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Pediatric Gliomas: A Survival Guide

Recent Advances in Diagnosis and Molecular Characteristics of Astrocytomas

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Professor of Pathology
Neuropathology Division
UCSF School of Medicine

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Objectives

1. LEARN THE GENETIC ALTERATIONS IN PILOCYTIC ASTROCYTOMA, ITS UNUSUAL HISTOLOGICAL FEATURES AND RECOGNIZE THE AGGRESSIVE VARIANT
2. UNDERSTAND THE GENETIC FEATURE AND KEY HISTOLOGIC FEATURES IN PXA-PLEOMORPHIC XANTHOASTROCYTOMA
3. DEFINE KEY ADVANCES IN THE MOLECULAR UNDERSTANDING OF INFILTRATING ASTROCYTOMAS IN CHILDREN

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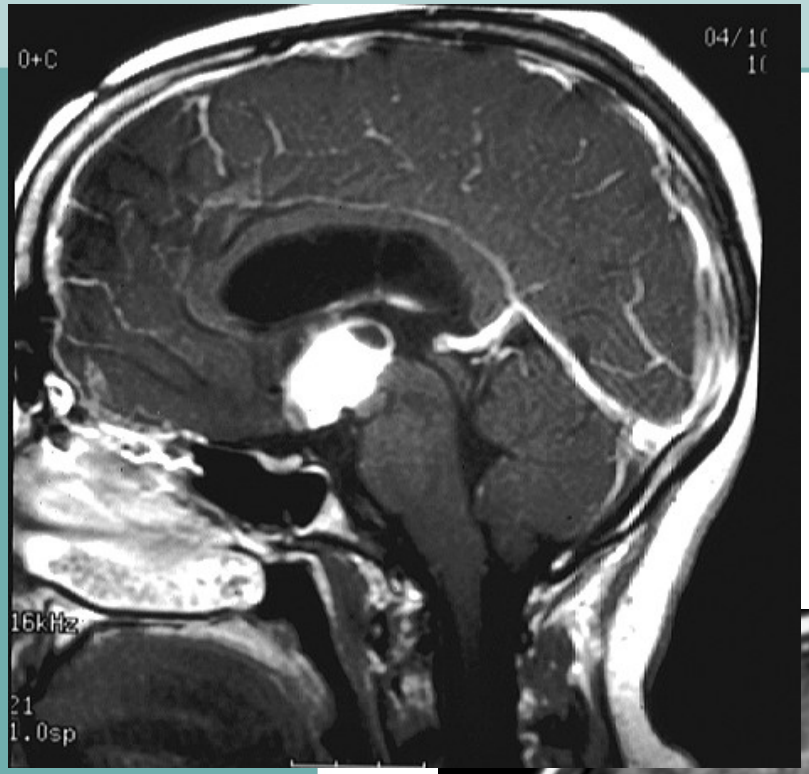
PILOCYTIC ASTROCYTOMA

- WHO GRADE I NEOPLASM
- SURGICAL DISEASE
  - Gross total resection often curative
  - Some tumors regress or remain dormant for long periods even after subtotal resection
  - Exceptional tumors show malignant transformation, and some do so after radiation treatment
  - Some atypical histological features are difficult to interpret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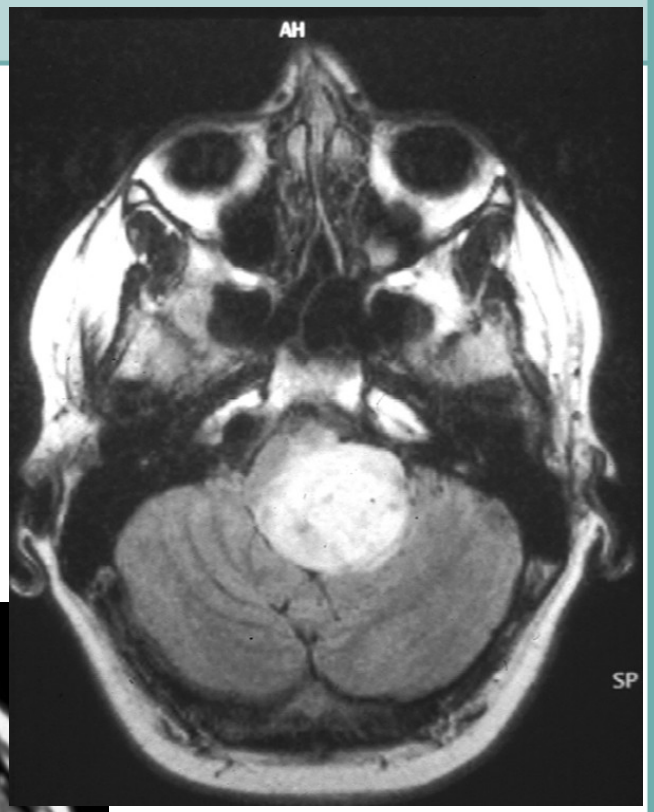
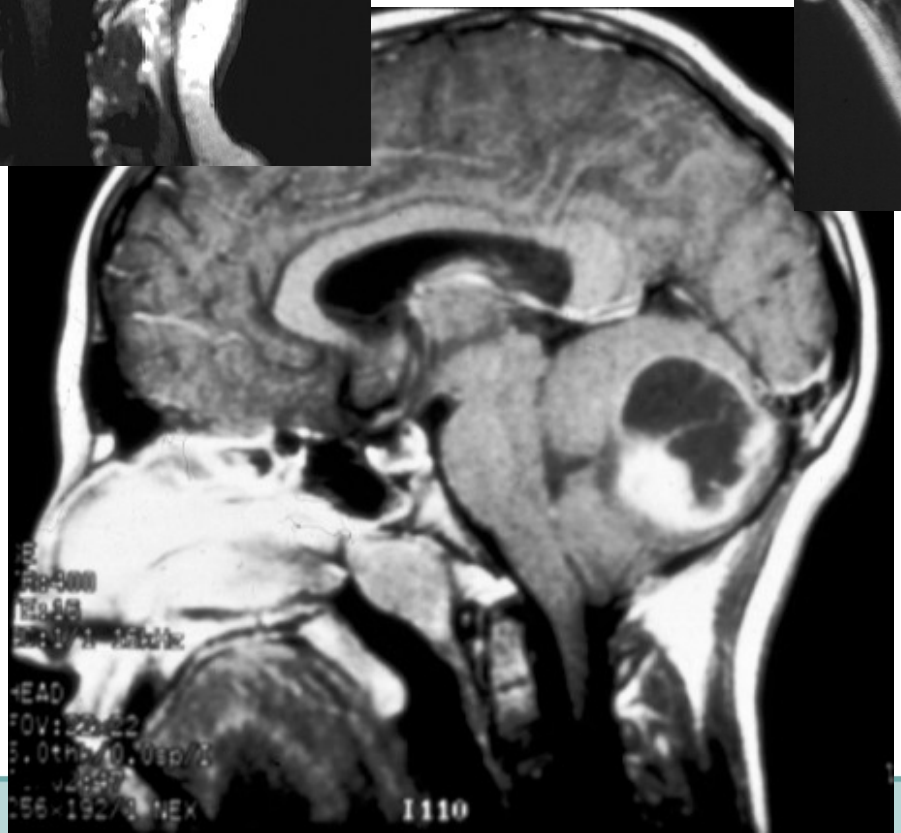

AH
SP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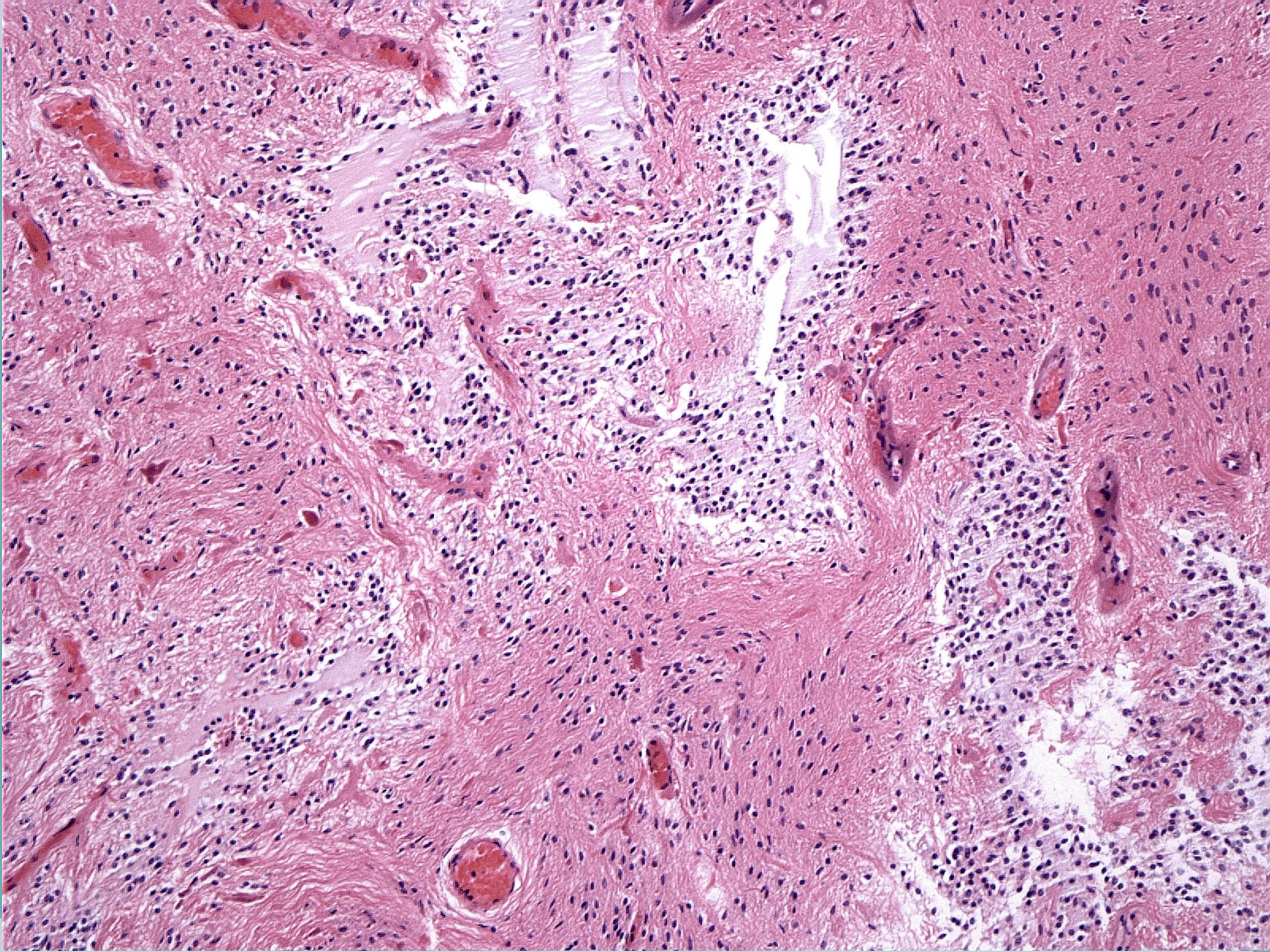
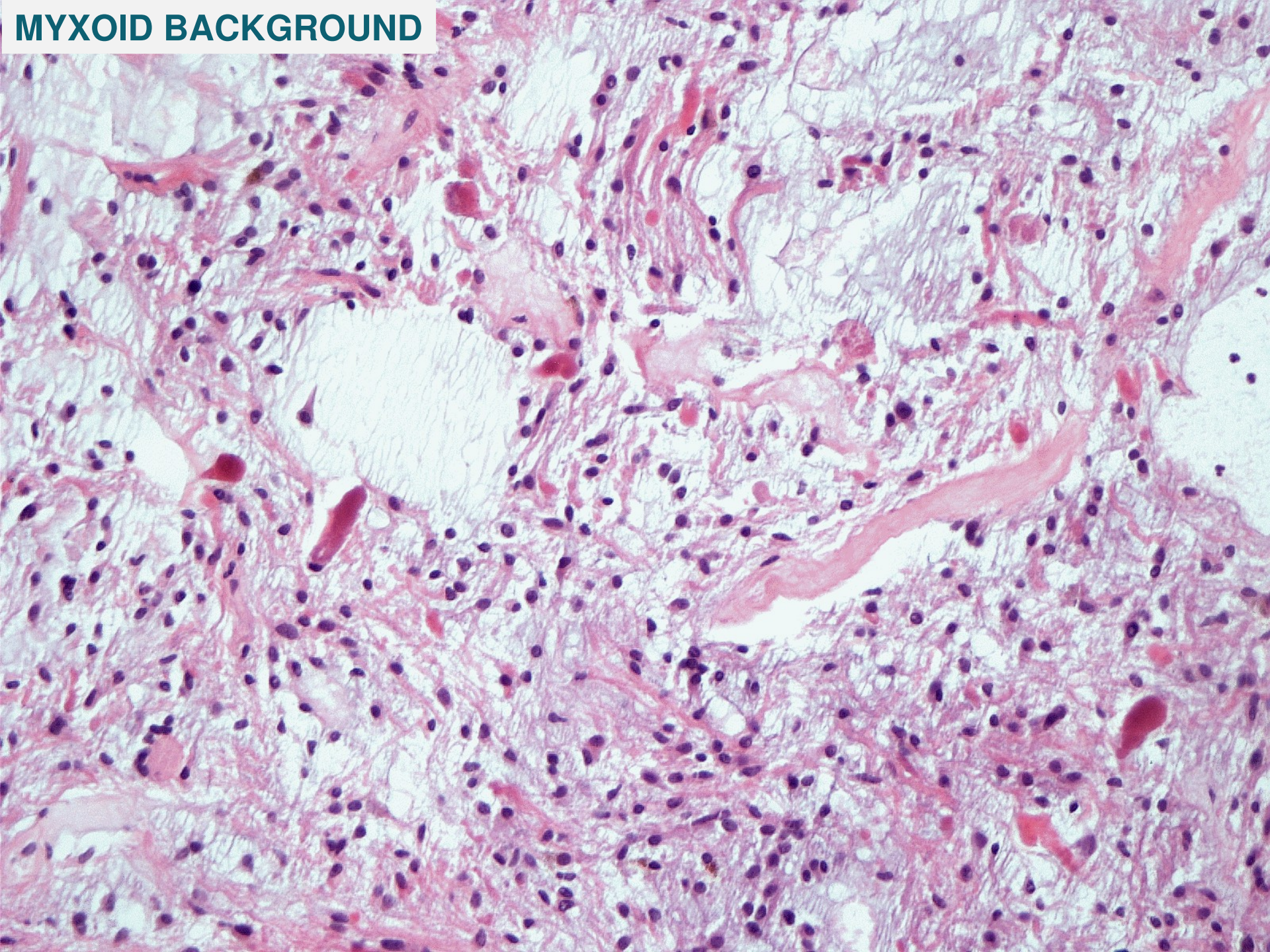
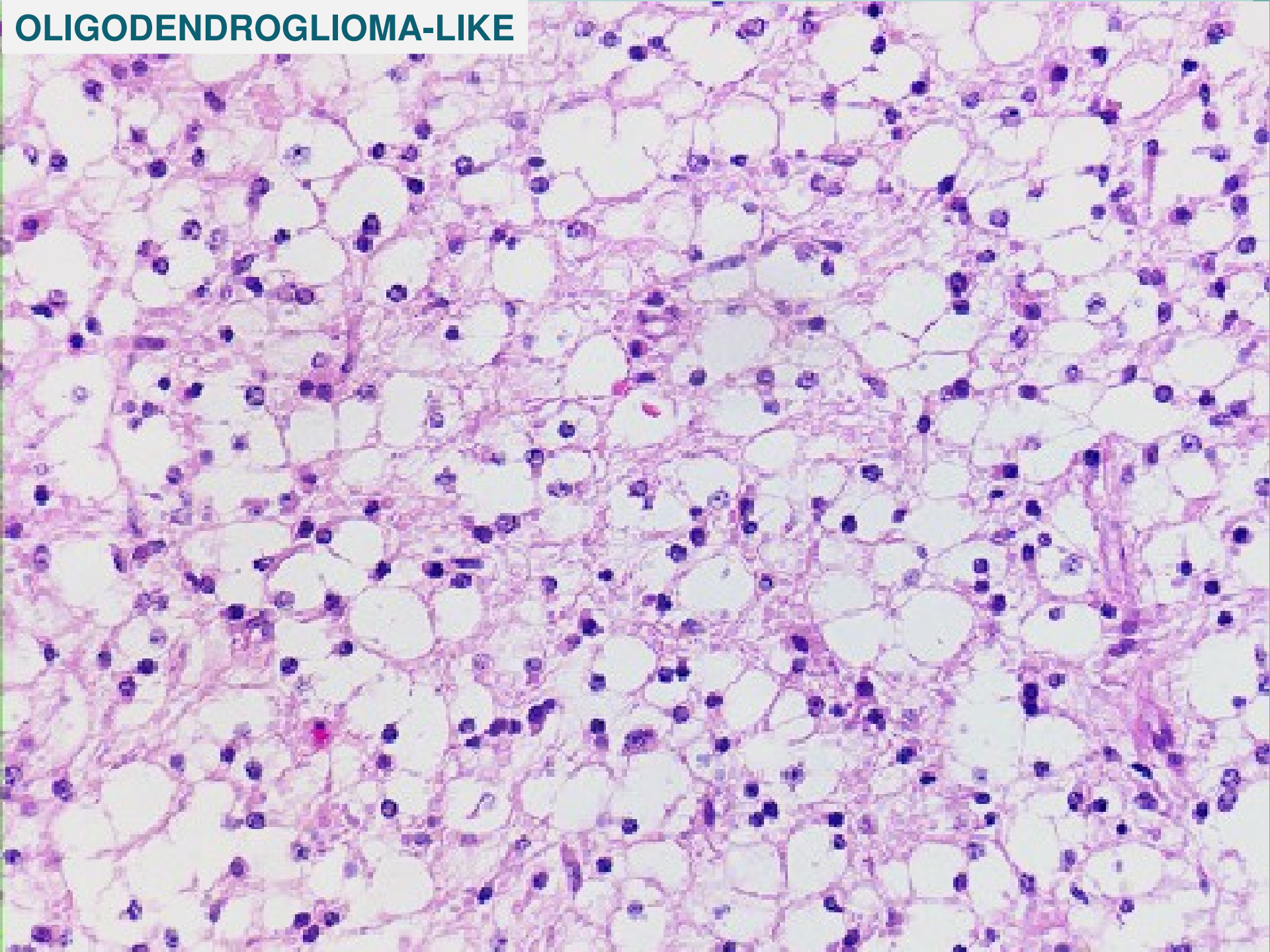
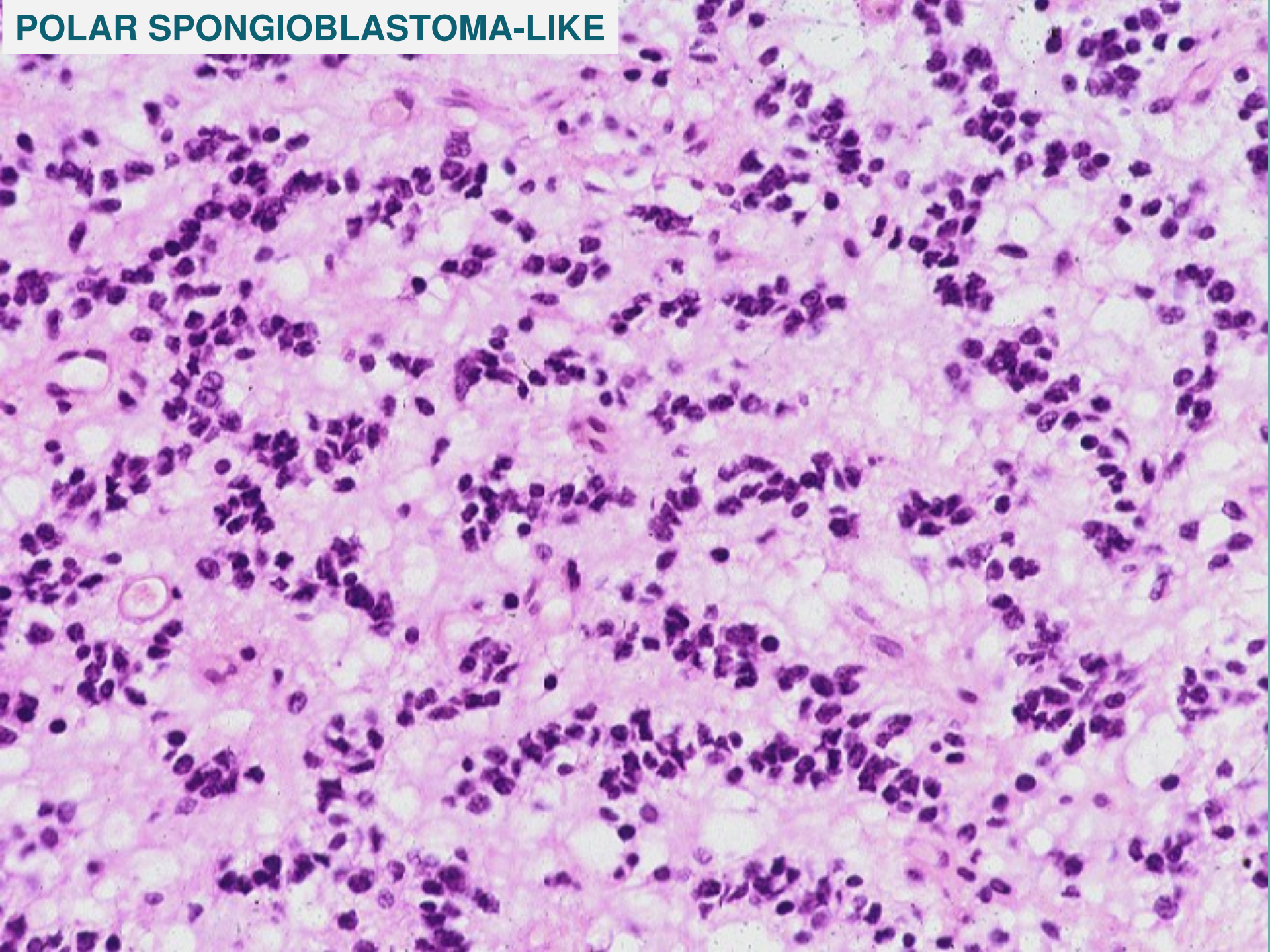



