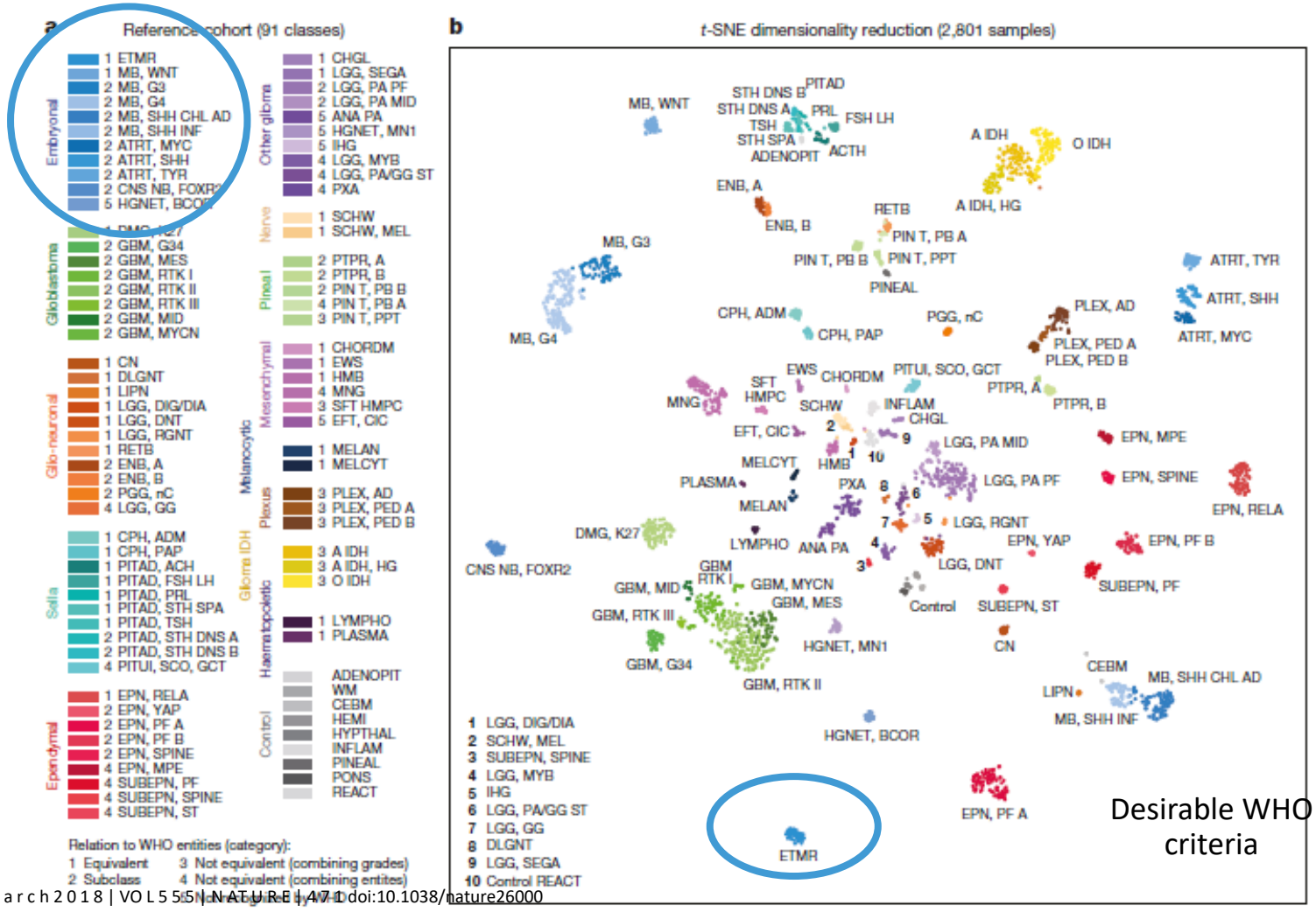




CRINET is a ventricular tumor characterized by histology and SMARCB1 mutation and INI1-loss
Behavior is still not very certain at this stage

8. ATRT should be confirmed with SMARCB1/ INI-1/ BAF47 immunostain

Methylation Profile
Embryonal tumors- ETMR



Desirable WHO criteria

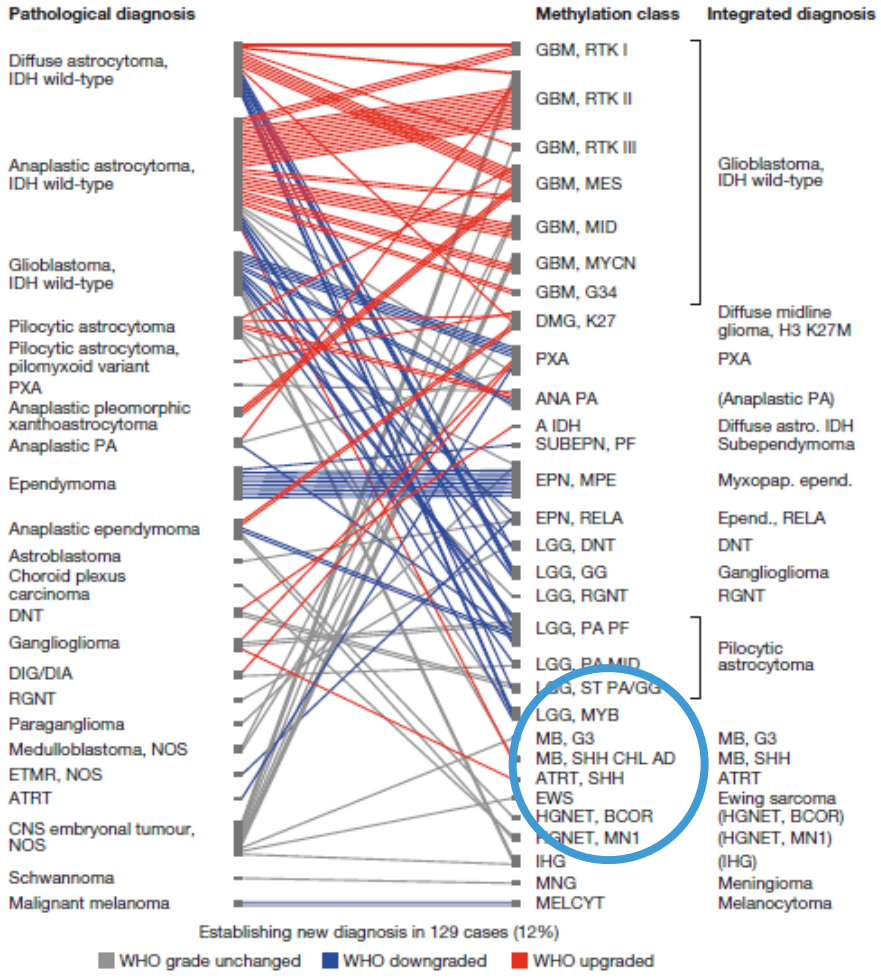
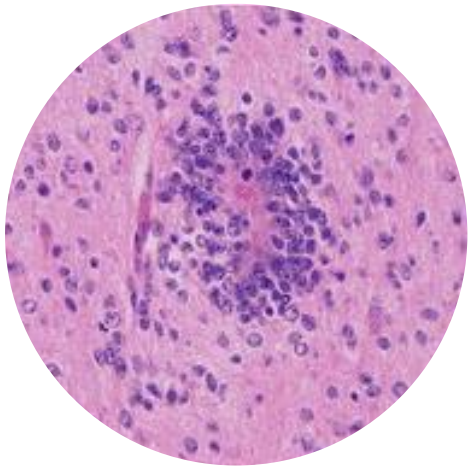


Figure 4 | Reassessment of discrepant cases and establishment of

Case Presentation: Embryonal Tumor with Unusual Stromal Desmoplasia





Background

- Embryonal tumors of the central nervous system (CNS) are heterogenous high-grade neoplasms predominantly affecting the pediatric population.

- Pathologic and molecular stratification is critical in determining the type and intensity of treatment.

Case Report

- A 3-year-old girl.
- The child complained of seizures, vomiting and headache.
- MRI showed a huge heterogenous left frontal lesion infiltrating the skull with extracranial soft tissue extension.