MYXOID BACKGROUND

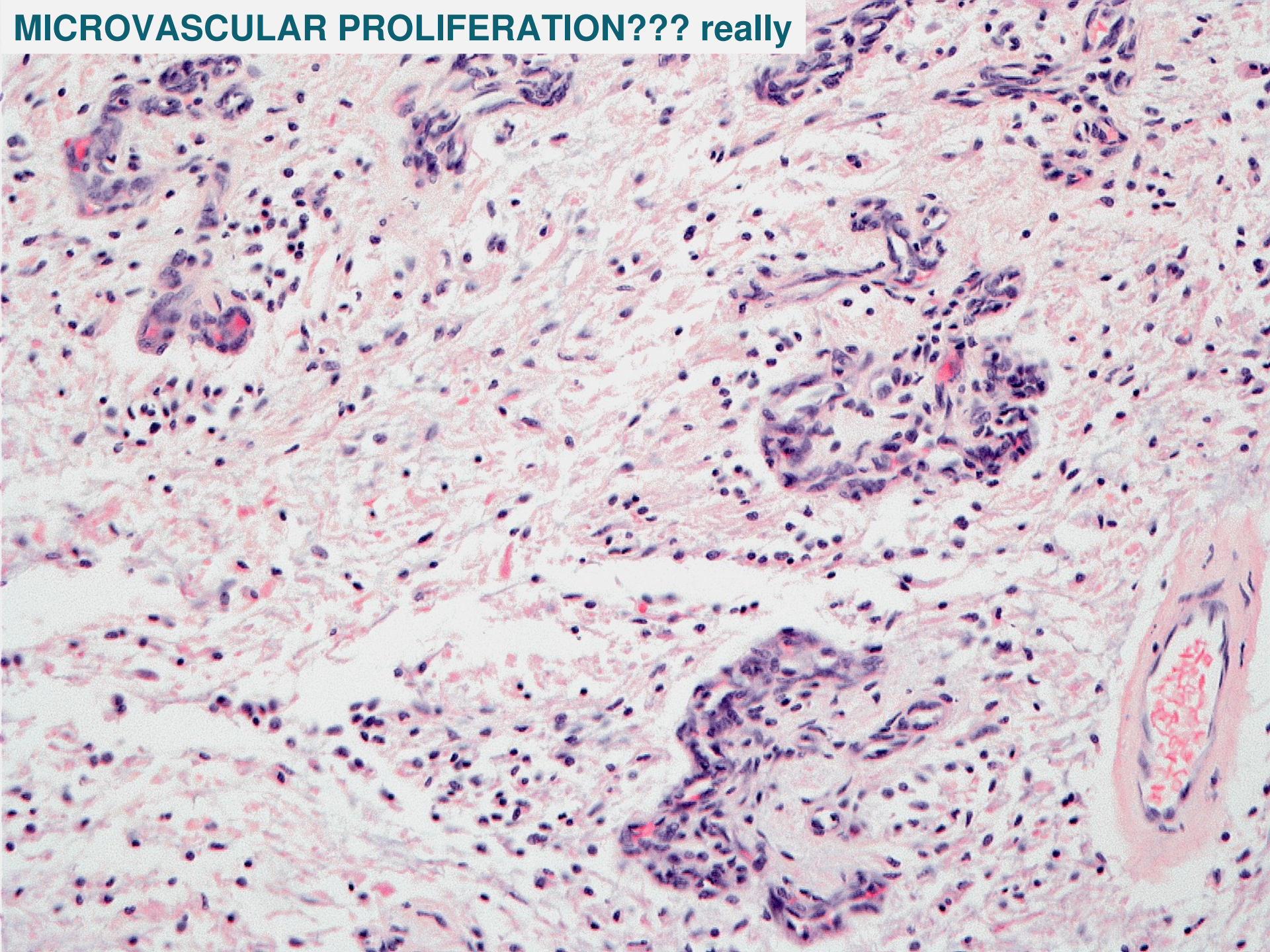
OLIGODENDROGLIOMA-LIKE



POLAR SPONGIOBLASTOMA-LIKE



MICROVASCULAR PROLIFERATION??? really



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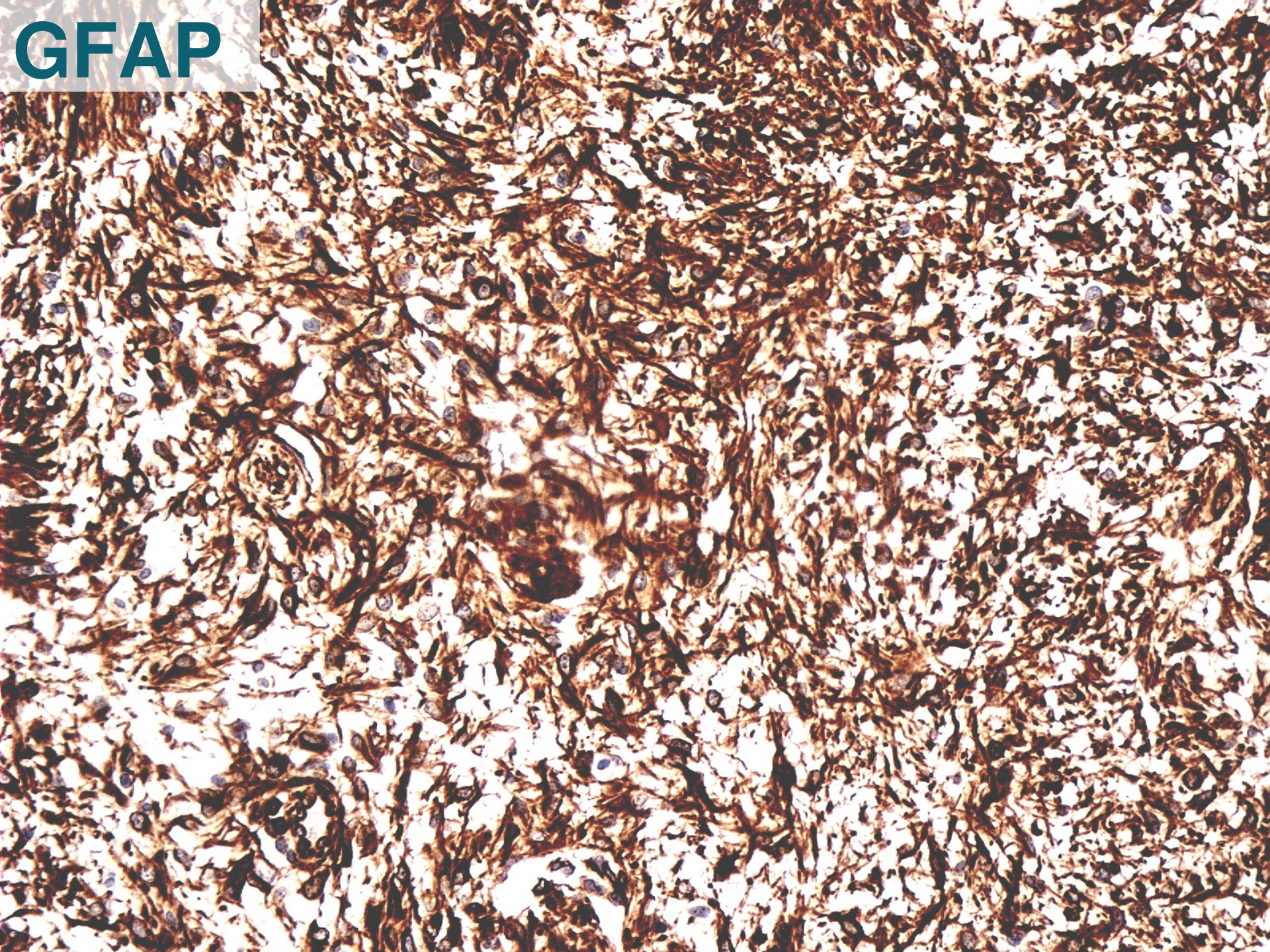
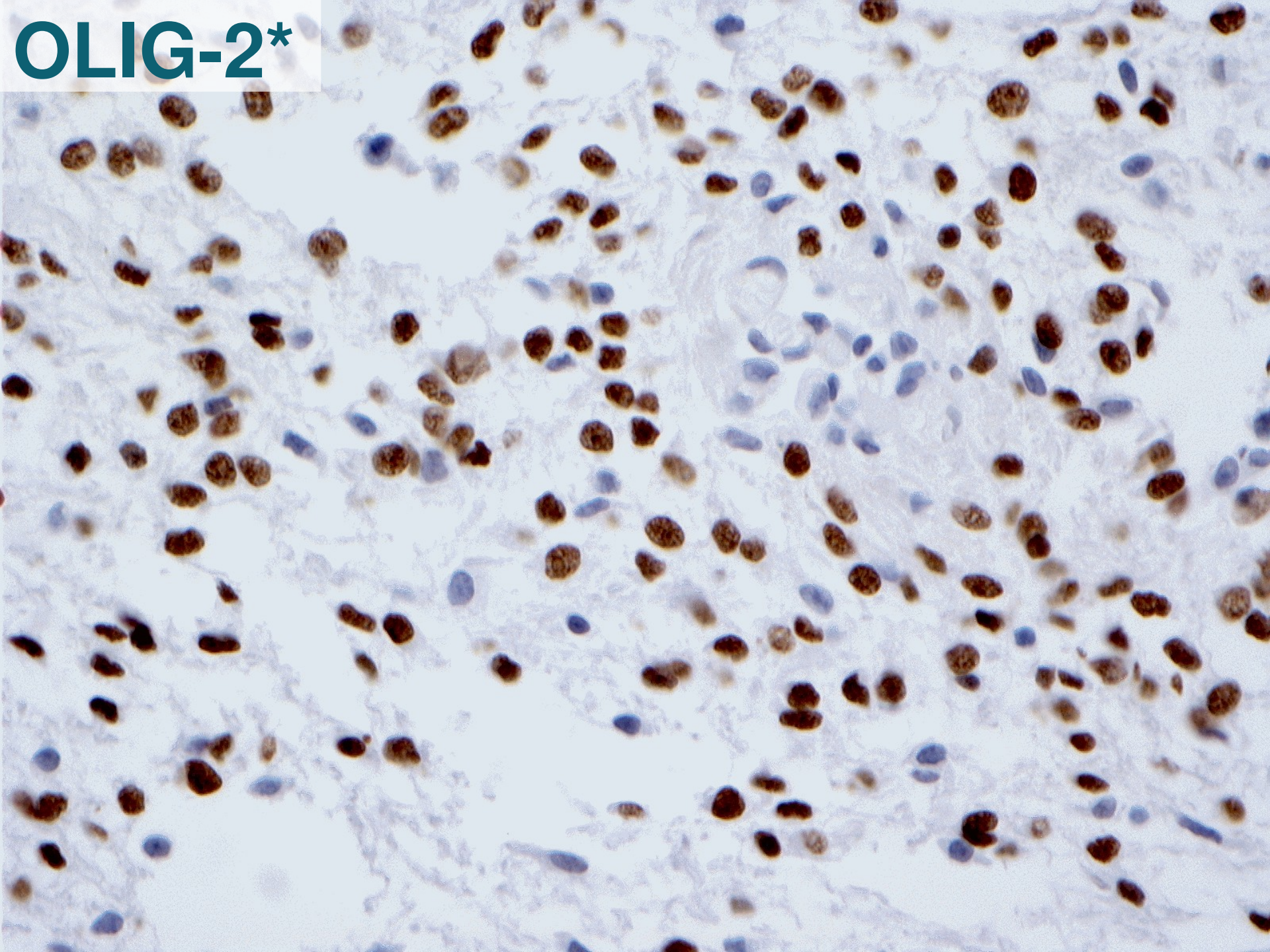
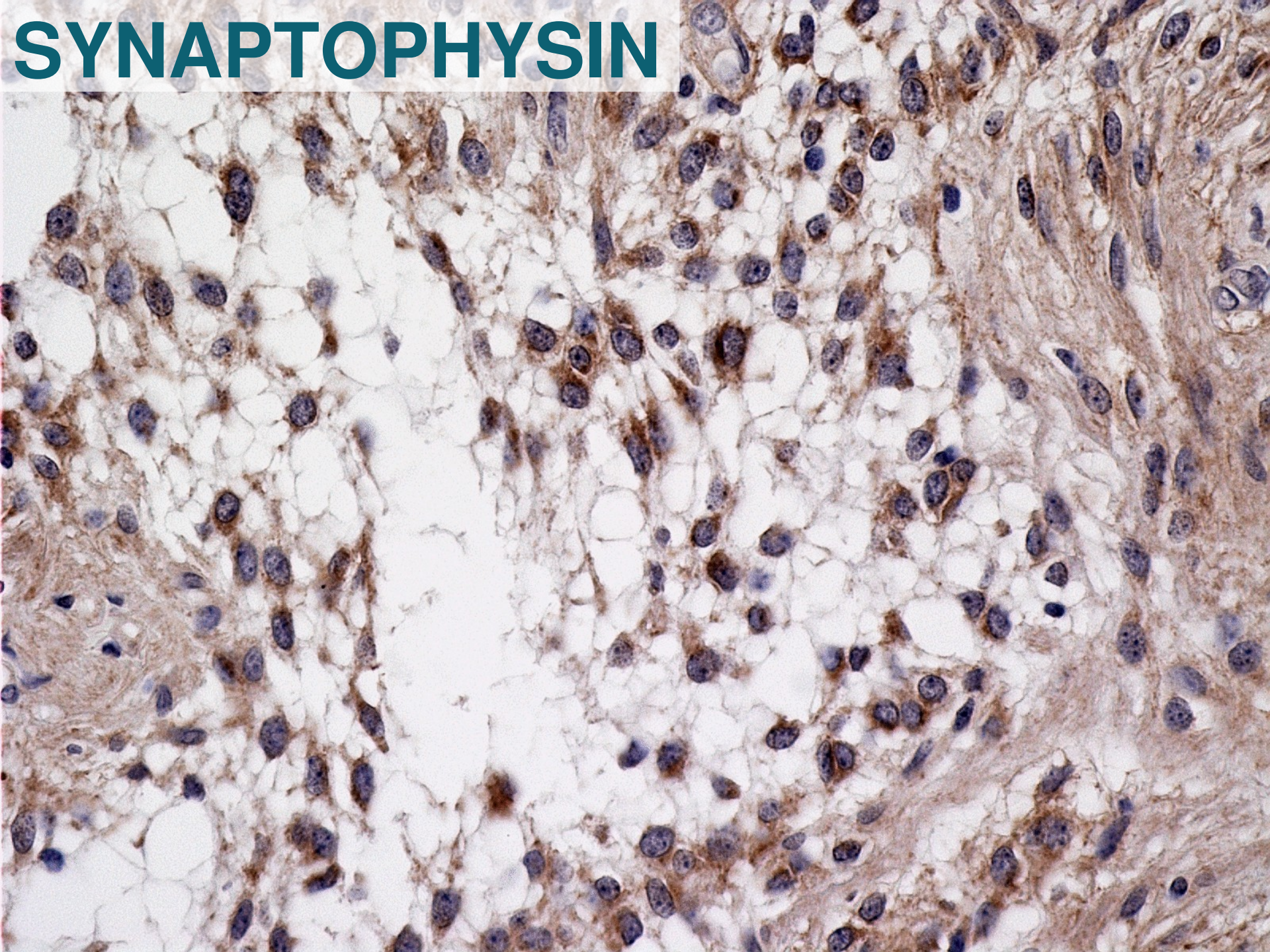
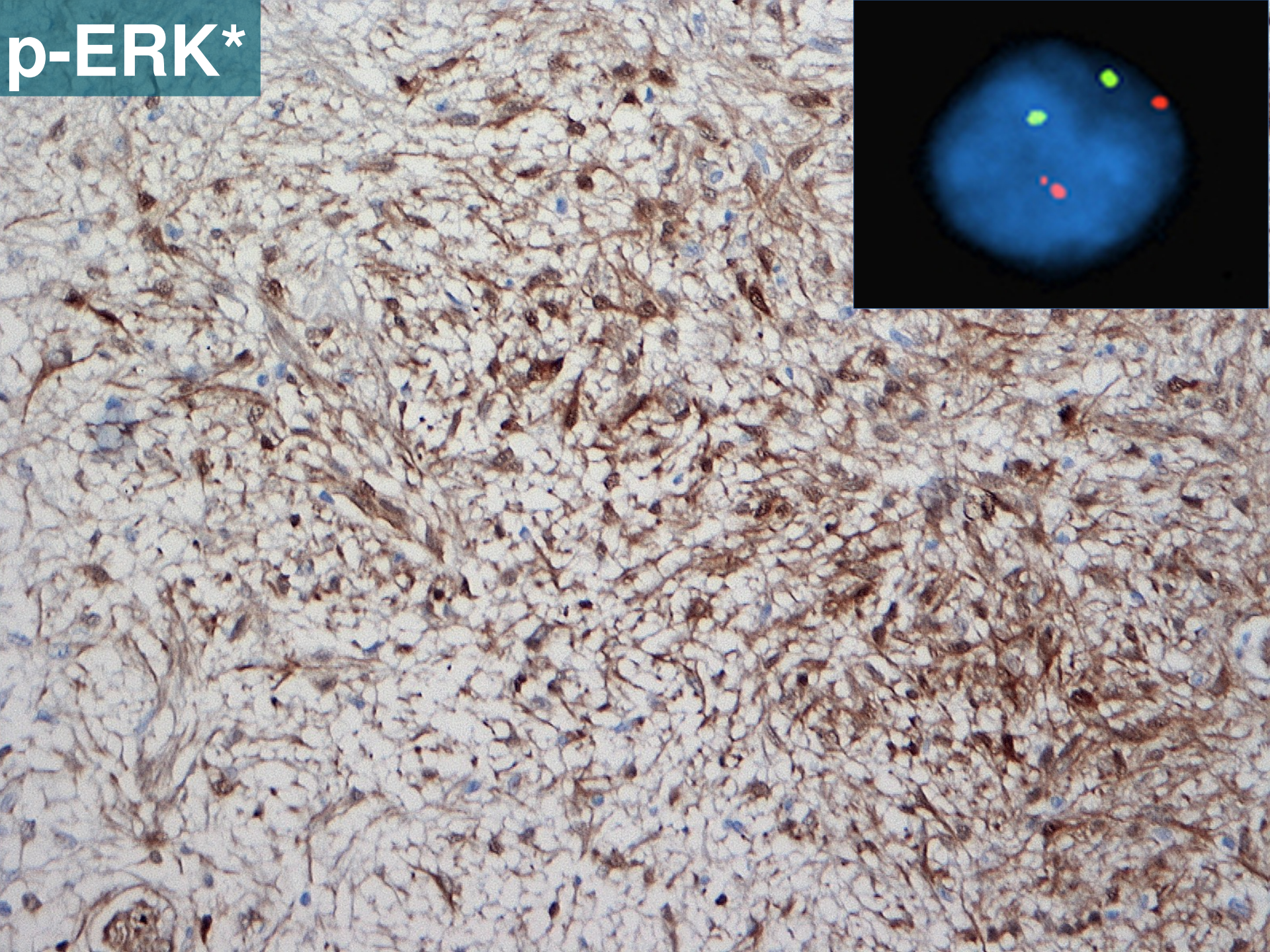
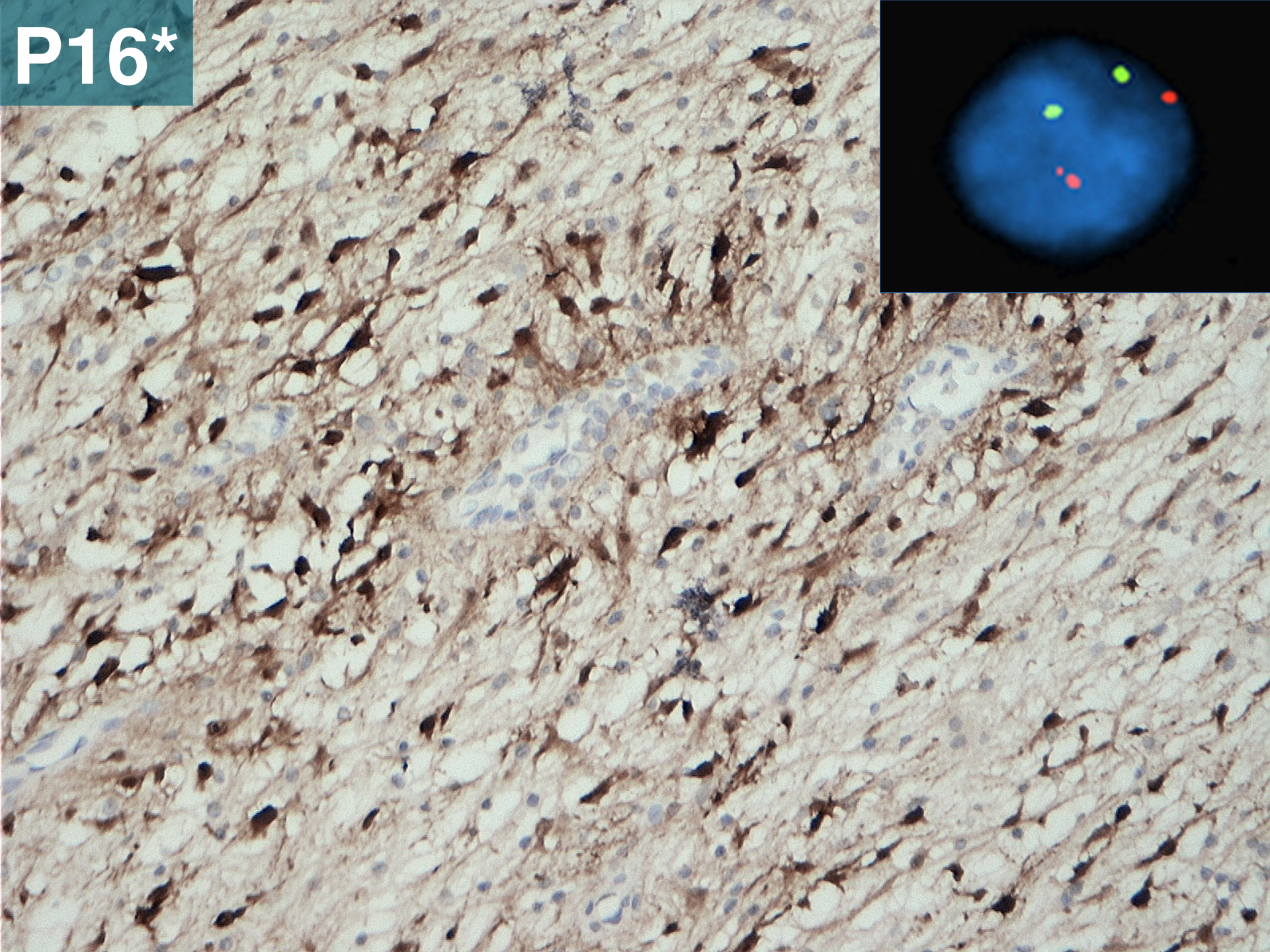

GFAP


OLIG-2*

SYNAPTOPHYSIN




p-ERK*


P16*

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USEFUL STAINS

- GFAP, SOX-2 and OLIG-2, strongly positive
- Synaptophysin positive in ~ 40%
- S-100 protein, Vimentin positive
- P-ERK and p16 strongly positive in BRAF duplicated tumors. P16 negativity is a bad sign
- Neurofilament protein typically negative (may highlight some processes at the periphery
- Neu-N negative
- MIB-1 (Ki-67) Labeling Index is typically <5%

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PILOCYTIC ASTROCYTOMA

Variables	Univariate Analysis	Multivariate Analysis
Age younger than 36 mo	<0.001	**=0.004***
Institute of Origin	=0.017	**=0.031***
NF-1 status	=0.650	
Tumor Location	=0.007	=0.108
Extent of Surgery	<0.001	**=0.012***
Ki-67 (MIB-1) LI	=0.021	=0.340
BRAF status	<0.01	=0.181

Pathologic Characteristics of Pediatric Intracranial Pilocytic Astrocytomas and Their Impact on Outcome in 3 Countries: A Multi-institutional Study

Tarik Tihan, MD, PhD, Ayca Ersen, MD,*† Ibrahim Qaddoumi, MD,‡ Maher A. Sughayer, MD,§ Sahsine Tolunay, MD,‖ Maysa Al-Hussaini, MD,§ Joanna Phillips, MD, PhD,*¶ Nalin Gupta, MD, PhD,¶ Patricia Goldhoff, MD,* and Anu Baneerjee, MD#*

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AGGRESSIVE VARIANT(S)

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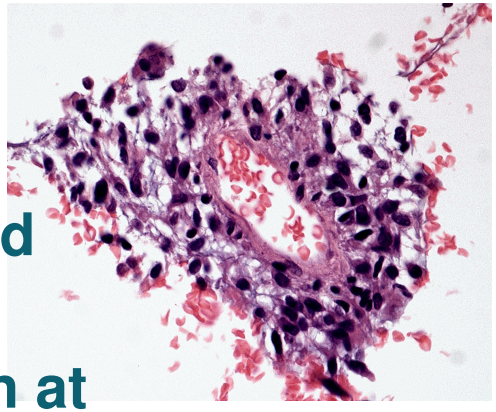
Journal of Neuropathology and Experimental Neurology
Vol. 58, No. 10
October, 1999
pp. 1061–1068

Pediatric Astrocytomas with Monomorphous Pilomyxoid Features and a Less Favorable Outcome

TARIK TIHAN, MD, PHD, PAUL G. FISHER, MD, JAMES L. KEPNER, PHD, CATHERINE GODFRAIND, MD, RODNEY D. MCCOMB, MD, PATRICIA T. GOLDTHWAITE, AND PETER C. BURGER, MD



- Young children (<4 yrs)
- Hypothalamic/chiasmatic region
- Signs and symptoms of increased intracranial pressure
- Some tumors have dissemination at onset or later disseminate
- Histologically distinct from typical pilocytic astrocytoma
- VARIANT of pilocytic astrocytoma

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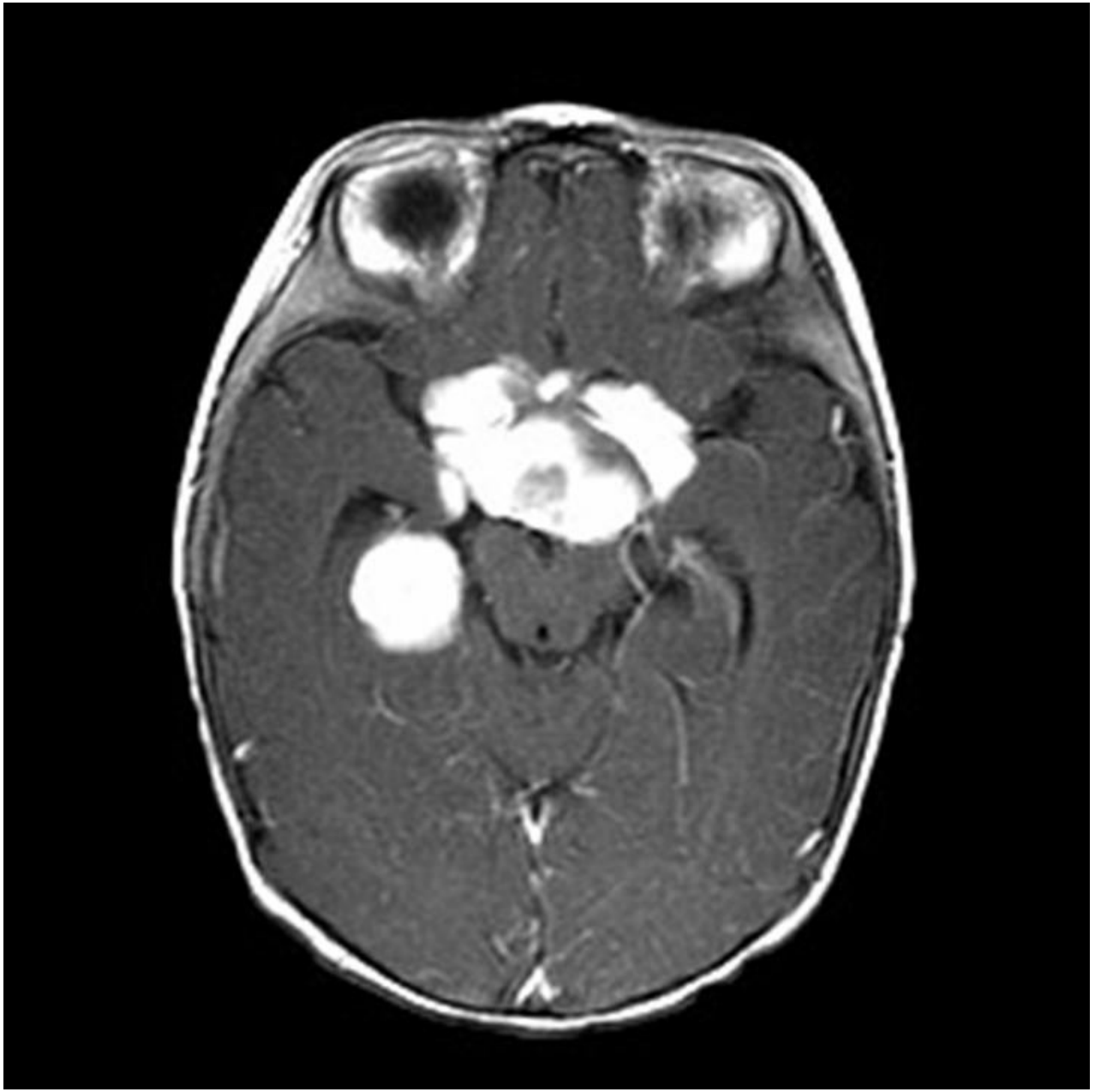