T1 W Images:

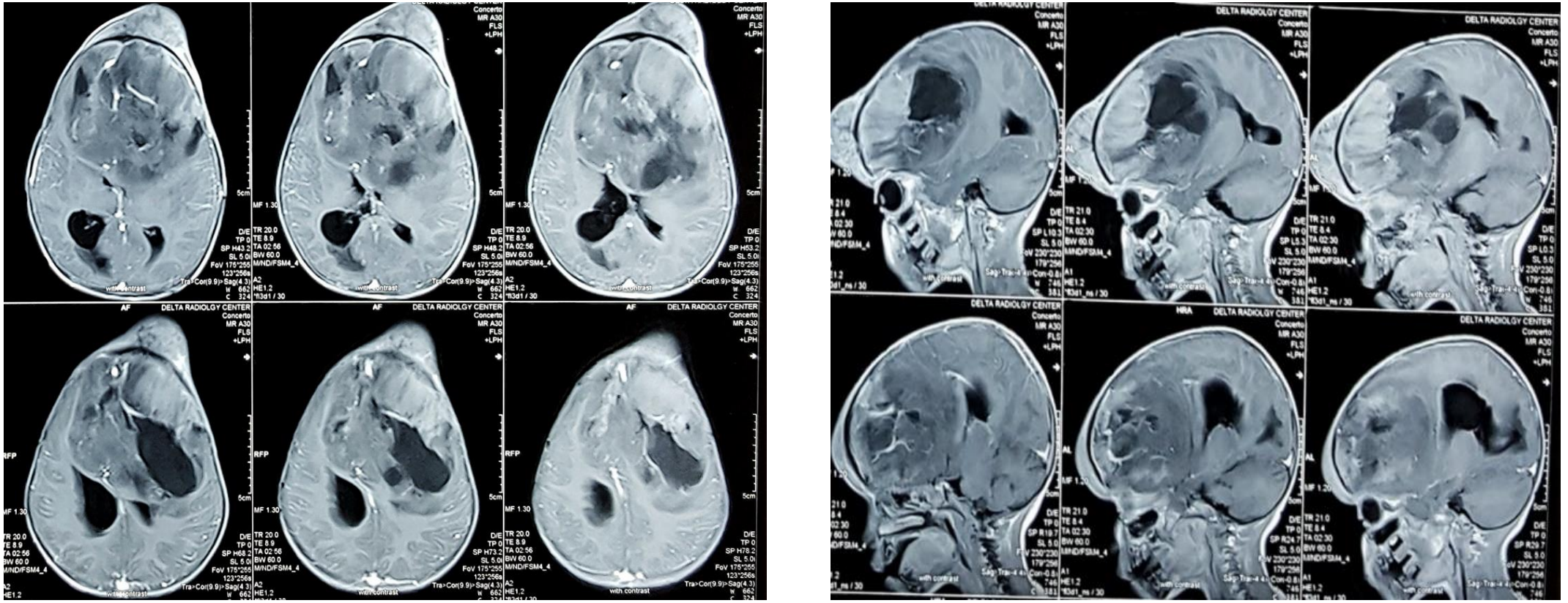
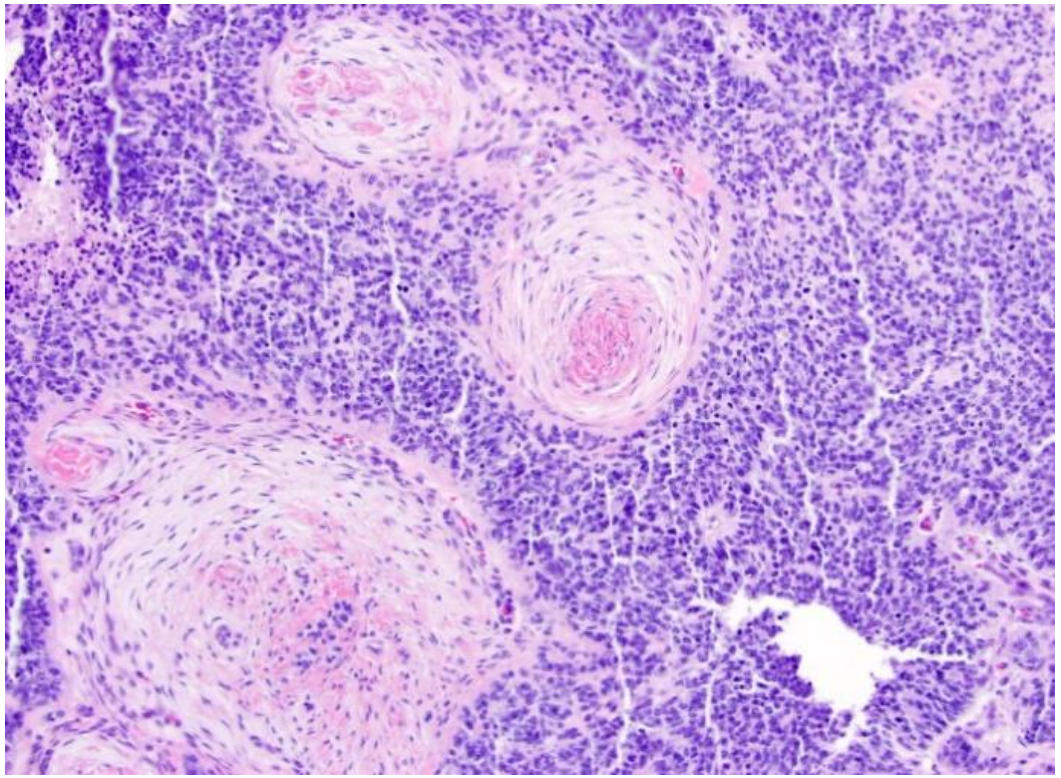
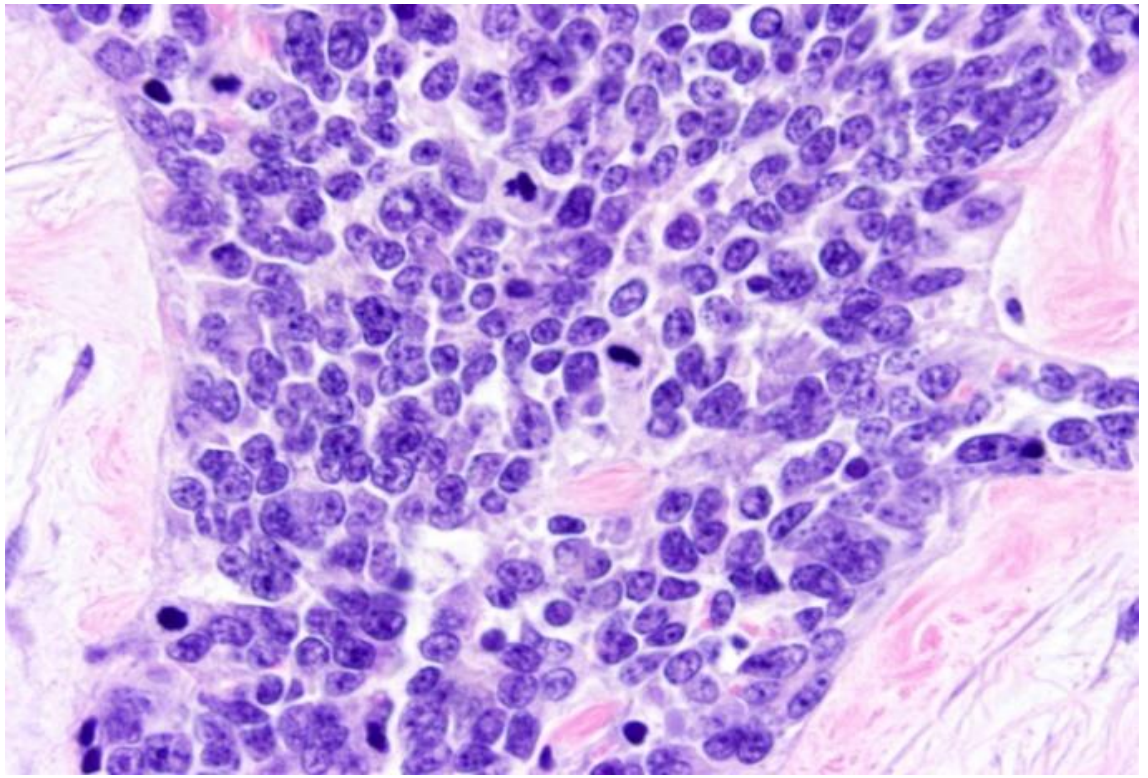