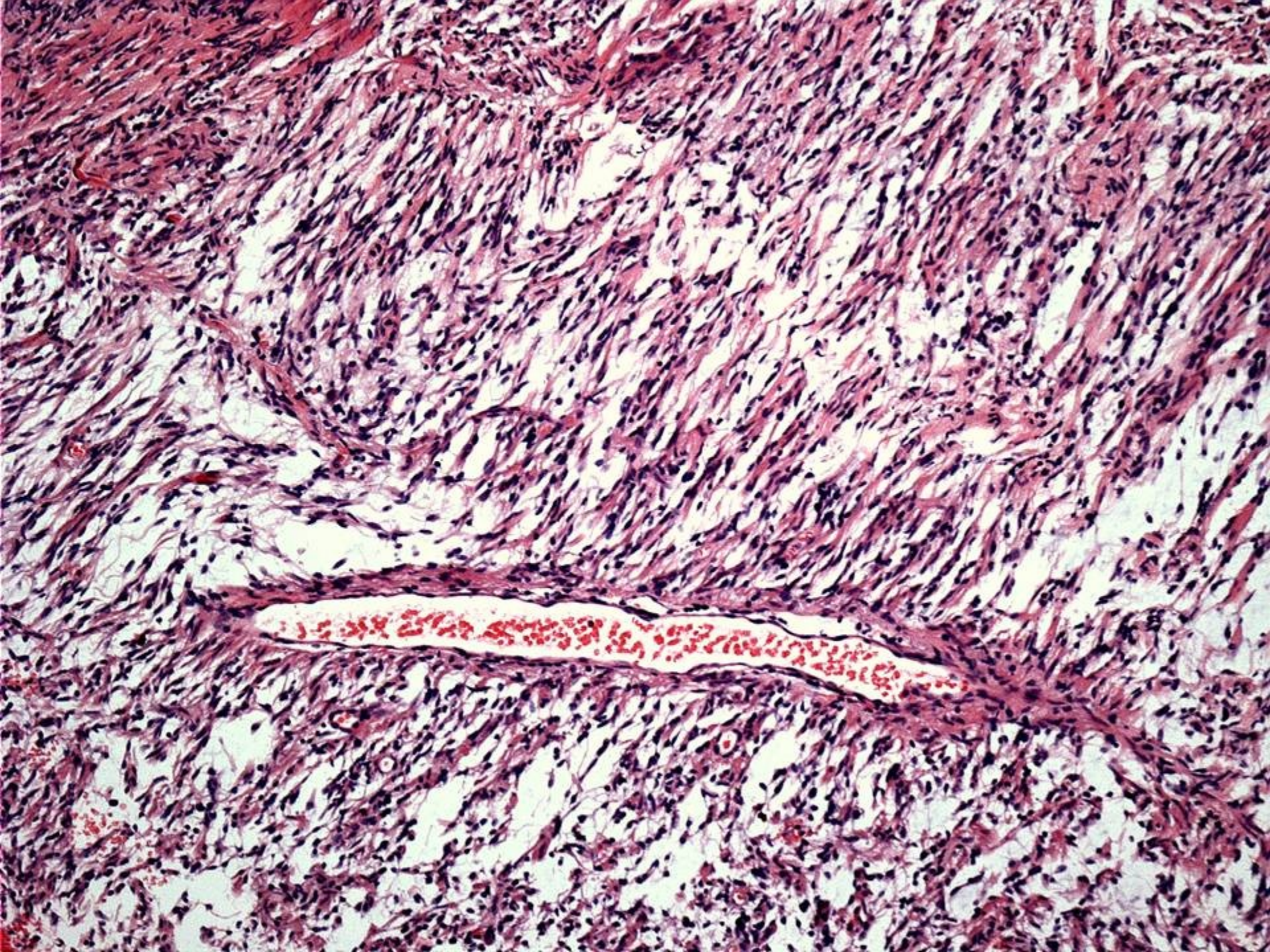

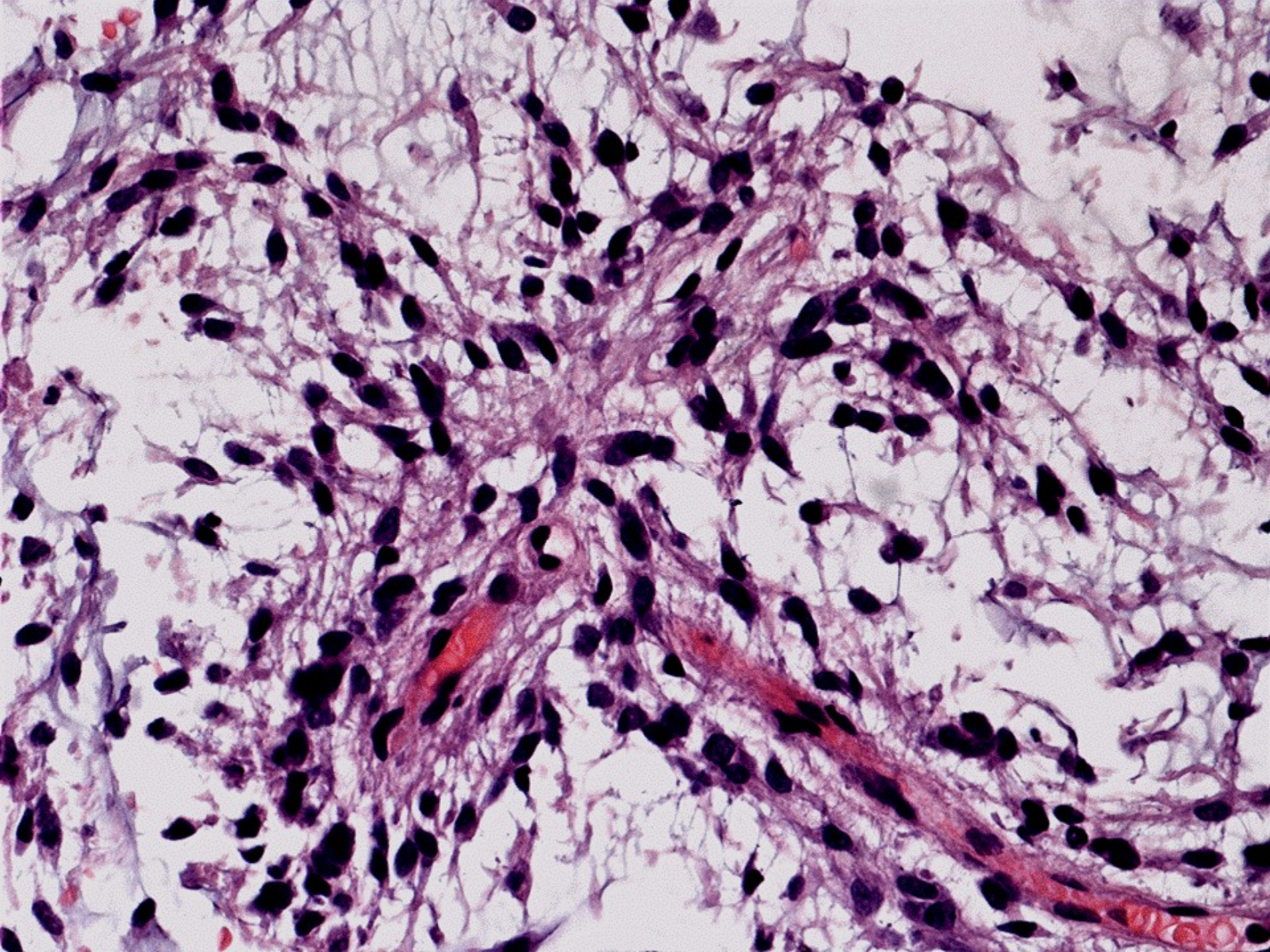

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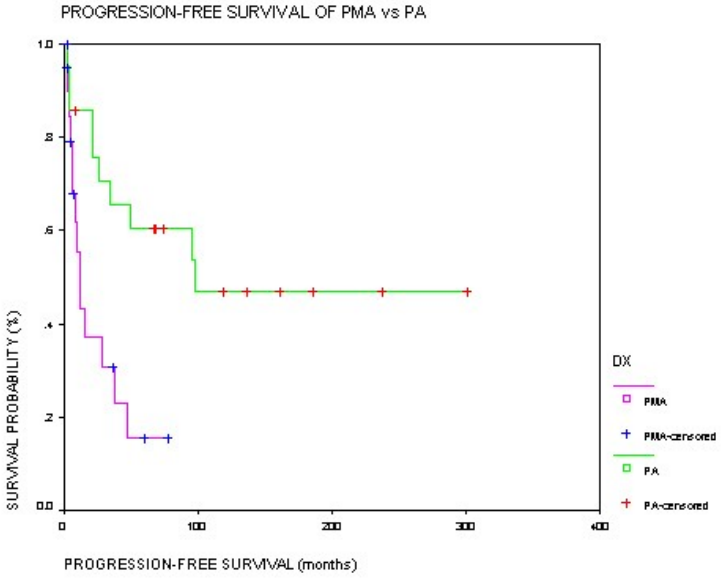
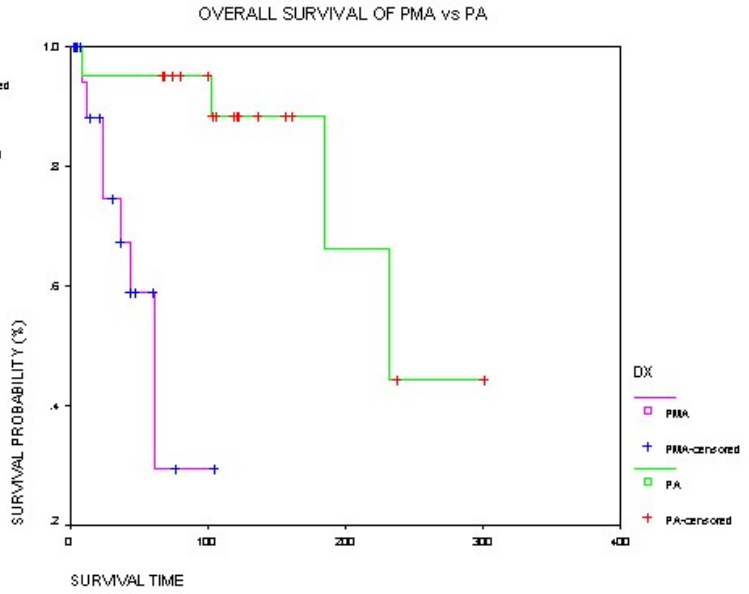
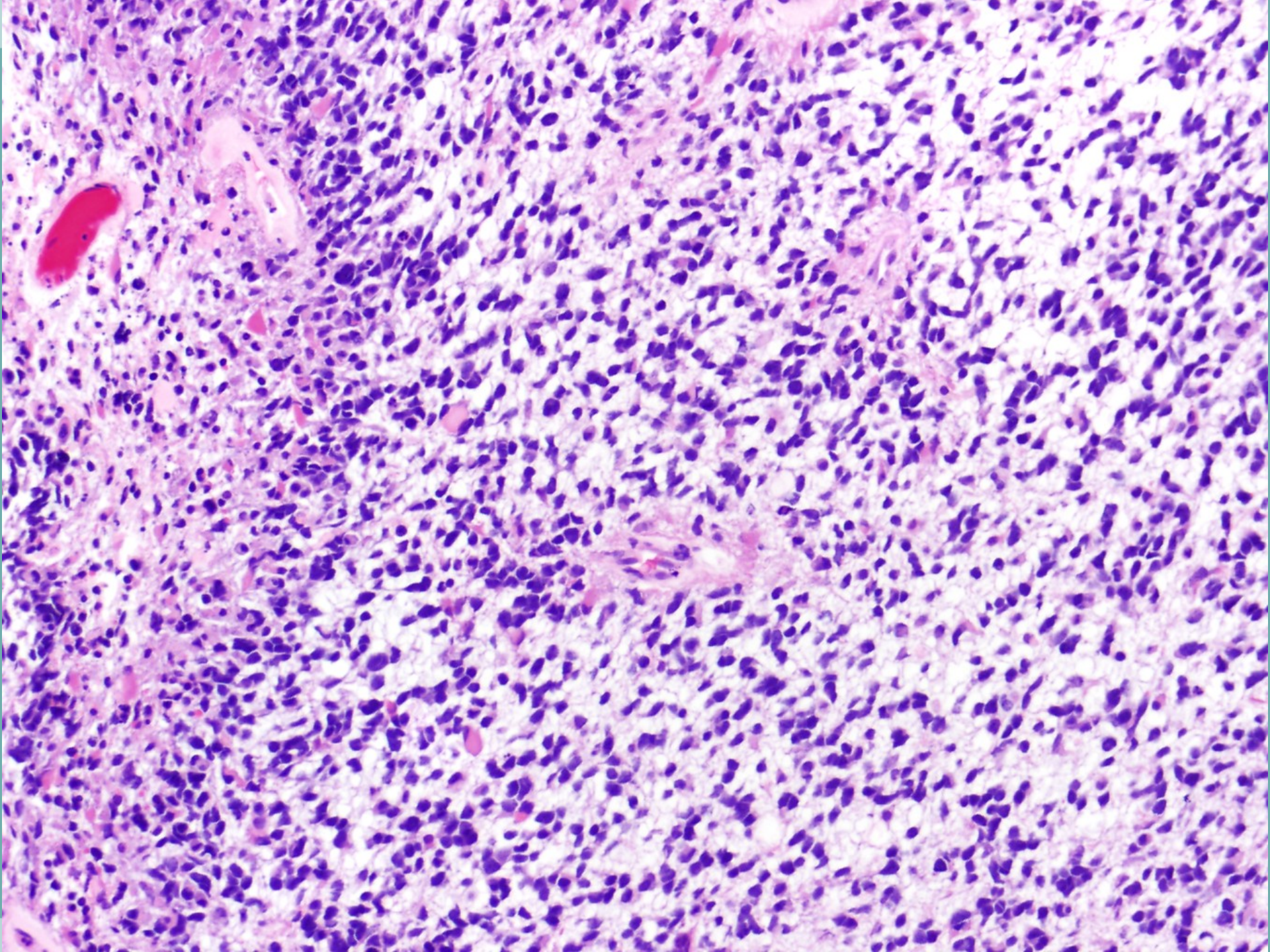
Pilomyxoid vs Pilocytic Astrocytoma







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MOLECULAR PATHOLOGY

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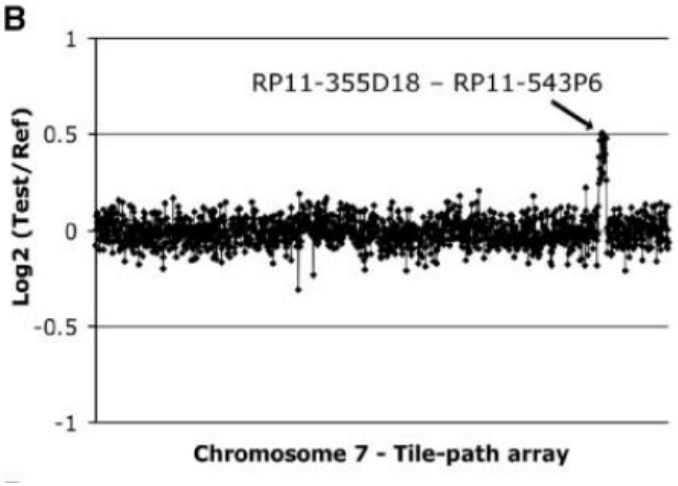
Tandem Duplication Producing a Novel Oncogenic *BRAF* Fusion Gene Defines the Majority of Pilocytic Astrocytomas

David T.W. Jones,[1] Sylvia Kocialkowski,[1] Lu Liu,[1] Danita M. Pearson,[1]
L. Magnus Bäcklund,[2] Koichi Ichimura,[1] and V. Peter Collins[1]

[1]Division of Molecular Histopathology, Department of Pathology, University of Cambridge, Cambridge, United Kingdom and
[2]Department of Oncology-Pathology, Karolinska Hospital, Stockholm, Sweden



ORIGINAL ARTICLE

Frequent Gains at Chromosome 7q34 Involving BRAF in Pilocytic Astrocytoma

Eli E. Bar, PhD, Alex Lin, MS, Tarik Tihan, MD, PhD, Peter C. Burger, MD,
and Charles G. Eberhart, MD, PhD

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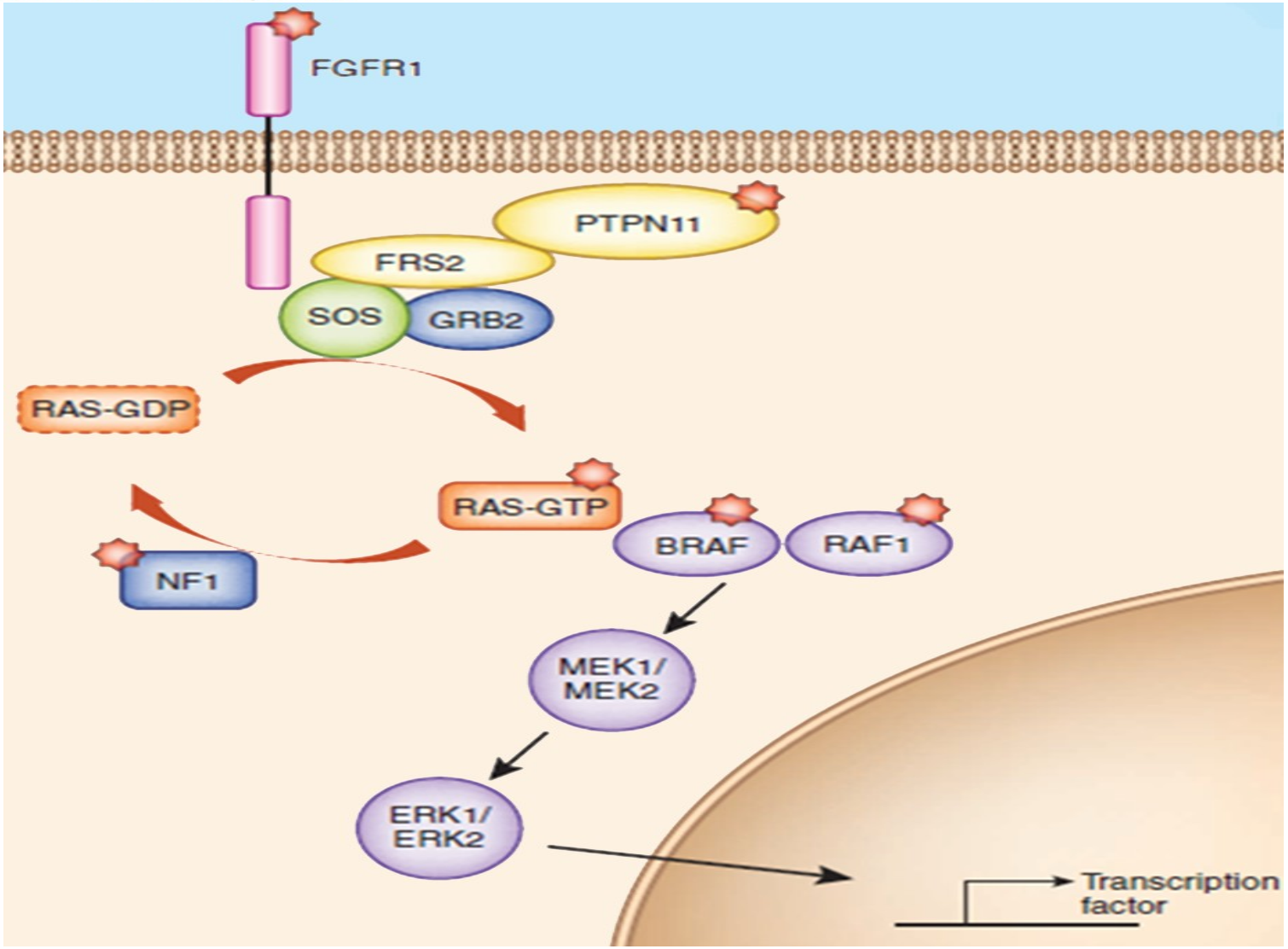
MAPping the genomic landscape of low-grade pediatric gliomas

NATURE GENETICS | VOLUME 45 | NUMBER 8 | AUGUST 2013

Sevin Turcan & Timothy A Chan



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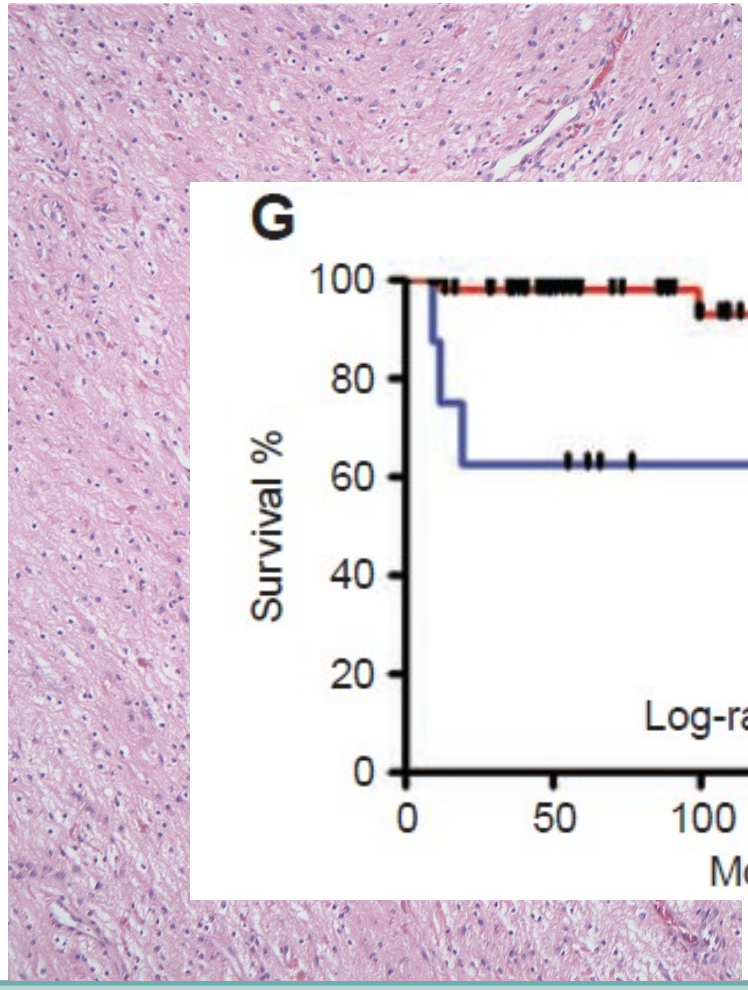
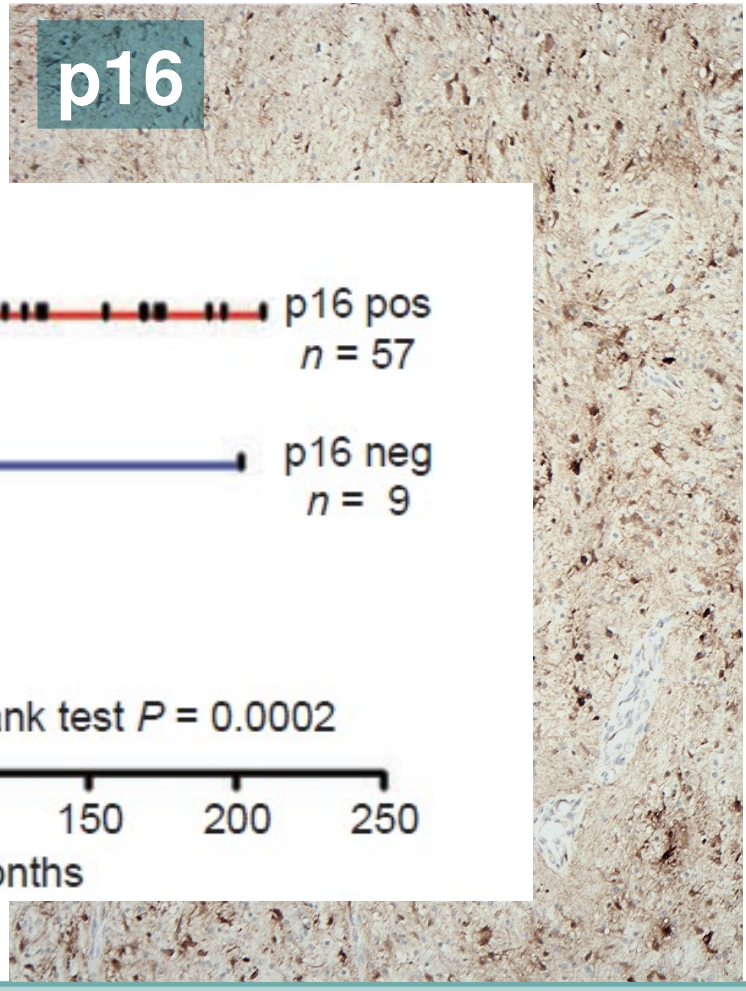
Clin Cancer Res. 2011 Jun 1;17(11):3590-9.

BRAF activation induces transformation and then senescence in human neural stem cells: a pilocytic astrocytoma model.

Raabe EH, Lim KS, Kim JM, Meeker A, Mao XG, Nikkhah G, Maciaczyk J, Kahlert U, Jain D, Bar E, Cohen KJ, Eberhart CG.