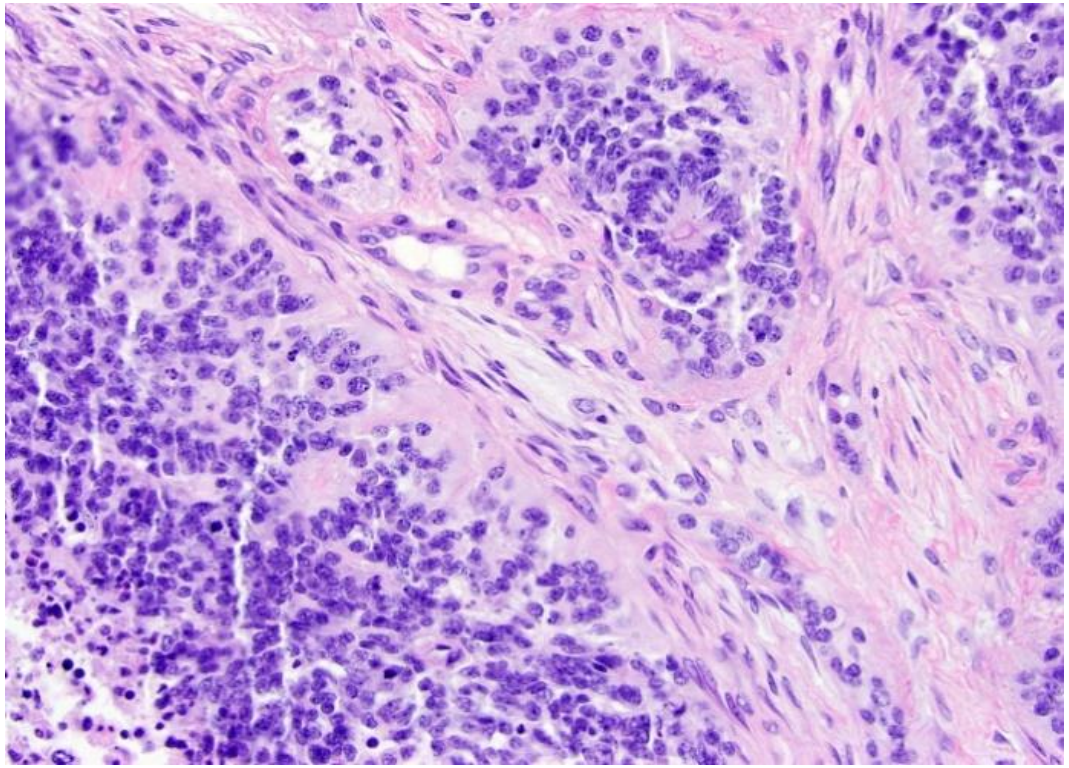
Fig. 1. (a) T1W transverse image showing a heterogeneous mass lesion in the left frontal region with solid and cystic components. (b) T1W Axial image showing heterogeneous enhancement of the lesion with extracranial extension

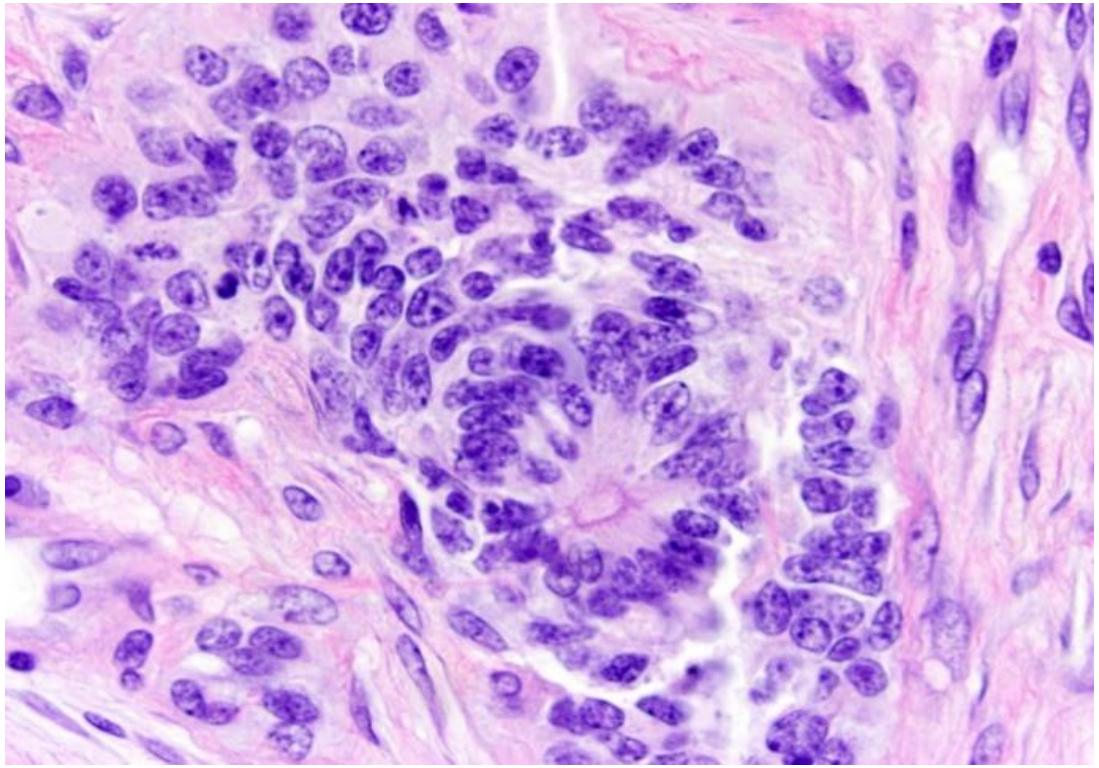
Histopathologic Examination



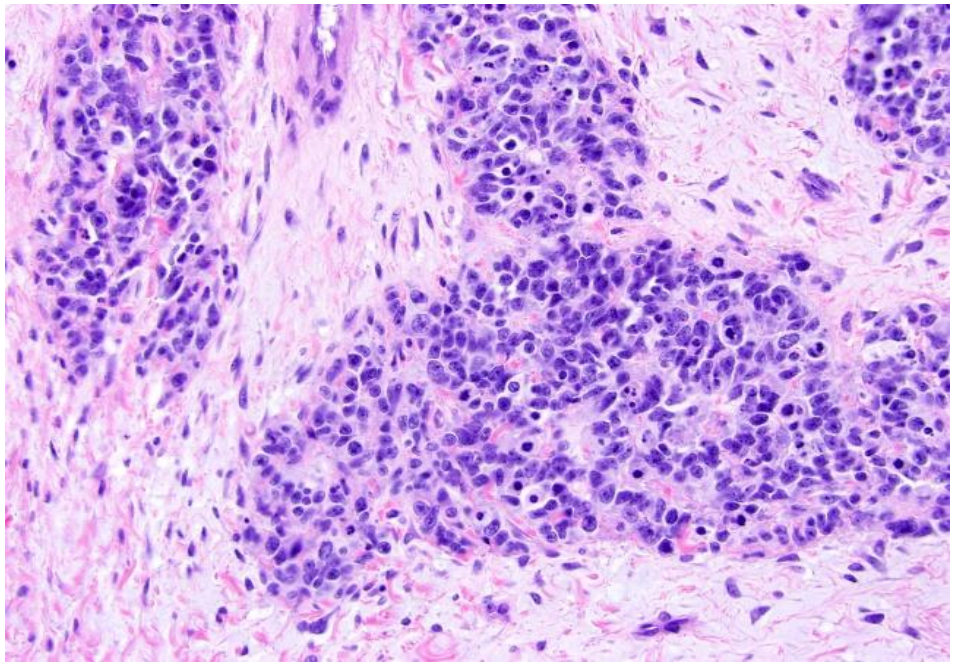


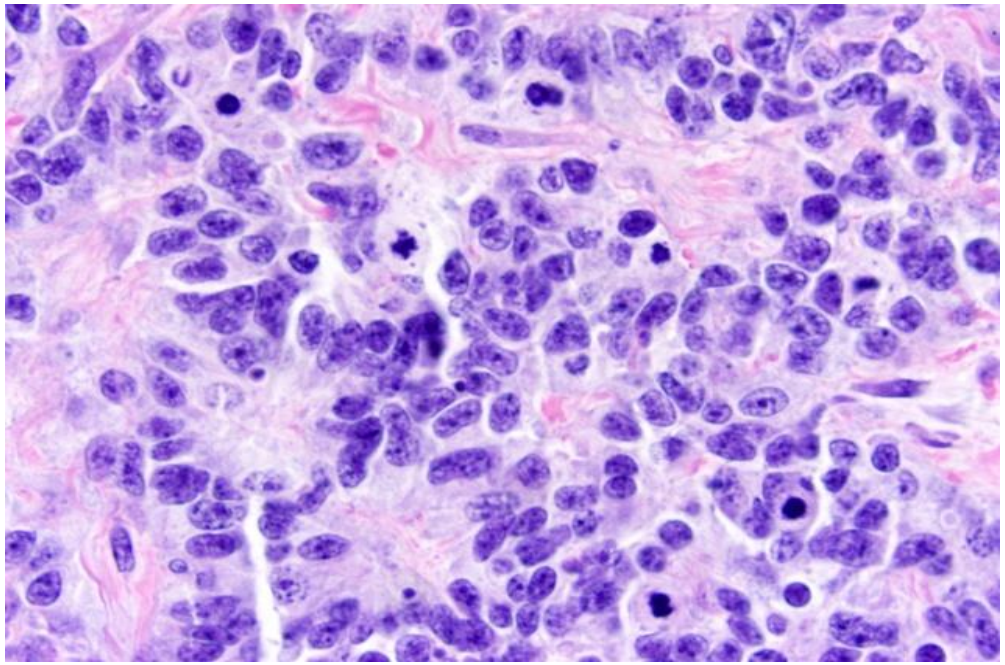
Histopathologic Examination



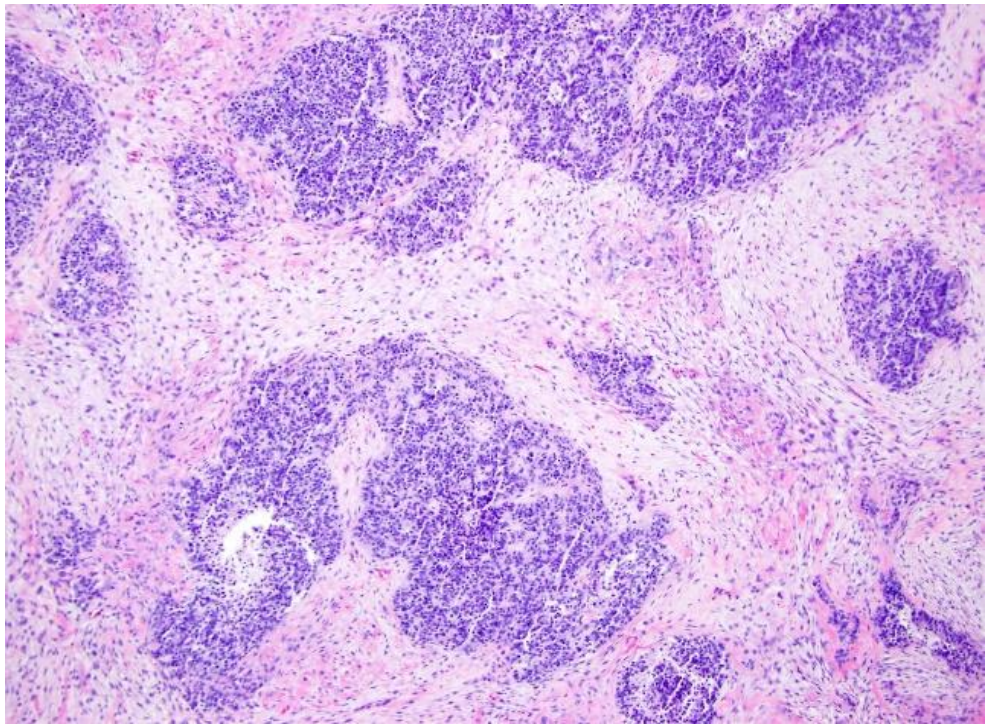


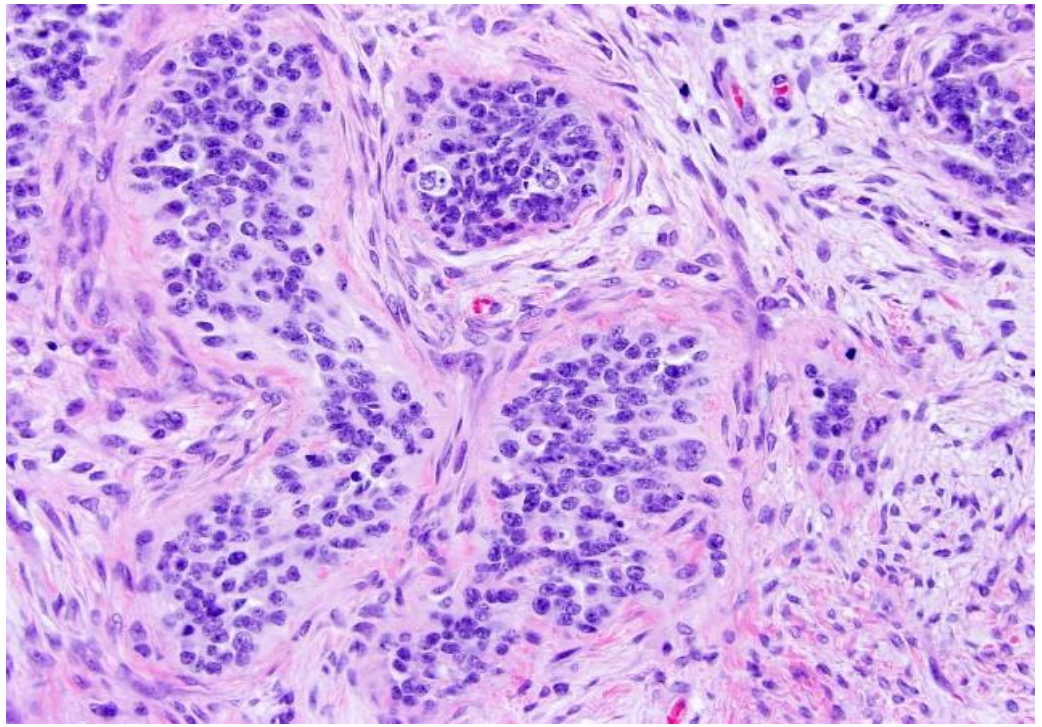
Histopathologic Examination



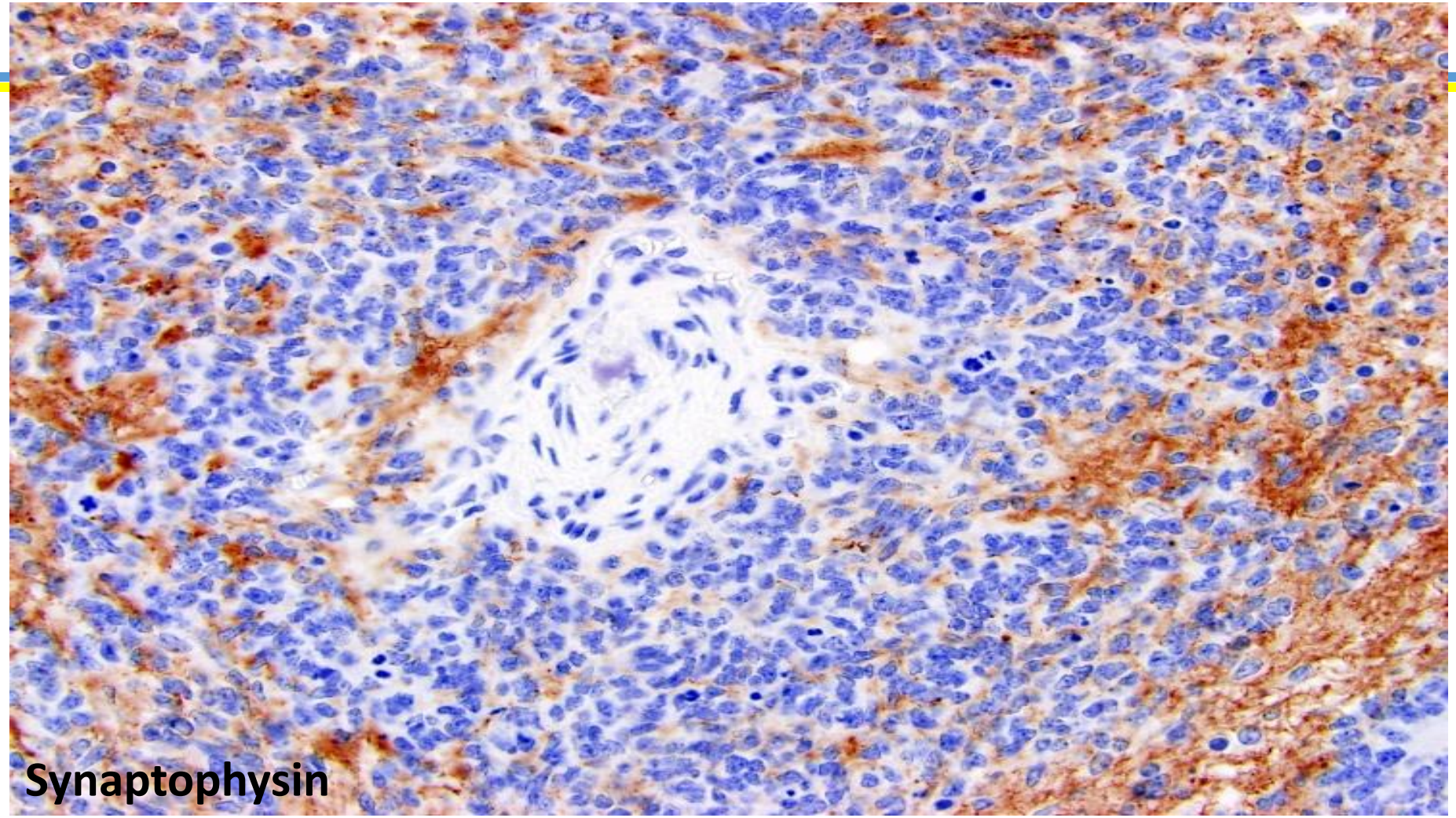


Histopathologic Examination

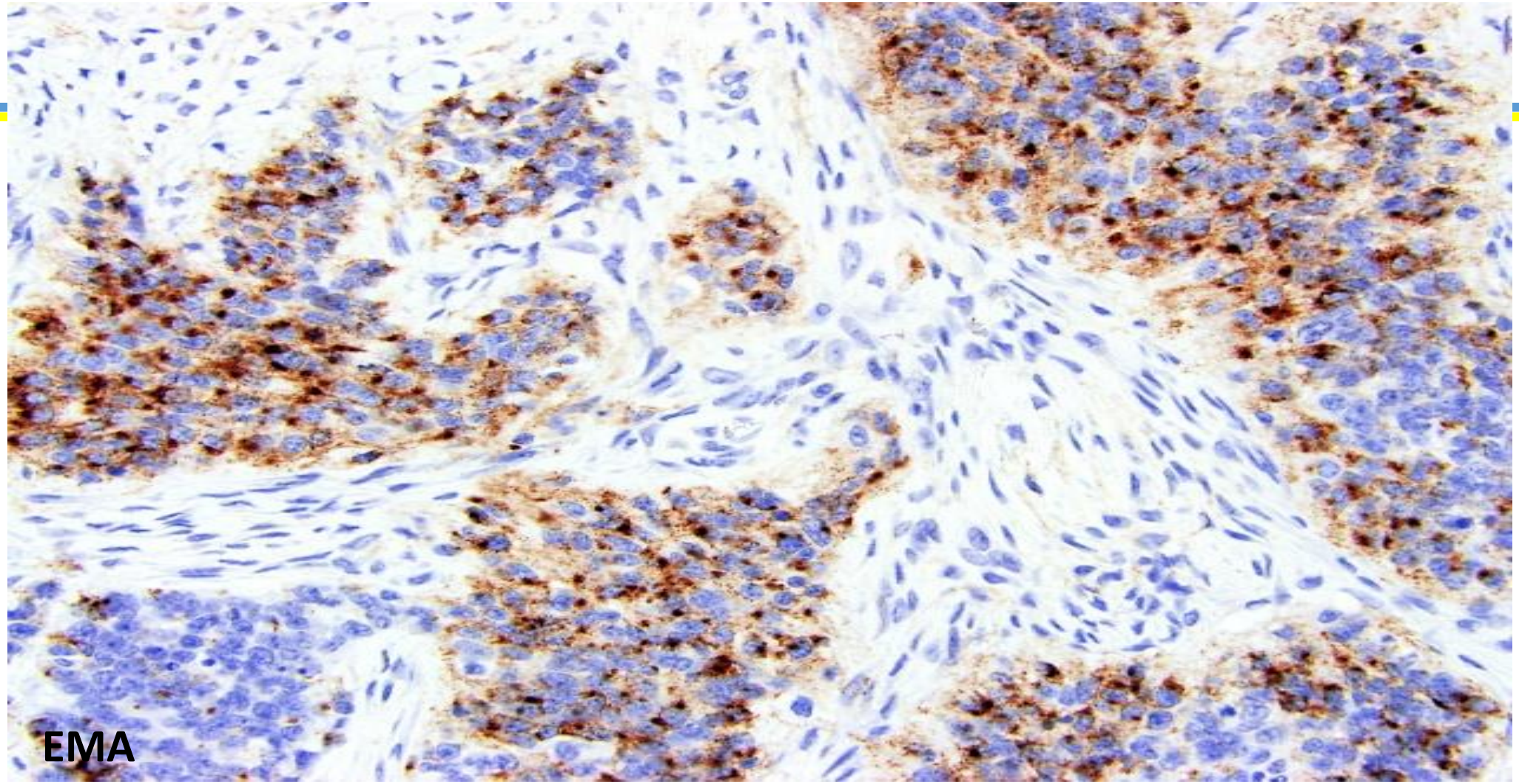