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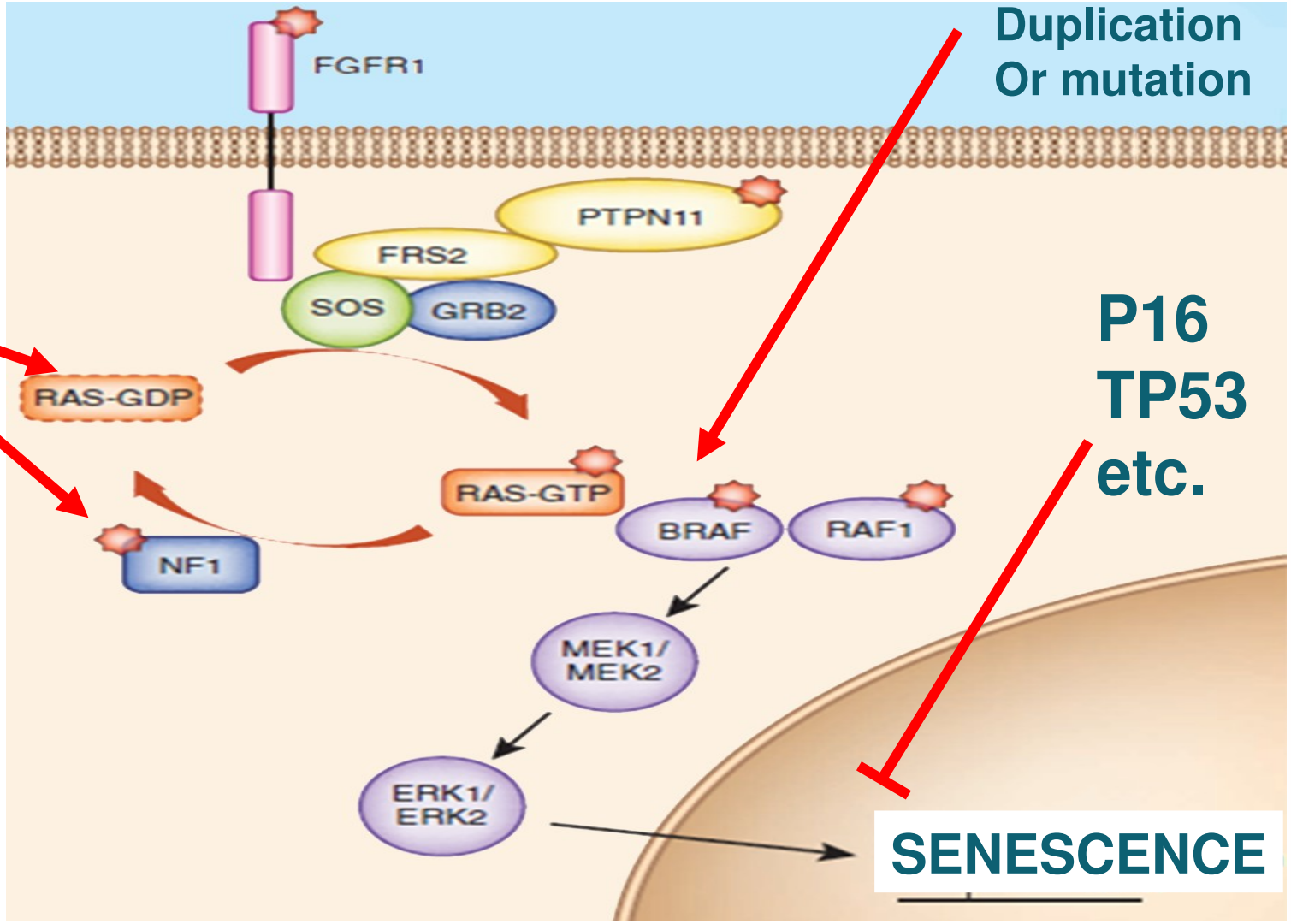
PILOCYTIC and PILOMYXOID ASTROCYTOMA



Mutation

P16
TP53
etc.

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PLEMORPHIC XANTHOASTROCYTOMA

- WHO GRADE II NEOPLASM
- Giant cells, EGBs, Reticulin-rich
- SURGICAL DISEASE
  - Supratentorial, solid-cystic
  - Pediatric, young adults
  - Typical histology
  - Gross total resection sometimes curative
  - Some tumors show malignant histological features and behave aggressively

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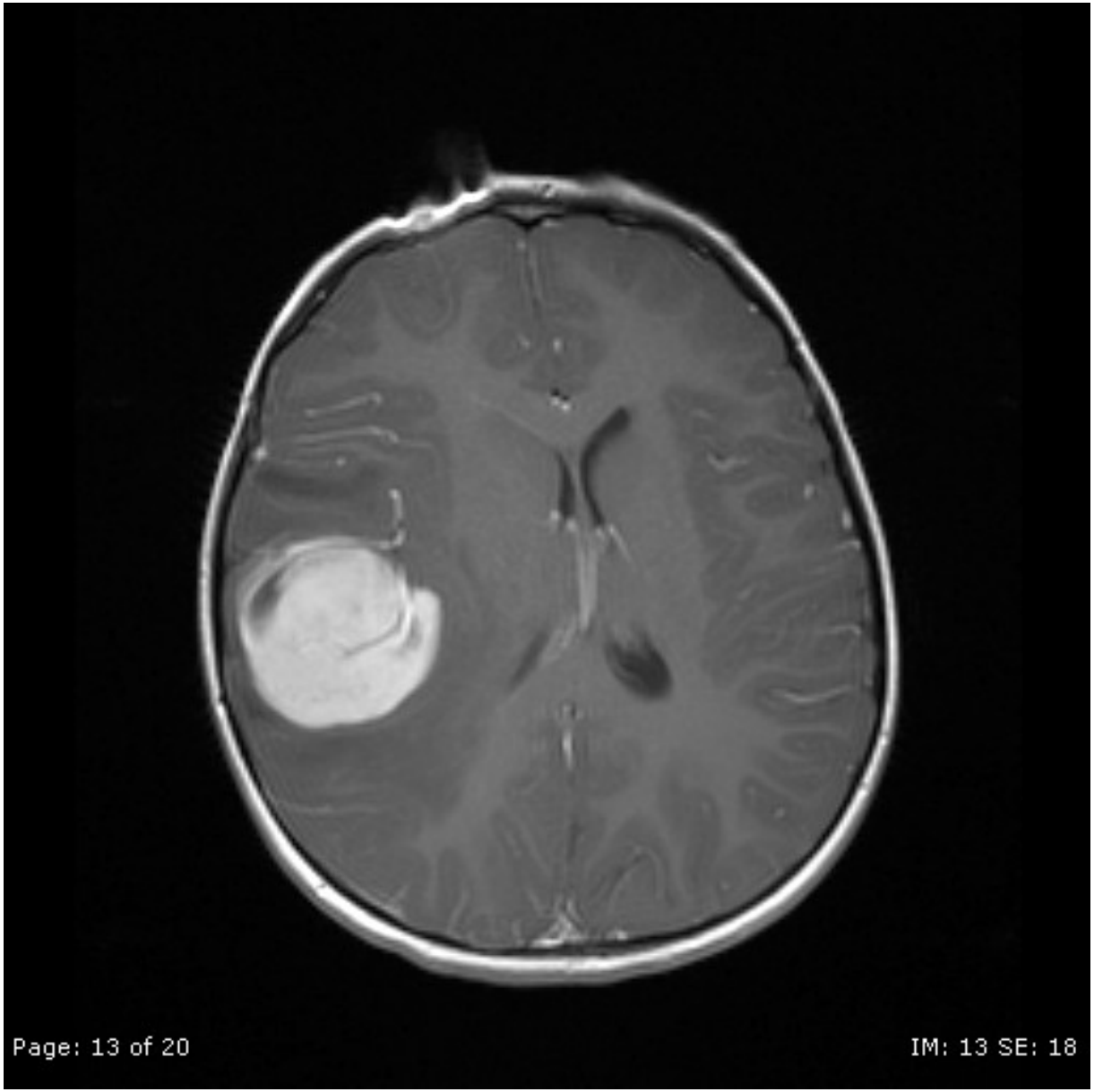

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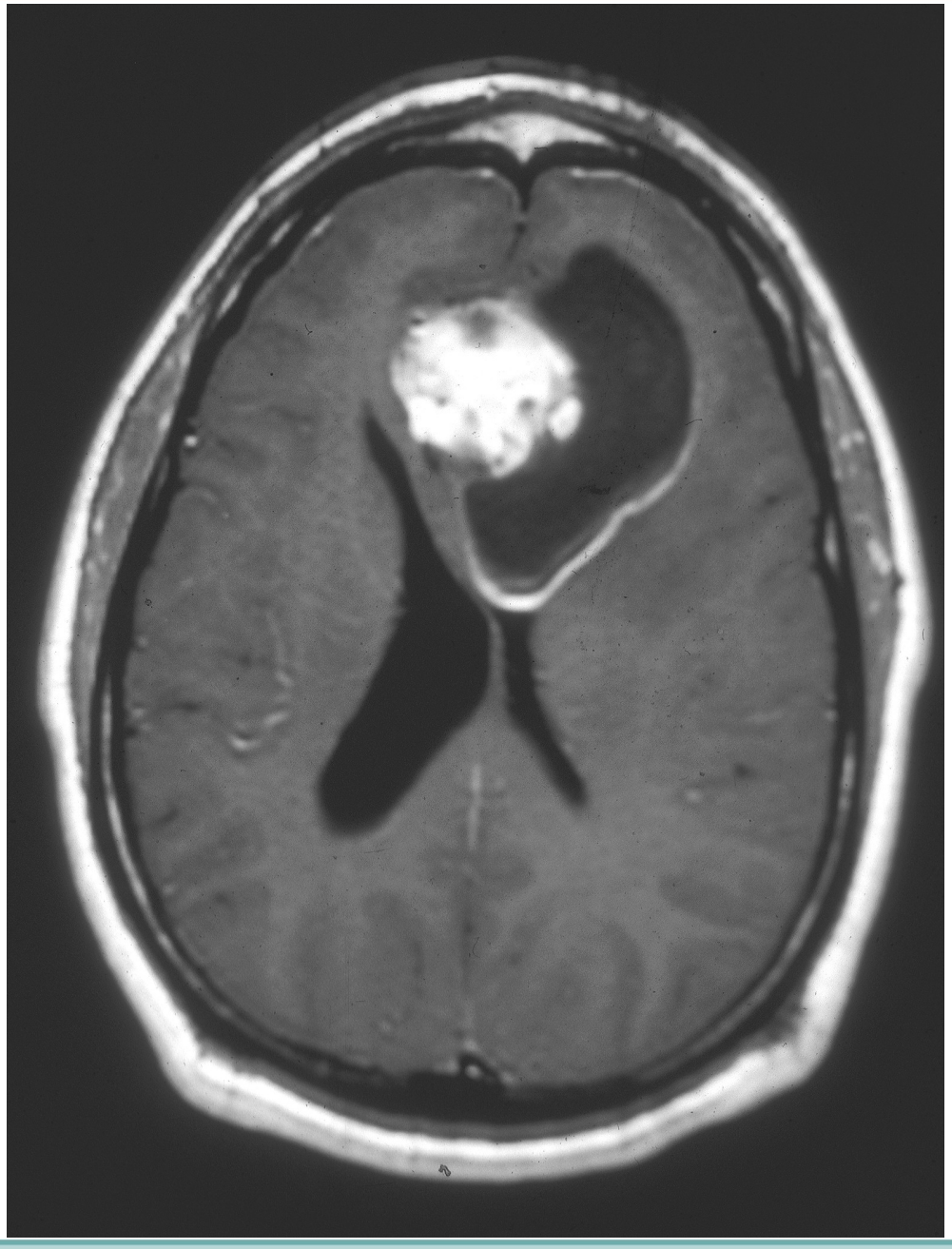
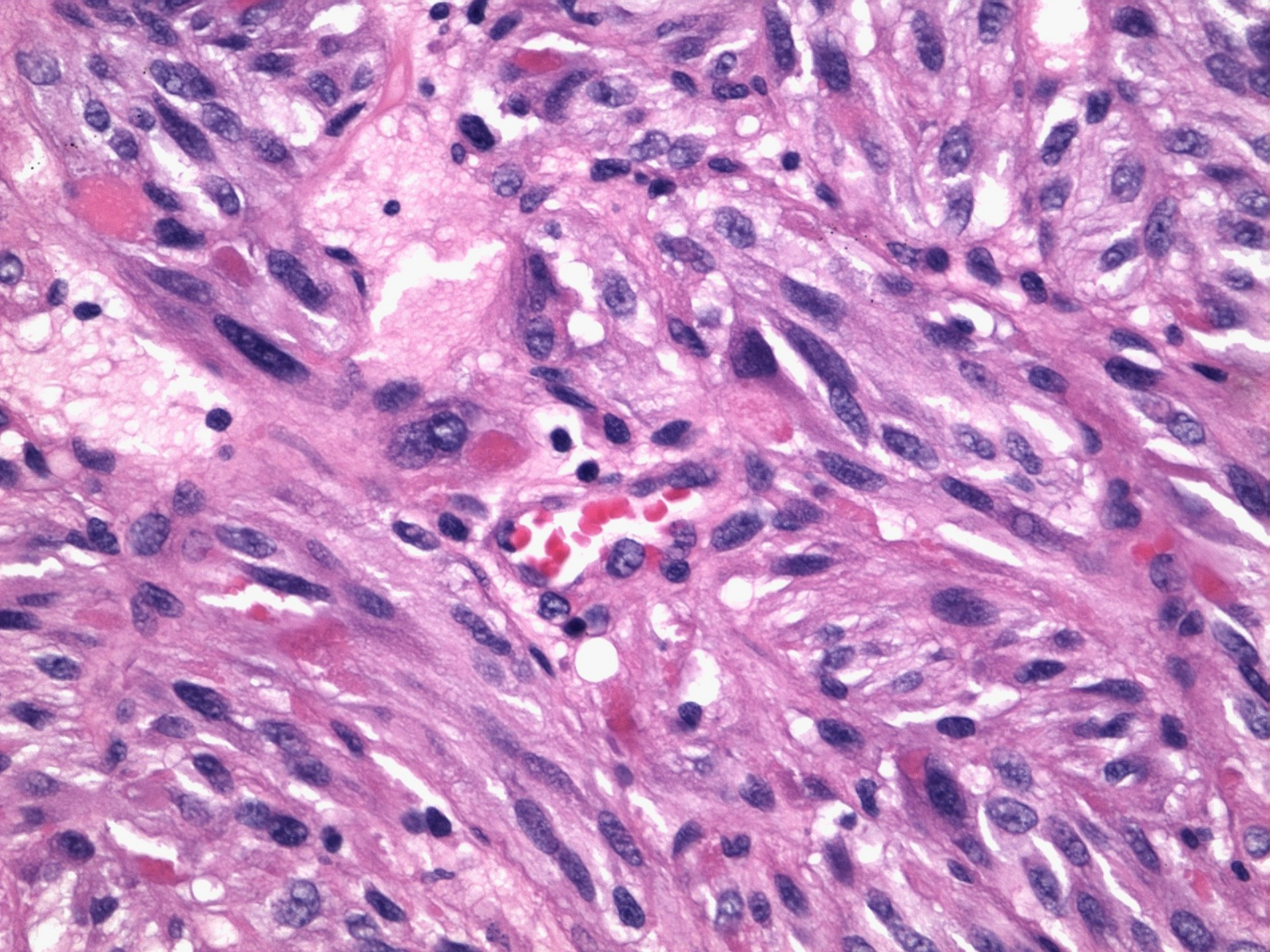
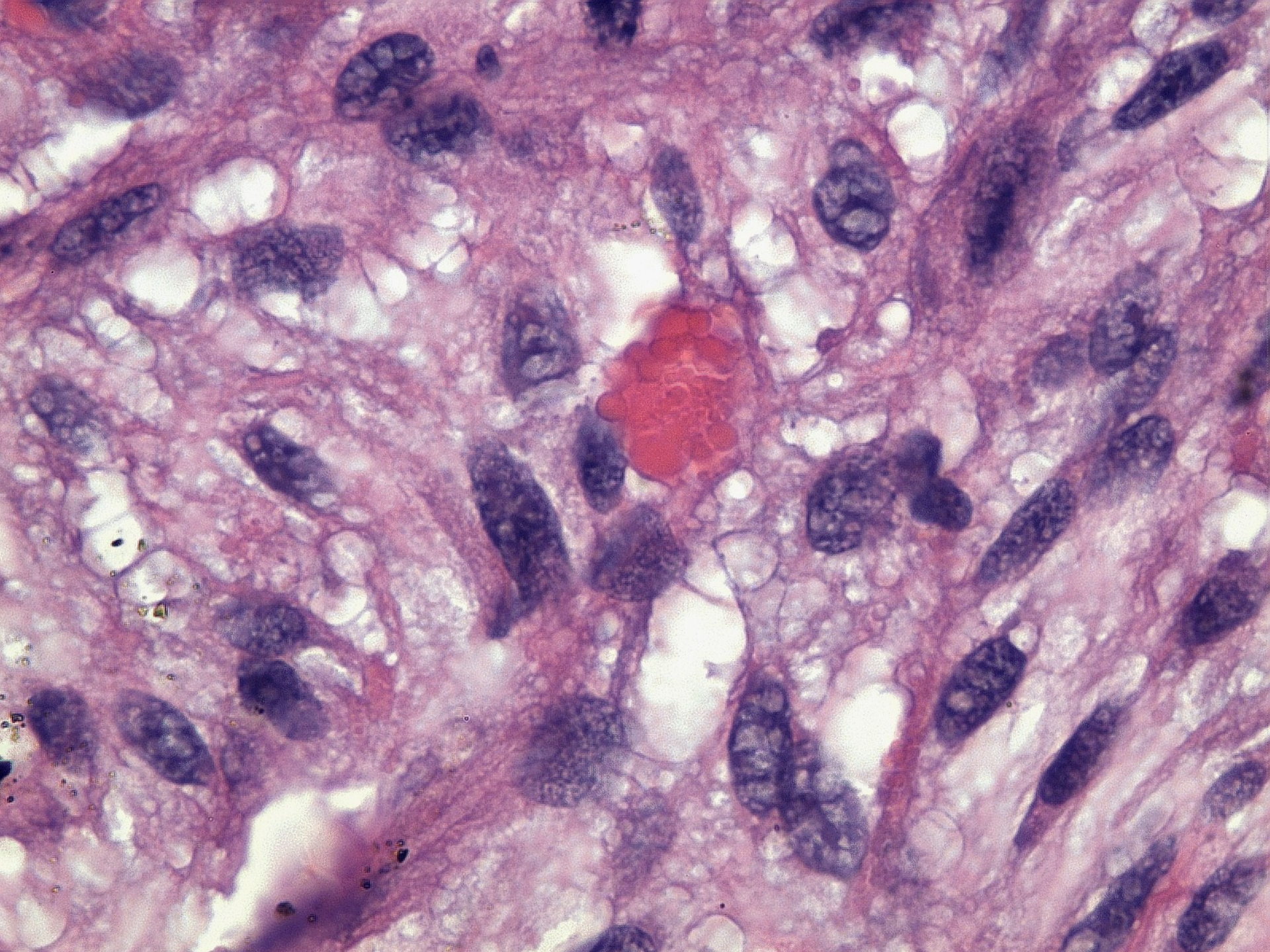
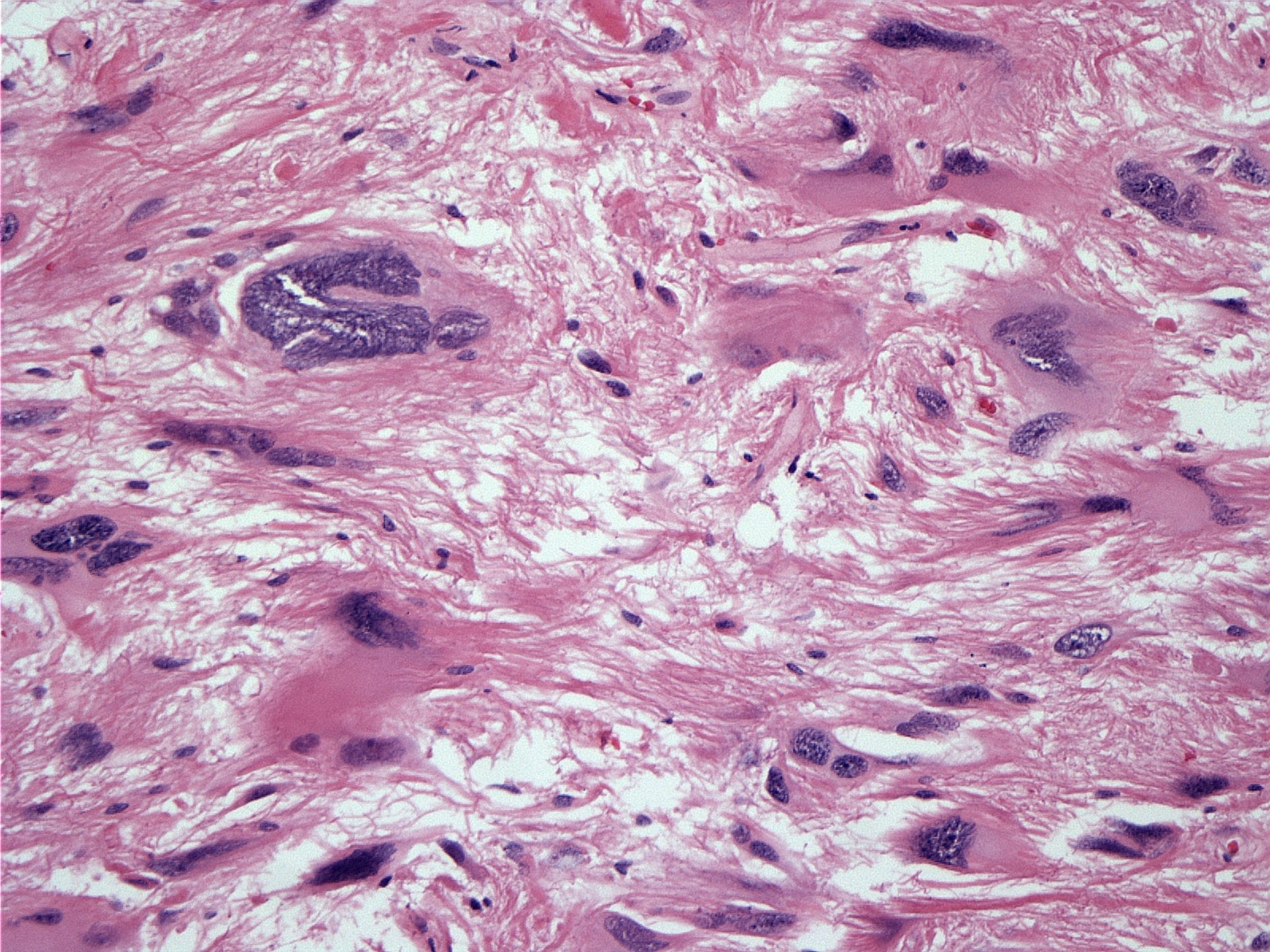
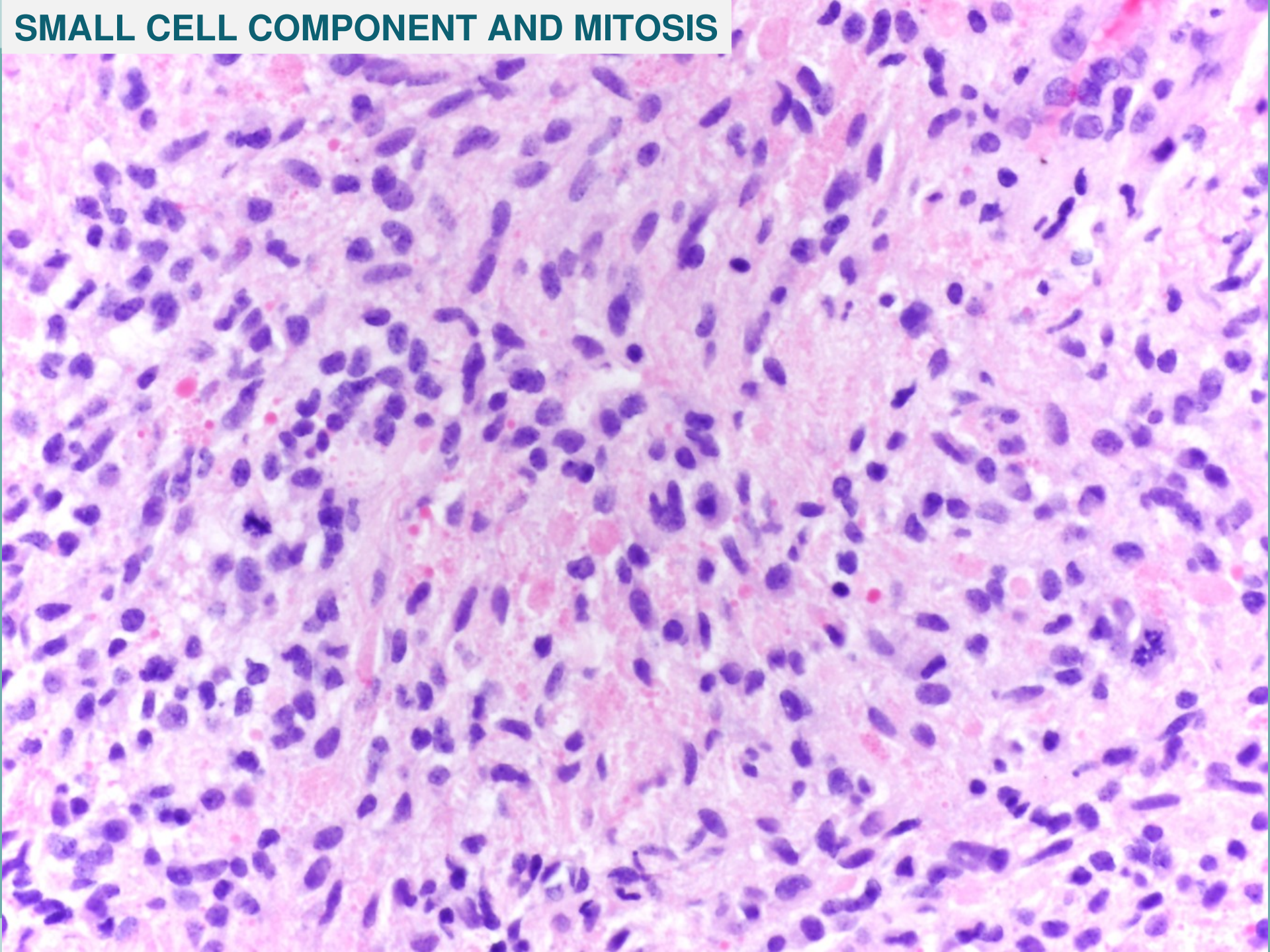