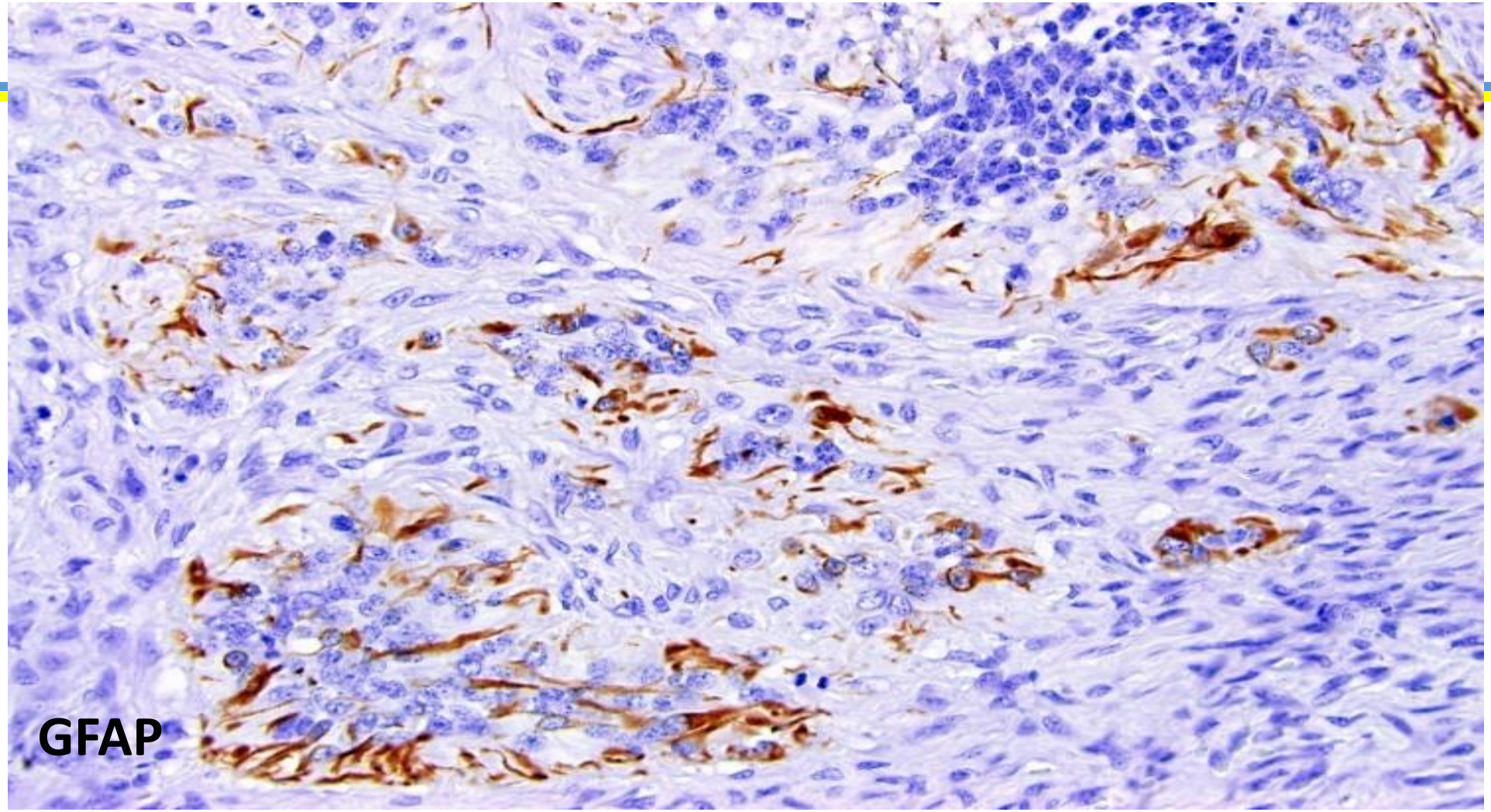
Immunohistochemical Results



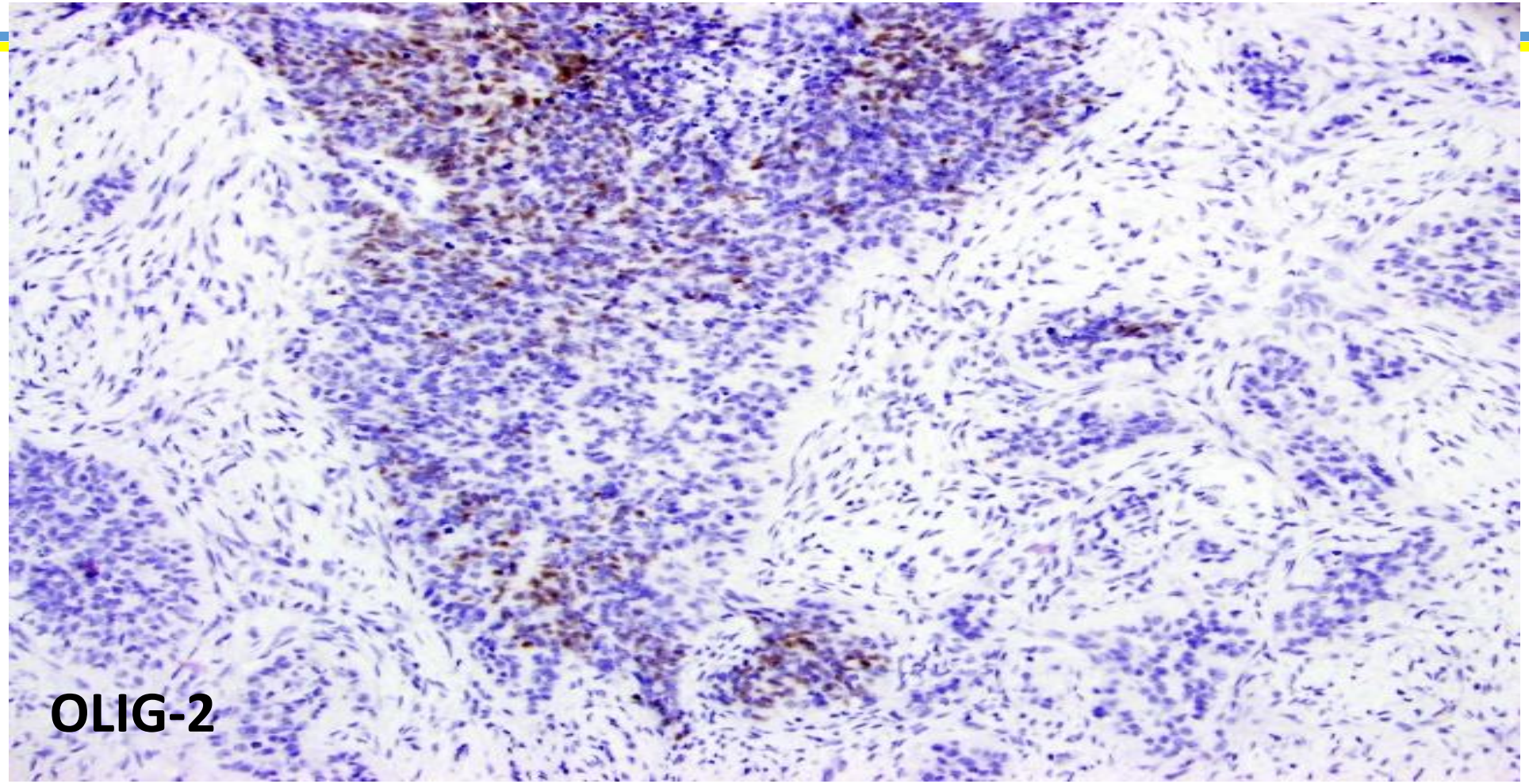
Immunohistochemical Results



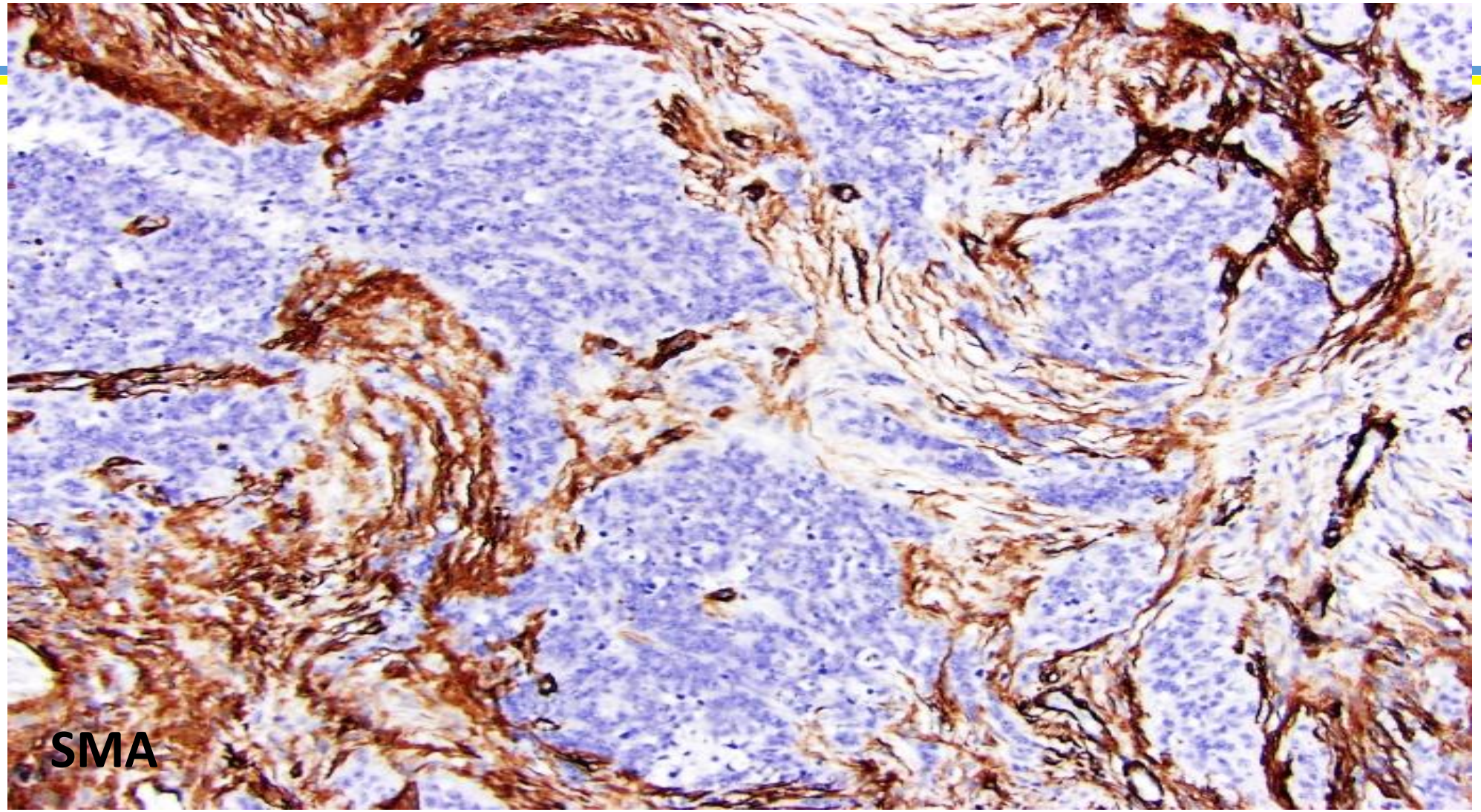
Immunohistochemical Results



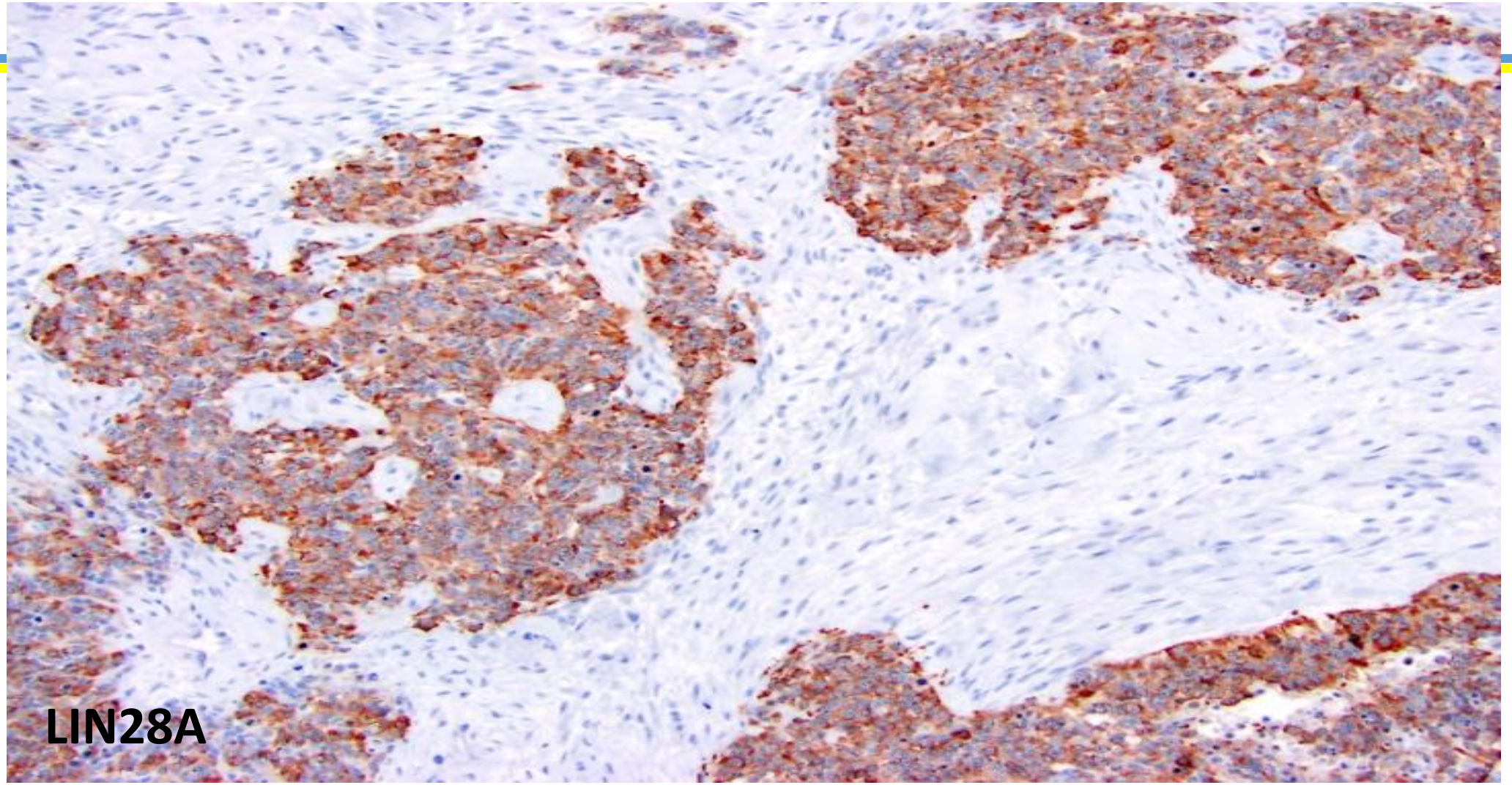
Immunohistochemical Results



Immunohistochemical Results



Immunohistochemical Results



Molecular Testing Results (UC, SF)