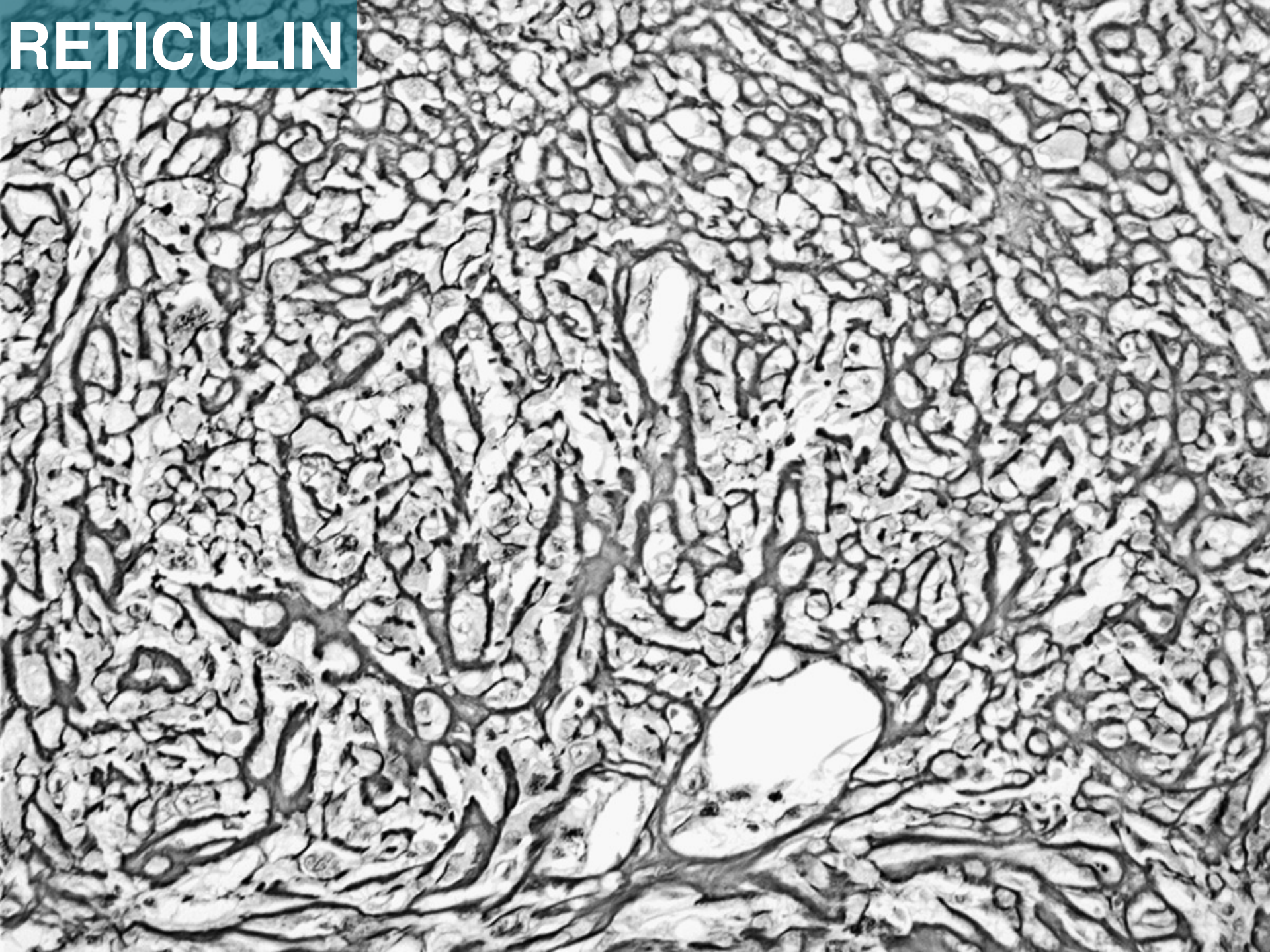




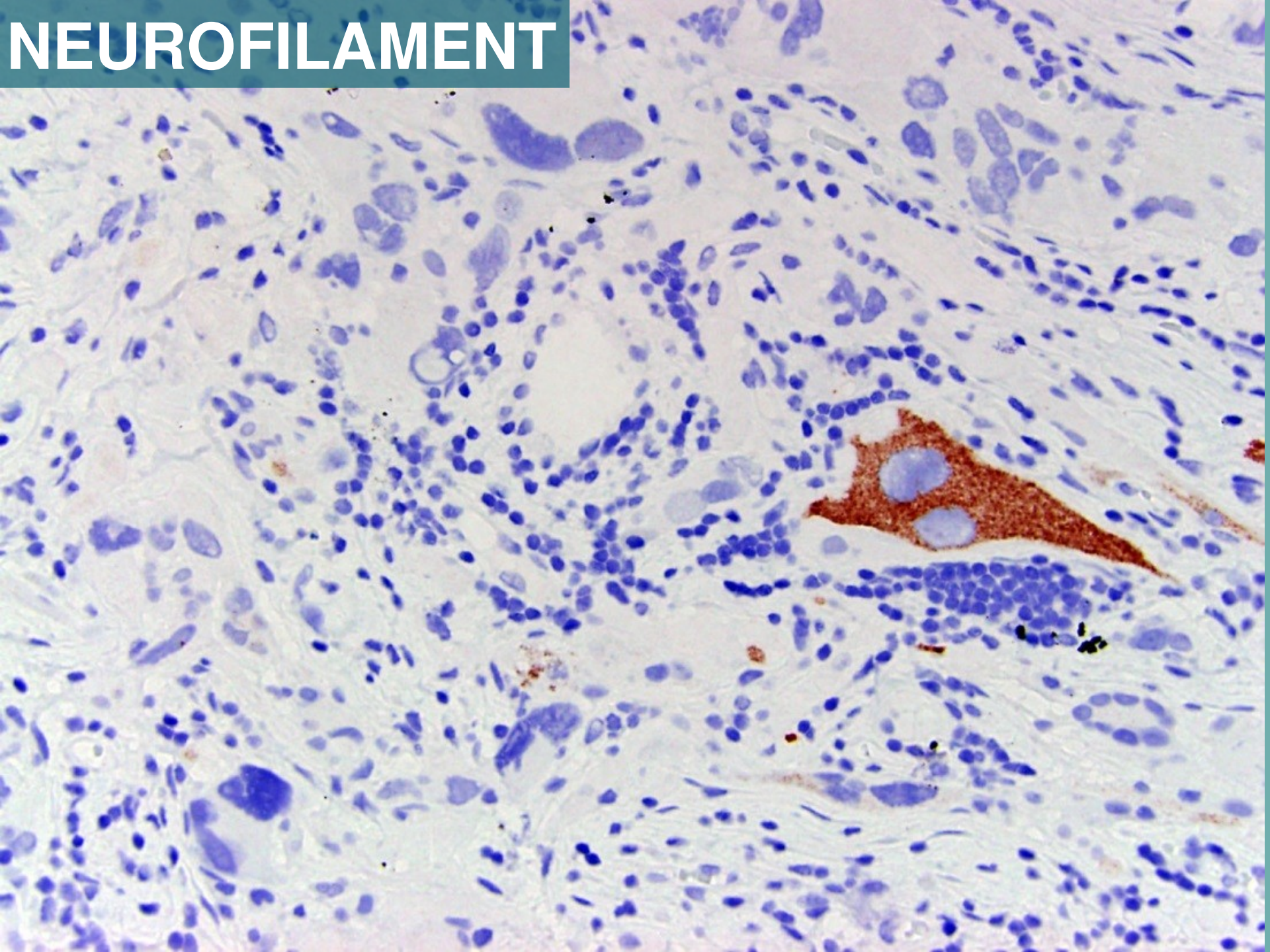
SMALL CELL COMPONENT AND MITOSIS



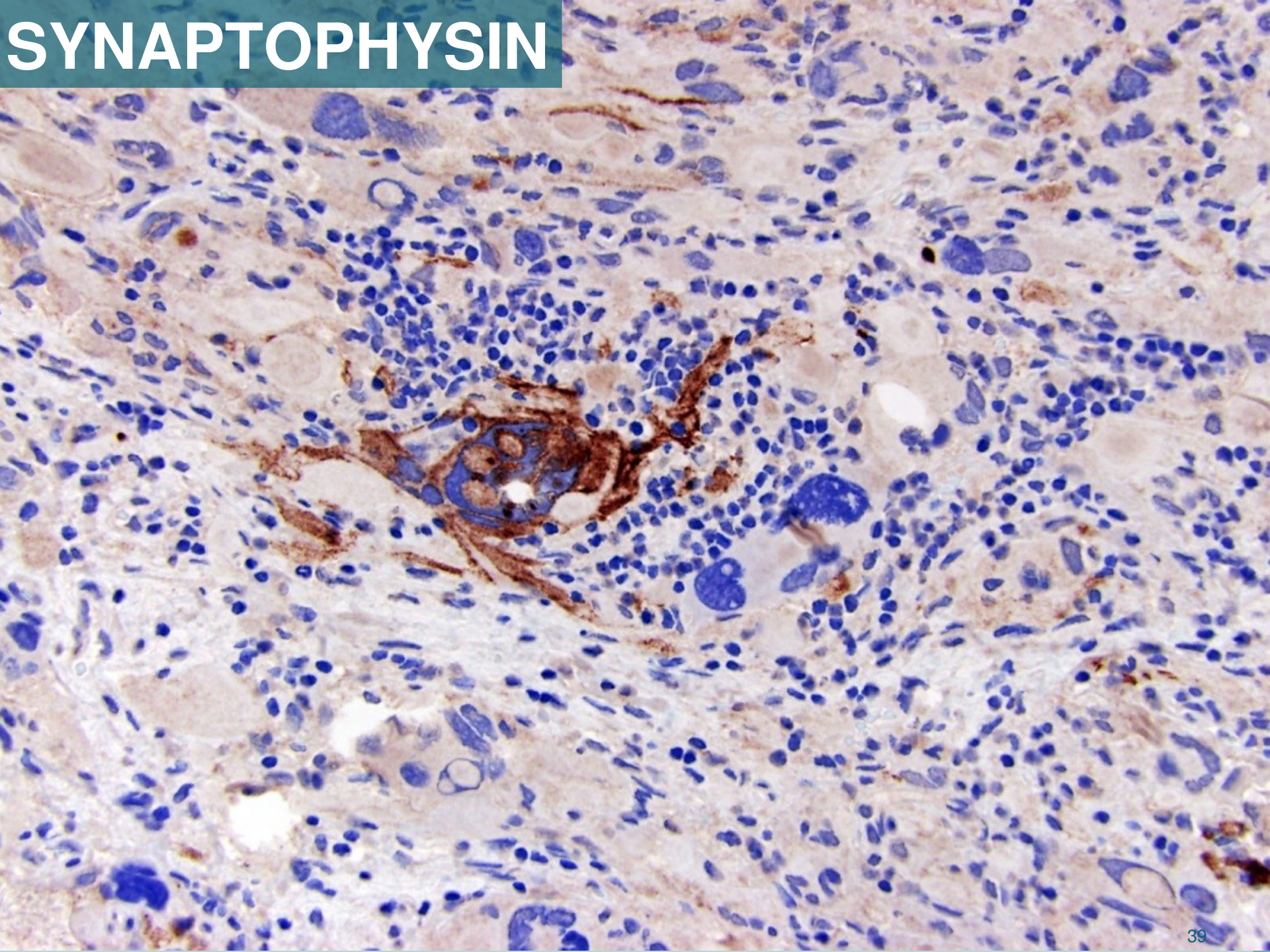
RETICULIN



NEUROFILAMENT



SYNAPTOPHYSIN



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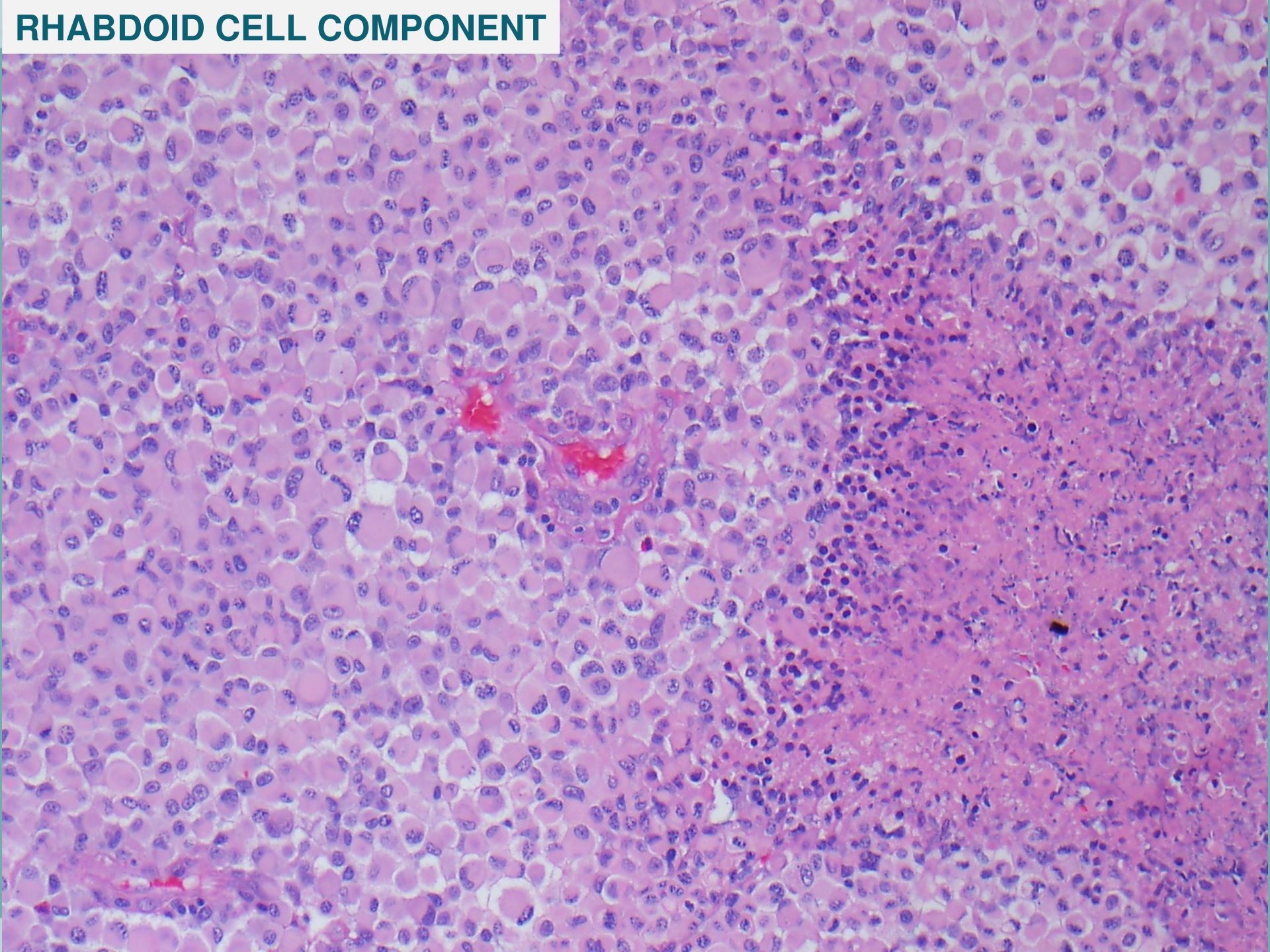
PLEMORPHIC XANTHOASTROCYTOMA

- **Classical PXA diagnosis is highly reproducible (EGBs, Giant cell, Extensive reticulin deposition, lipidized astrocytes**
- **PXA with anaplastic features**
  - Classical PXA with increased mitotic rate (low interobserver variability in diagnosis)
  - Malignant glioma with rare EGBs that resembles PXA (high interobserver variability in diagnosis)
- **BRAF V600E mutation defines >70% of PXAs**

RHABDOID CELL COMPONENT



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DIFFUSE ASTROCYTOMAS

- **DIFFUSE BRAINSTEM GLIOMA**
  - P53 mutations <5%
  - EGFR amplification or mutation <5-10%
  - IDH-1 mutations <20%
    - **Most children with the above genetic alterations are older than 10 years and often older than 15!**
  - **BRAF V600E**
- **DIFFUSE THALAMIC/BITHALAMIC GLIOMA**
- **PEDIATRIC GLIOBLASTOMA**

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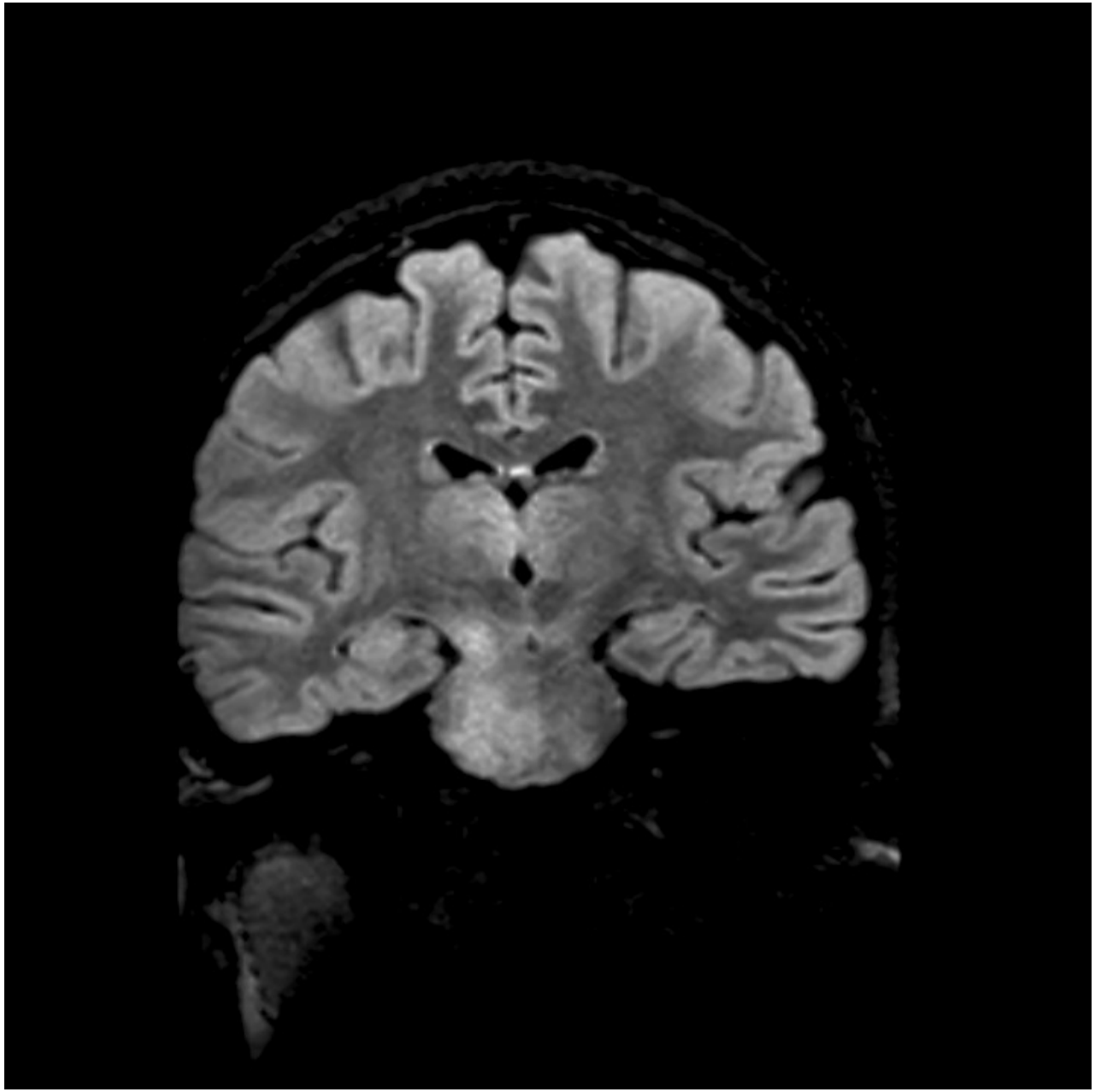

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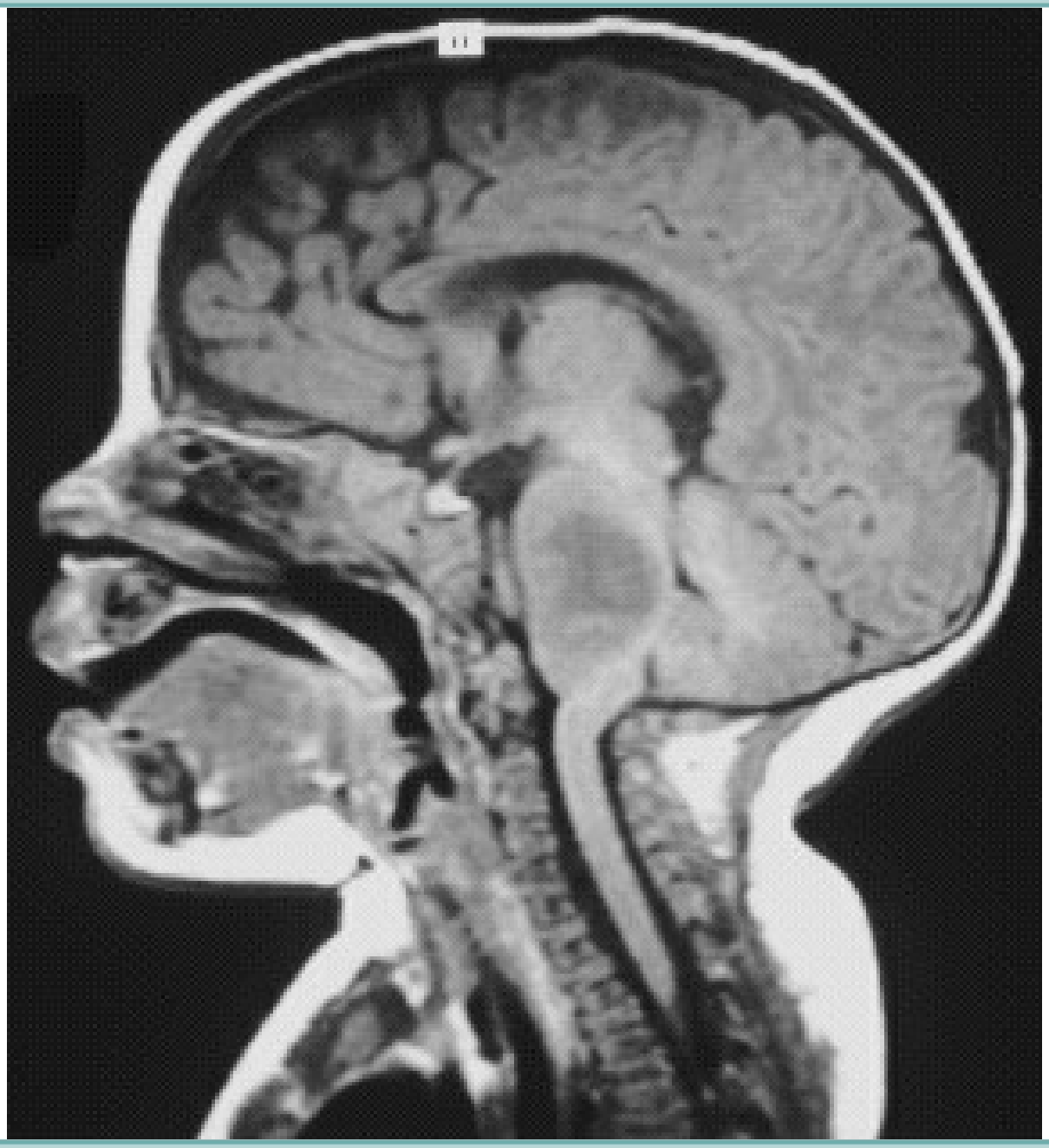