- Amplification of the chromosome 19q13.42 microRNA cluster (C19MC), with breakpoints of the amplification immediately preceding the C19MC locus at the 5' boundary and within the TTYH1 gene at the 3' boundary.

- The other chromosomal copy number changes in the tumor were losses of interstitial 5q and portions of 10q.

Diagnosis

Integrated diagnosis of ETMR, C19MC-Altered, WHO Grade 4, with Extracranial Extension.

ETMR

- In 2000, Eberhart *et al*. described a unique embryonal tumor for which he coined pediatric neuroblastic tumor containing abundant neuropil and ependymoblastic rosettes (PNTANTR).

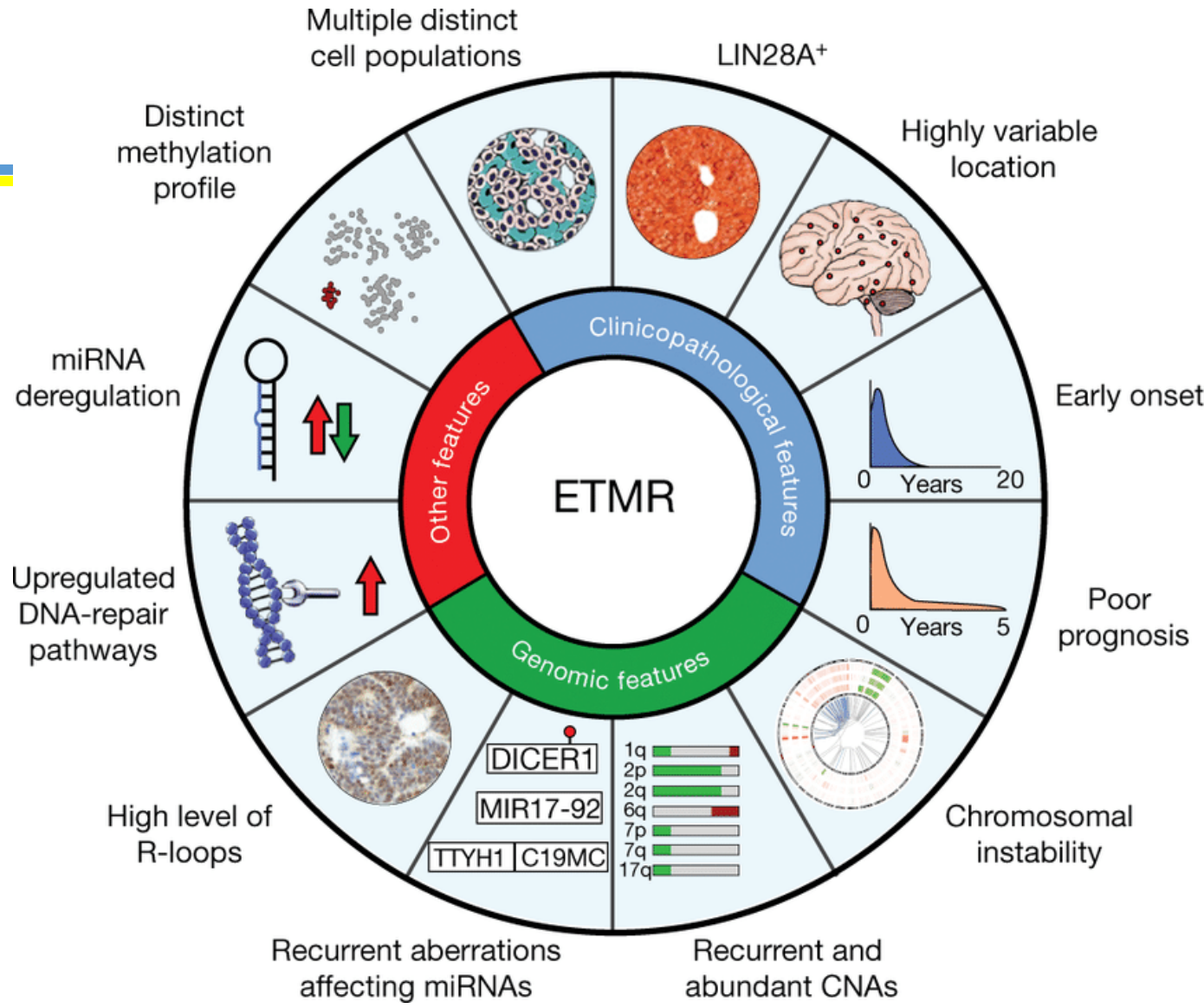
- This tumor showed a biphasic pattern with undifferentiated cells containing small hyperchromatic nuclei, and clusters of multilayered rosettes (ependymoblastic and perivascular) distributed in a paucicellular fibrillary neuropil background.