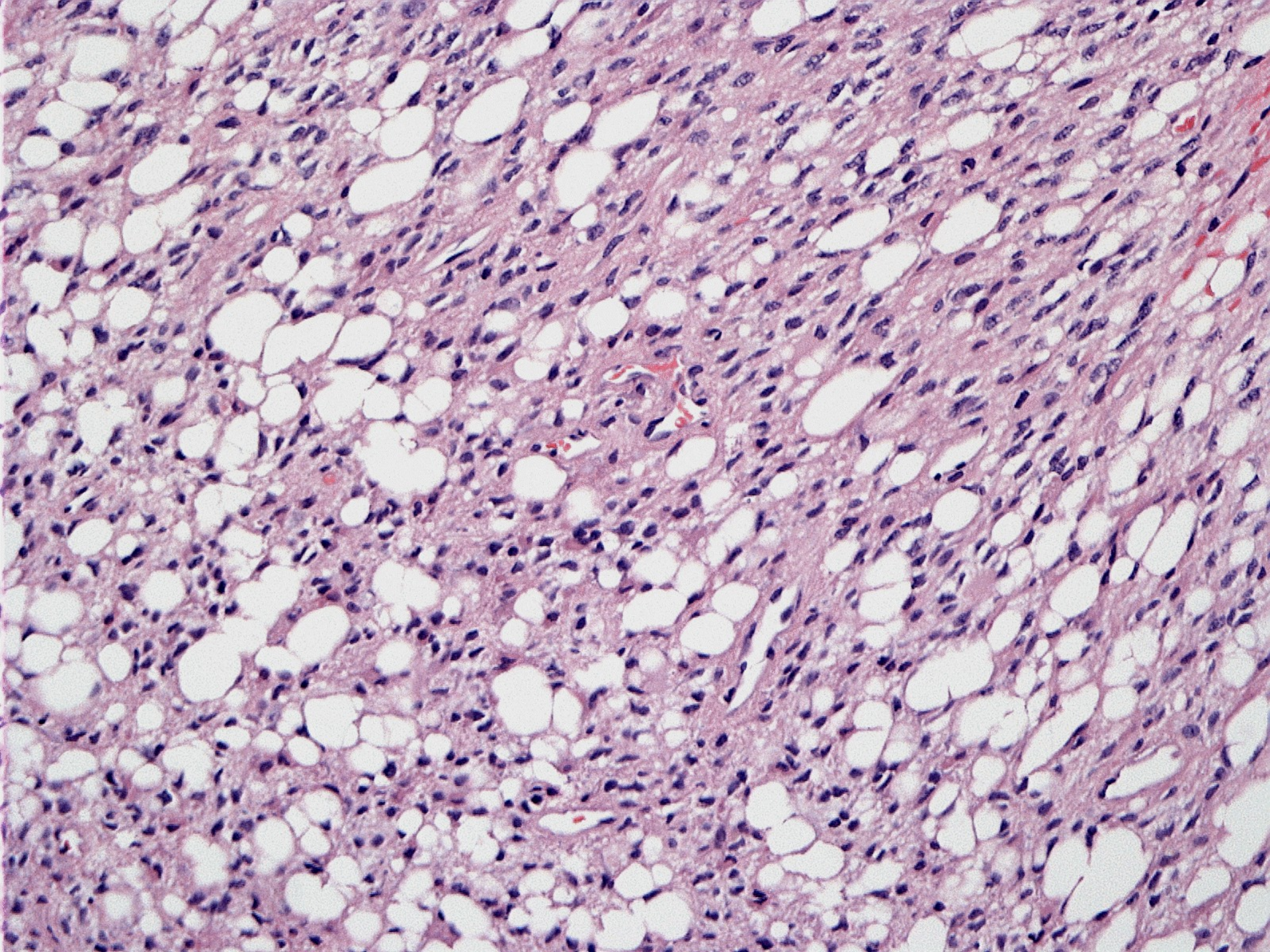

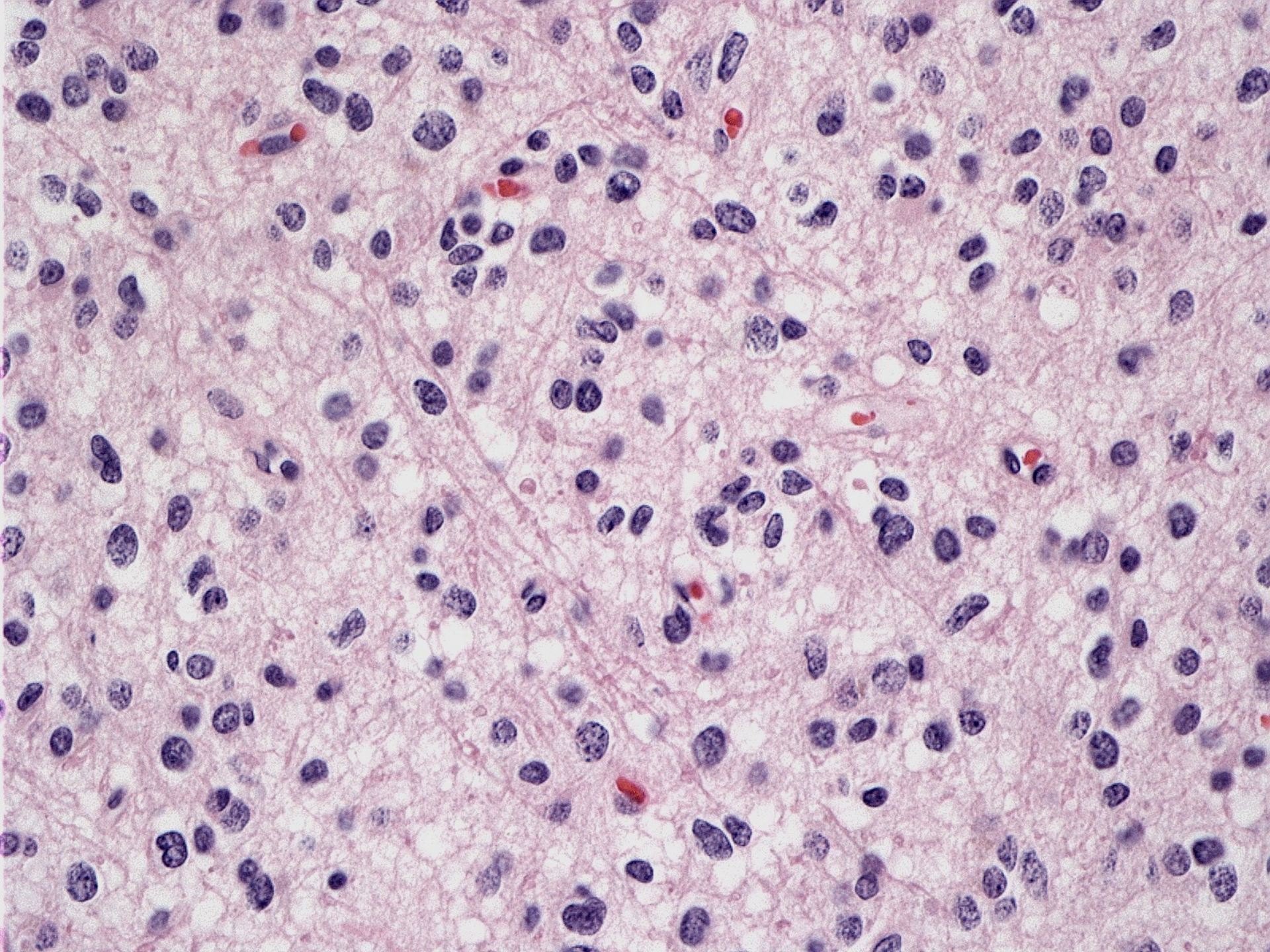

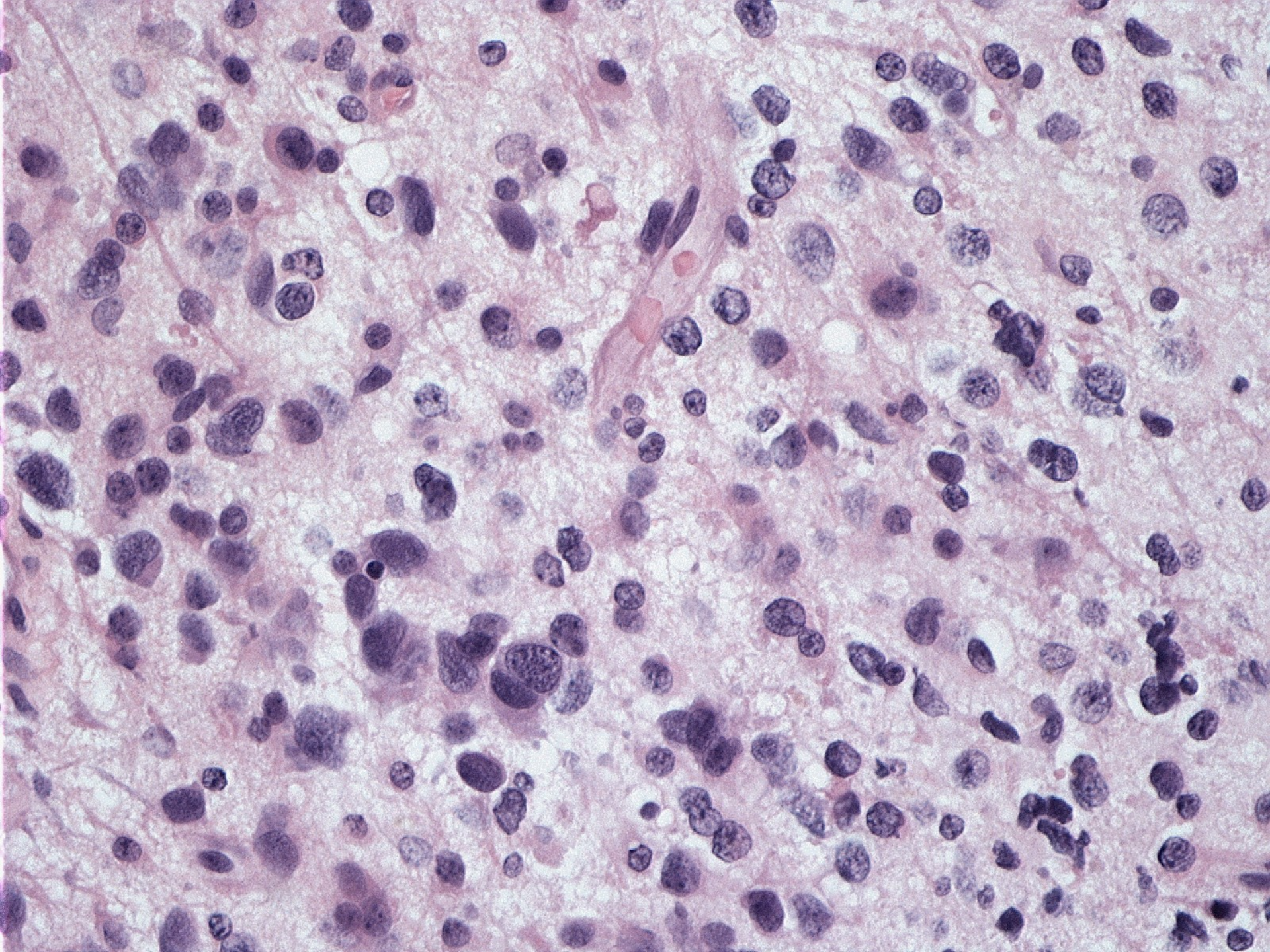

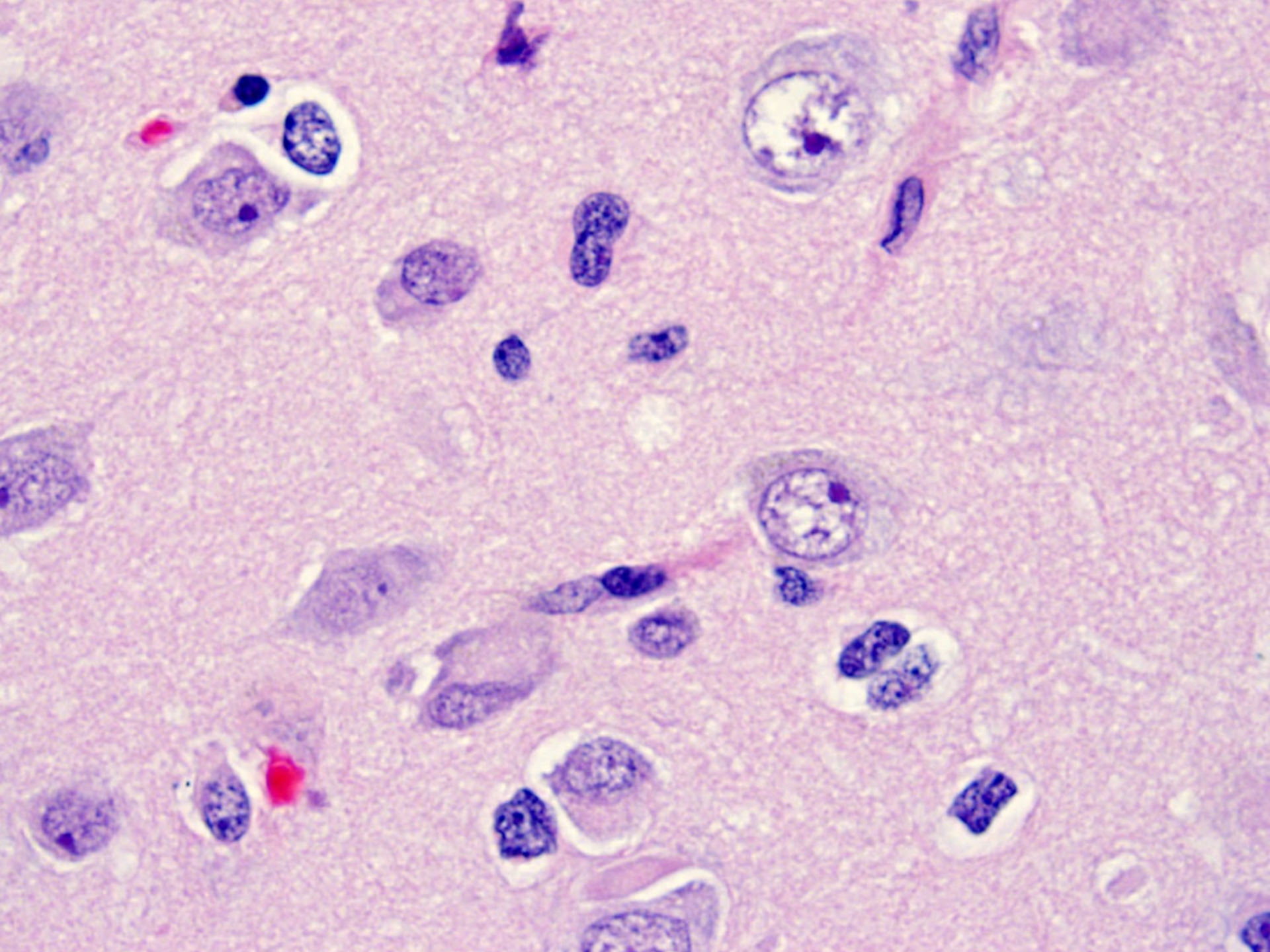

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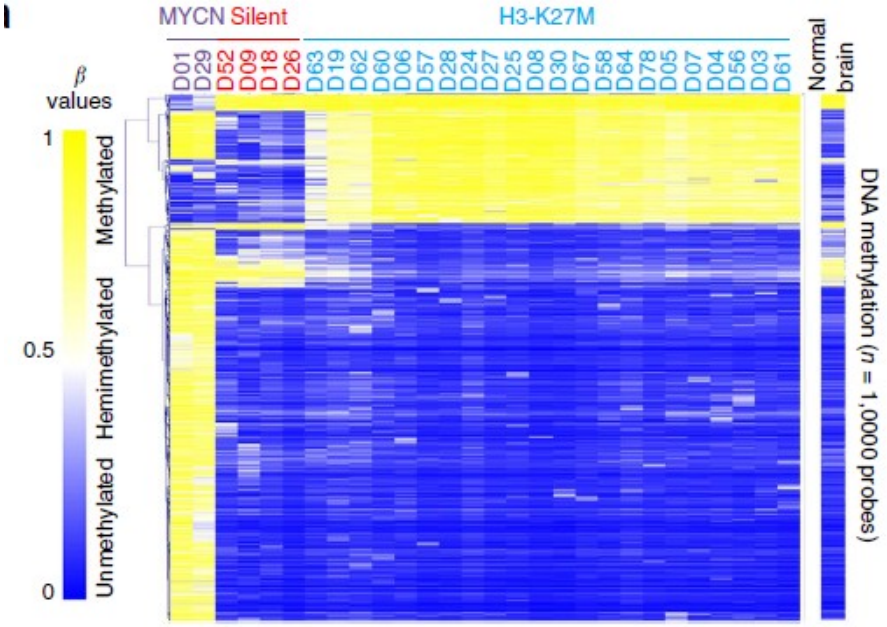
NATURE GENETICS ADVANCE ONLINE PUBLICATION published online 6 April 2014;

Genomic analysis of diffuse intrinsic pontine gliomas identifies three molecular subgroups and recurrent activating *ACVR1* mutations

Pawel Buczkowicz[1–3,24], Christine Hoeman[4,24], Patricia Rakopoulos[2,3], Sanja Pajovic[2], Louis Letourneau[5], Misko Dzamba[6], Andrew Morrison[2], Peter Lewis[7], Eric Bouffet[8], Ute Bartels[8], Jennifer Zuccaro[2], Sameer Agnihotri[2], Scott Ryall[2], Mark Barszczyk[2,3], Yevgen Chornenkyy[2,3], Mathieu Bourgey[5], Guillaume Bourque[5], Alexandre Montpetit[5], Francisco Cordero[4], Pedro Castelo-Branco[2], Joshua Mangerel[2], Uri Tabori[2,8], King Ching Ho[2], Annie Huang[2,8], Kathryn R Taylor[9], Alan Mackay[9], Anne E Bendel[10], Javad Nazarian[11], Jason R Fangusaro[12], Matthias A Karajannis[13], David Zagzag[13], Nicholas K Foreman[14], Andrew Donson[14], Julia V Hegert[15], Amy Smith[15], Jennifer Chan[16], Lucy Lafay-Cousin[16], Sandra Dunn[17], Juliette Hukin[17], Chris Dunham[17], Katrin Scheinemann[18], Jean Michaud[19], Shayna Zelcer[20], David Ramsay[20], Jason Cain[21], Cameron Brennan[22], Mark M Souweidane[22], Chris Jones[9], C David Allis[7], Michael Brudno[6,23], Oren Becher[4,25] & Cynthia Hawkins[1–3,25]



published online 6 April 2014;
NATURE GENETICS ADVANCE ONLINE PUBLICATION

Recurrent activating *ACVR1* mutations in diffuse intrinsic pontine glioma

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LETTER

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Driver mutations in histone H3.3 and chromatin remodelling genes in paediatric glioblastoma

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Table 1 Frequency of recurrent somatic mutations in DIPG and GBM

Gene	Amino acid change	DIPG[a] (%)	non-BS-PG[b] (%)
H3F3A	p.Lys27Met	30 (60)	7 (19)
H3F3A	p.Gly34Arg	0	5 (14)
HIST1H3B	p.Lys27Met	9 (18)	1 (3)
All H3		39 (78)	13 (36)

[a]For DIPGs, total $n = 50$. [b]For non-BS-PGs, total $n = 36$.

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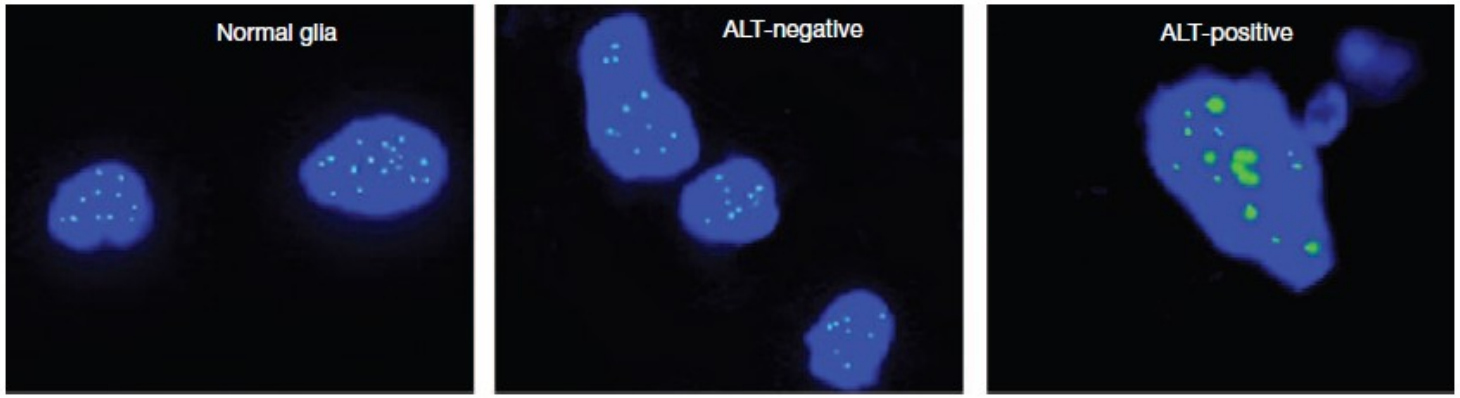
H3F3A/ATRX mutations are associated with alternative lengthening of telomeres

Schwartzentruber et al, *Nature* February 2012



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The histone H3.3K27M mutation in pediatric glioma reprograms H3K27 methylation and gene expression

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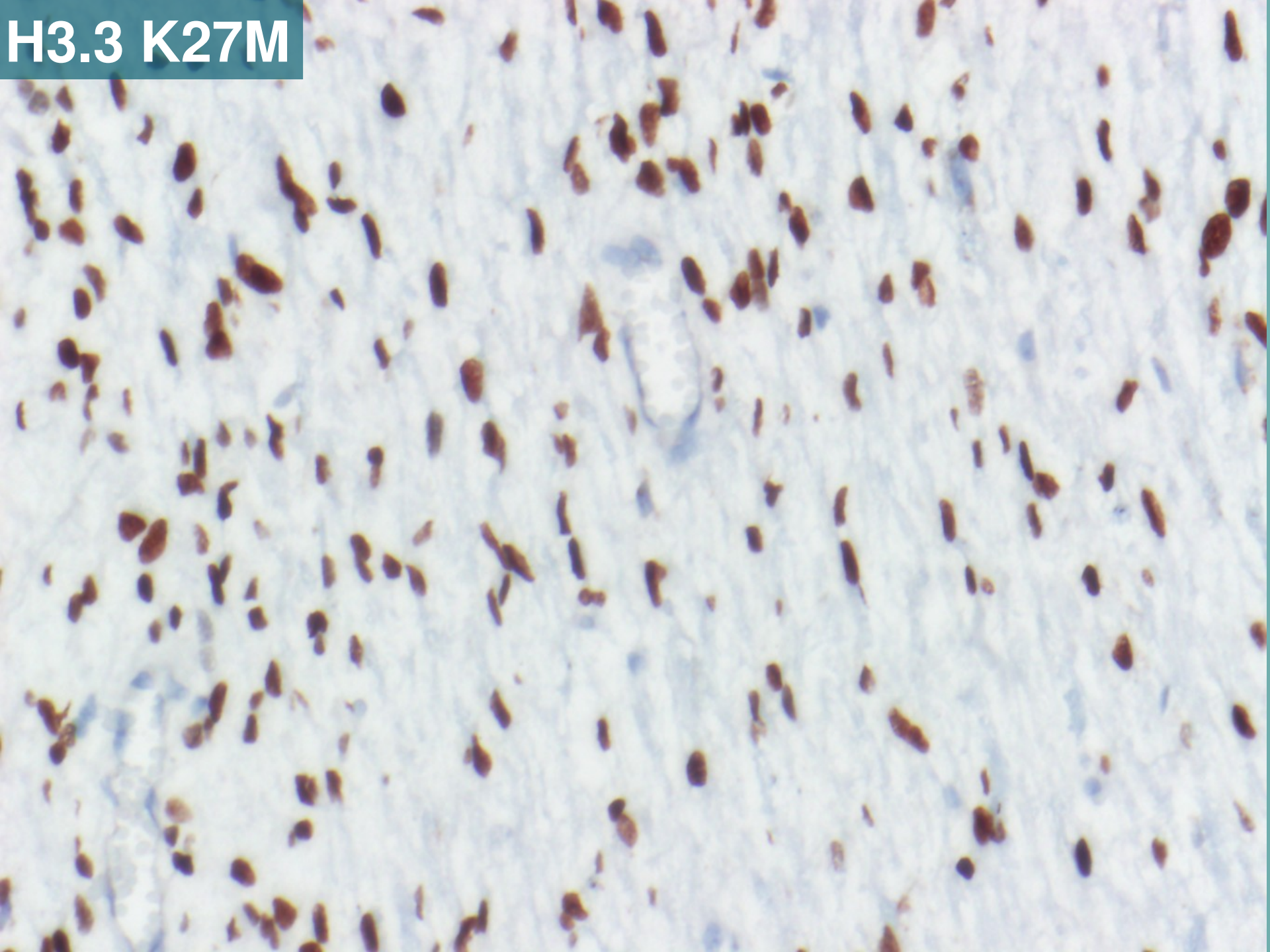
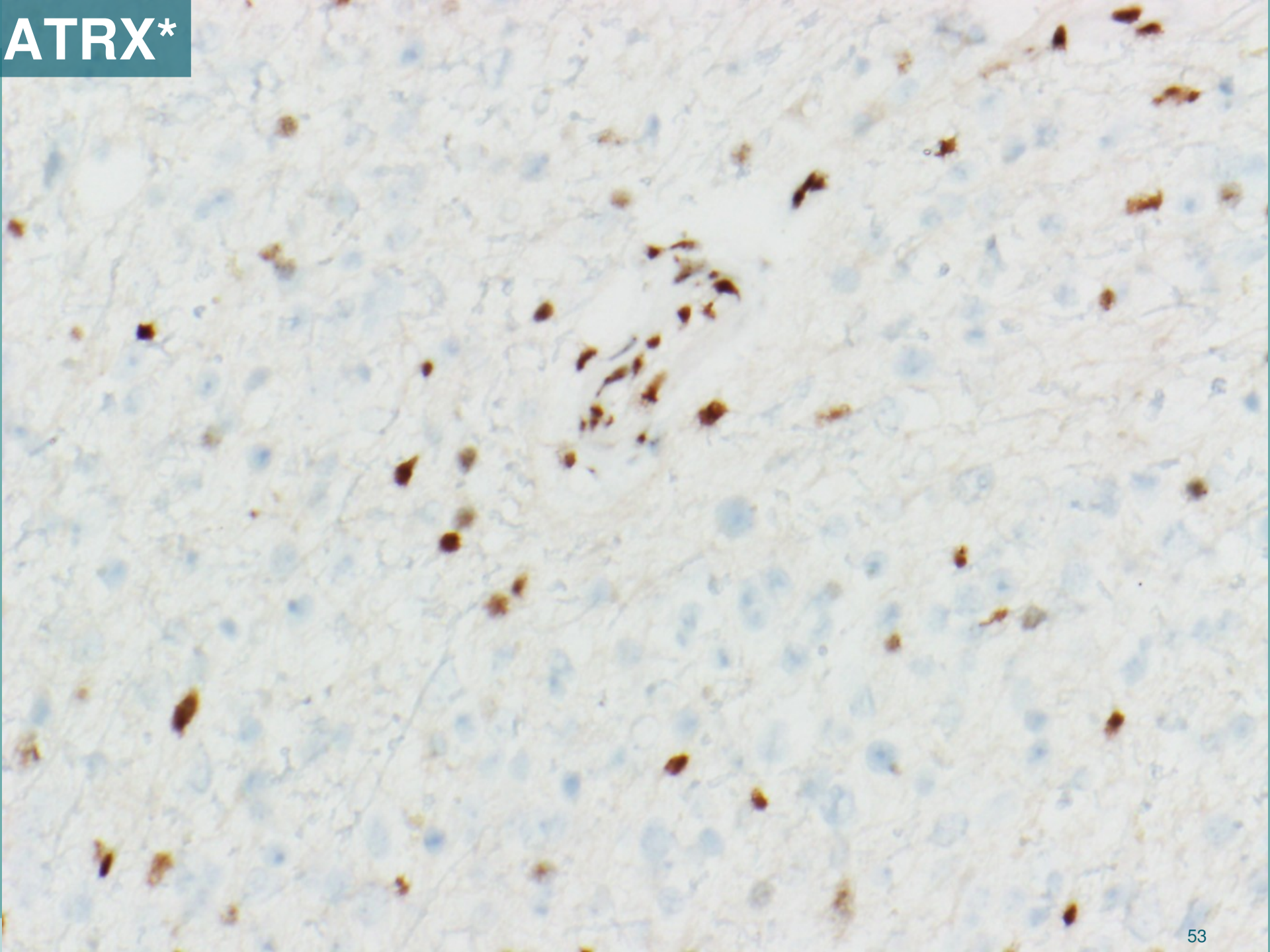

H3.3 K27M


ATRX*

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CONCLUSIONS (1 of 3)

- MAPK pathway activation is defining molecular change for pilocytic astrocytomas and BRAF fusion is typical for posterior fossa examples
- Senescence and potential for aggressive growth in pilocytic astrocytomas may be predicted in some patients
- BRAF V600E mutation defines PXAs and the anaplastic variant
- There are frequent ACVR1 mutations in DIPGs, and germline ACVR1 mutation is bad.
- H3F3-K27M mutations define most DIPGs in the pediatric population

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CONCLUSIONS (2 of 3)

- Specific genetic lesions can define a histologic type of pediatric gliomas (e.g. KIAA1549-BRAF fusions), while other mutations (e.g. H3K27M) are more common in a certain brain location
- A histone H3.3-K27M mutant-specific antibody is now commercially available and diagnostically useful.
- BRAF V600E antibody has been developed but has limited utility
- The molecular classification of pediatric infiltrating astrocytomas await additional data

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CONCLUSIONS (3 of 3)