Epidemiology

- Mostly < 4 years of age
- Equal in males and females

Location

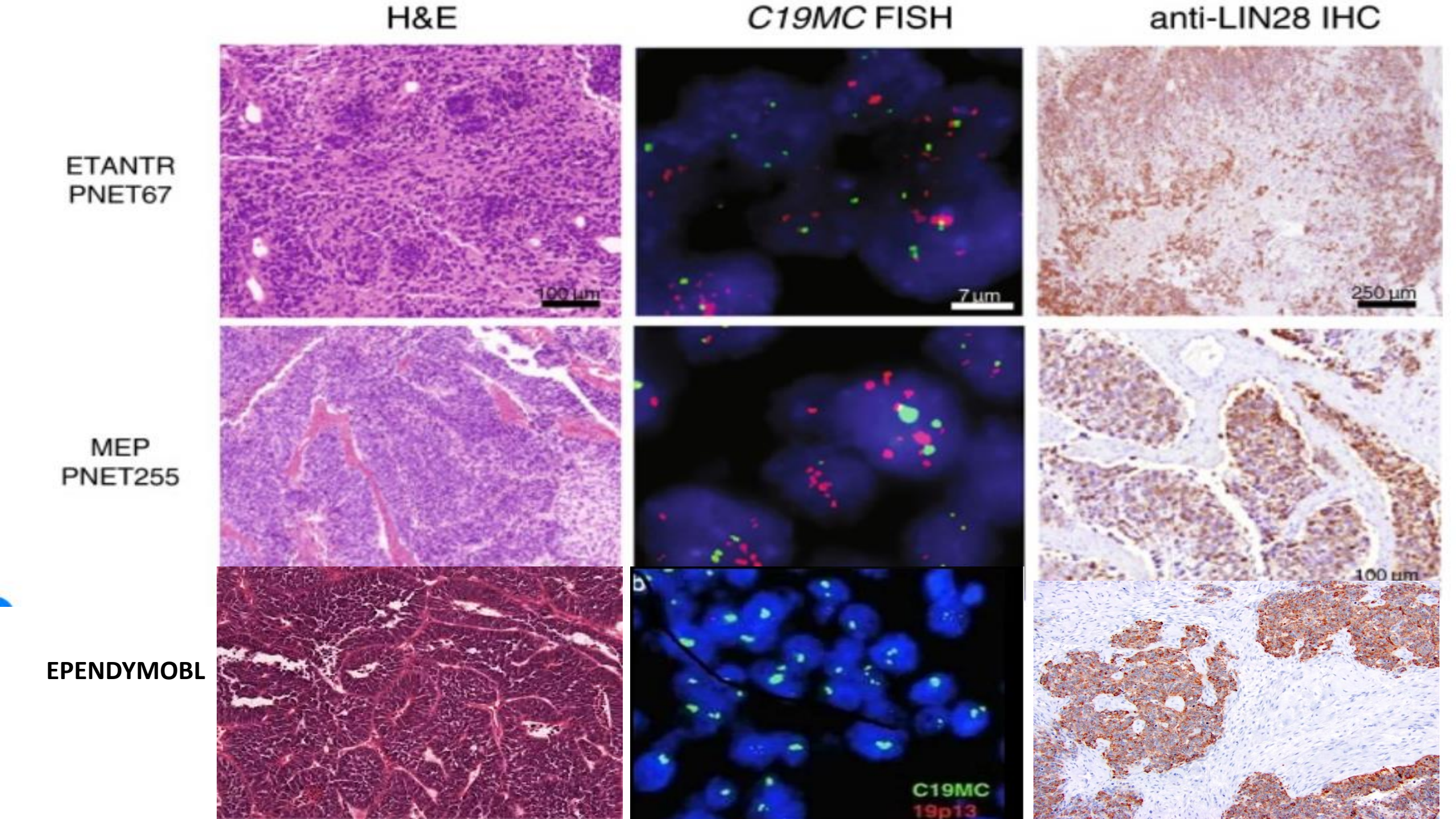
- Supratentorial in both hemispheres (70%)
- Infratentorial in cerebellum and brain stem (30%)



ETMR

- Prior to the reclassification of ETMR as a single entity, three distinct tumors, namely, embryonal tumor with abundant neuropil and true rosettes (ETANTR), ependymoblastoma (EBL) and medulloepithelioma (MEPL) were recognized.

- Recent studies showed that all the three entities have multilayered rosettes on morphology, sharing a common amplification of the C19MC locus at the chromosome 19q13.42 by fluorescence in situ hybridization, and highly specific immunohistochemical staining for LIN28A rendered their reclassification as a single entity.


H&E
C19MC FISH
anti-LIN28 IHC
ETANTR
PNET67
100 µm
7 µm
250 µm
MEP
PNET255
100 µm
EPENDYMOBL
C19MC
19p13

ETMR

- Desmoplasia may be a defense mechanism used by the body to wall off tumors and limit the invasive growth of the tumor cells.

- The presence of desmoplasia is an unusual histologic finding in ETMR and is possibly explained by the tumor invasion into dura, skull bone and the surrounding skeletal muscles and subcutaneous fat.

ETMR

- Local recurrence is frequent and widespread dissemination (CSF) has been observed.

- ETMR, C19MC-altered behaves very aggressively and the average survival of 12 months.

Differential Diagnoses

- ATRT (EMA+ve, INI1-ve, Some cases F+ve LIN28A).

Differential Diagnosis

- ATRT (EMA+ve, INI1-ve, Some cases F+ve LIN28A).
- Medulloblastoma (+Synaptophysin, -ve LIN28A).

Differential Diagnosis

- ATRT (EMA+ve, INI1-ve, Some cases LIN28A F+ve).
- Medulloblastoma (Synaptophysin +ve, LIN28A-ve).
- Ependymoma (GFAP, EMA+ve, LIN28A, Synatophysin-ve).

Differential Diagnosis

- ATRT (EMA+ve, INI1-ve, Some cases F+ve LIN28A).
- Medulloblastoma (+Synaptophysin, -ve LIN28A).
- Ependymoma (GFAP, EMA+ve, -ve LIN28A, Synatophysin).
- CNS Emryonal tumor, NOS.

Differential Diagnosis

- ATRT (EMA+ve, INI1-ve, Some cases F+ve LIN28A).
- Medulloblastoma (+Synaptophysin, -ve LIN28A).
- Ependymoma (GFAP, EMA+ve, -ve LIN28A, -ve Synatophysin).
- CNS Emryonal tumor, NOS.
- Pediatric high grade glioma (GFAP +ve, LIN28A –ve).

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Case Report

Embryonal tumor with multilayered rosettes (ETMR) with extracranial extension: A case report and review of literature

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ABSTRACT

Embryonal tumor with multilayered rosettes (ETMR) is an aggressive central nervous system (CNS) embryonal tumor with alterations in the chromosome 19q13.42 microRNA cluster (C19MC) and resultant overexpression of the LIN28A protein. Although the prior world health organization (WHO) recognized 3 distinct histopathological entities-embryonal tumour with abundant neuropil and true rosettes (ETANTR), ependymoblastoma, and medulloepithelioma, it now combines most of these under the rubric of ETMR, C19MC-altered based on recent studies indicating a common molecular profile and clinical course.

We present a case of ETMR located in the left frontal lobe in a 3-year-old girl with extracranial extension and an associated extensive desmoplastic stromal reaction. The child complained of seizure, vomiting and headache. MRI showed a huge heterogenous left frontal mass infiltrating the skull with extracranial soft tissue infiltration. The diagnosis of ETMR was established based on histopathologic, immunohistochemical and molecular features.

Co-Authors

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. Khaled El Bahy, Neurosurgery Department, Faculty of Medicine, Ain Shams University.

Conclusion

- Multilayered rosettes are a useful clue to histologic diagnosis.

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- The immunohistochemical staining for LIN28A and the molecular alterations are considered a major helping tool.

Conclusion

- Multilayered rosettes are a useful clue to histologic diagnosis of ETMR.
- The immunohistochemical staining for LIN28A and the molecular alterations (C19MC) are considered a major helping tool.
- Desmoplastic stroma can occur as a very rare and unusual histologic finding in ETMR due to tumor invasiveness with extracranial extension.


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